Desmin and its molecular chaperone, the αB-crystallin: how post-translational modifications modulate their functions in heart and skeletal muscles?

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ABSTRACT

Maintenance of the highly organized striated muscle tissue requires a cell-wide dynamic network through protein-protein interactions providing an effective mechanochemical integrator of morphology and function. Through a continuous and complex trans-cytoplasmic network, desmin intermediate filaments ensure this essential role in heart and in skeletal muscle. Besides their role in the maintenance of cell shape and architecture (permitting contractile activity efficiency and conferring resistance towards mechanical stress), desmin intermediate filaments are also key actors of cell and tissue homeostasis. Desmin participates to several cellular processes such as differentiation, apoptosis, intracellular signalisation, mechanotransduction, vesicle trafficking, organelle biogenesis and/or positioning, calcium homeostasis, protein homeostasis, cell adhesion, metabolism and gene expression. Desmin intermediate filaments assembly requires αB-crystallin, a small heat shock protein. Over its chaperone activity, αB-crystallin is involved in several cellular functions such as cell integrity, cytoskeleton stabilization, apoptosis, autophagy, differentiation, mitochondria function or aggresome formation. Importantly, both proteins are known to be strongly associated to the aetiology of several cardiac and skeletal muscles pathologies related to desmin filaments disorganisation and a strong disturbance of desmin interactome. Note that these key proteins of cytoskeleton architecture are extensively modified by post-translational modifications that could affect their functional properties. Therefore, we reviewed in the herein paper the impact of post-translational modifications on the modulation of cellular functions of desmin and its molecular chaperone, the αB-crystallin.

KEYWORDS: intermediate filaments, desmin, αB-crystallin, phosphorylation, O-GlcNAcylation, striated muscles.

ABBREVIATIONS

AA: amino acid

ACD: "α-crystallin" domain

ADPRT: ADP ribosyl transferase

CamKII: calcium-calmodulin-dependant protein kinase II

Cdk1: cyclin-dependant kinase 1

CTE: C-terminal extension

GSK3: glycogen synthase kinase 3

HSP: heat shock protein

IFs: intermediate filaments

IXI/V: Ile-X-Ile/Val motif

KO: knock-out

MAPK: mitogen activated protein kinase

MAPKAP: MAPK activated protein kinase

MFM: myofibrillar myopathy

NTD: N-terminal domain

OGA: O-GlcNAcase, N-acetyl-β-D-glucosaminidase

O-GlcNAcylation: O-N-acetyl-β-D-glucosaminylation

OGT: O-GlcNAc transferase, Uridine diphospho-N-acetylglucosamine polypeptide β-N-acetyl-glucosaminyl-transferase

PAK: p21-activated kinase

PKA: cAMP-dependent protein kinase

PKC: calcium/phospholipid-dependant kinase

PP1: protein phosphatase 1

PTM(s): post-translational modification(s)

ROK: p160 Rho kinase

sHSP: small heat shock protein

UPS: ubiquitin proteasome system

1. THE SARCOMERIC CYTOSKELETON

The striated muscle, whose organization is highly complex through an intricate interconnected cytoskeletal network, is an efficient machinery composed of specialized myofibrils that convert chemical energy into mechanical work [1-3]. The sarcomere, the functional contractile unit of striated muscle, is delimited by two Z-discs and corresponds to a strictly and complex macromolecular assembly requiring precise and regulated localization of their constitutive proteins. It results from regular arrangement of two key filaments, the thin and the thick filaments mainly composed of actin and myosin, motor proteins at the origin of the contraction and the generation of force. Titin completes this sarcomeric organization; this giant protein, a genuine scaffold protein, permits the anchoring of several protein partners regulating thus their subsarcomeric position and modulates the intracellular signalling pathways as a function of contractile activity [4]. While thin and thick filaments interact to generate the contraction force, other proteins constitute an intricate and interconnected network, termed nowadays "sarcomeric cytoskeleton" [2] whose role is the regulation of sarcomere function to ensure its efficient work. Amazingly, although the contractile apparatus must be maintained in almost crystalline order, this framework is not passive or static. Instead, this semi-crystalline organized structure is highly dynamic and the constituted components are in a required equilibrium with constant coordinated changes in structural protein homeostasis as well as in its assembly and maintenance.

Intermediate filaments (IFs), a large family of around 70 members [5], are essential actors of the substantial and elaborated cytoskeletal network with a crucial role in the maintenance of cell shape and architecture, conferring resistance of cells towards mechanical stress [6-8]. They also contribute to the structuration of cells thanks to their interaction with organelles [9, 10], but also the organization of cells into tissues since IFs interact with adhesive structures such as focal adhesions or desmosomes [11]. Initially considered as static structure, it is now well admitted that IFs are on the contrary highly dynamic, able to respond rapidly to changes in cellular activities. Post-translational modifications (PTMs) are strong regulators of IFs dynamics since they could interfere for the fine modulation of the IFs dynamics and interactions in response to signalling pathways [12-17]. Thus, beyond their mechanical role, IFs are a nodal point within cells because of their interactions with a growing number of proteins, in particular proteins of signalling pathways [18, 19]; therefore, IFs are both targets and active contributors of intracellular signalling. As modifiers and organizers of signalling, IFs contribute to dynamic cell behaviour (*e.g*. development, cell division, cell proliferation, cell migration, cell adhesion, aging, apoptosis) and in larger extent to tissue homeostasis (*e.g.* regeneration, wound healing, inflammation, immune response) [12, 20-23]. Moreover, some studies describe that IFs can also be localized at the surface of the plasma membrane or released in the extracellular environment in different physiological and pathological conditions [24-26]. Indeed, the type III IFs vimentin was identified outside the cell where it serves as an attachment site for viral proteins, highlighting the role of the IFs

in viral infection [27, 28]. Importantly, it is now reported that IFs are involved in around 80 human diseases [29-32].

2. THE DESMIN INTERMEDIATE FILAMENTS

2.1. Roles of desmin filaments

Desmin, a 470-amino acids protein whose predicted molecular weight is 53.5 kDa (UniProtKB/ Swiss-Prot entry: P17661 for human desmin), is the major protein of type III IFs in adult striated muscle cells, representing 2% and 0.35% of total proteins in heart and skeletal muscles, respectively [33]. Desmin is present in various cell types, such as smooth muscle cells, liver stellate cells, cardiac Purkinje fibres, vascular pericytes, Sertoli cells and primary lung fibroblasts [34-39]. Encoded by *DES* gene on 2q35 in human, desmin shares a tripartite organization, with a head, an α-helical rod and a tail from N- to C-terminus **(Table I, figure 1)**; this organization is common to type III IFs family regrouping desmin, vimentin, glial fibrillary acidic protein, peripherin and syncoilin [40].

More specifically, for desmin, the rod domain plays a role in desmin polymerization and consists of four α-helix domains (termed 1A, 1B, 2A and 2B) separated by three linkers (L1, L12 and L2). However, it should be mentioned that only flexible segments L1 and L12 are now considered as linkers [40-43]. In addition to this rod domain, desmin head is involved in polymerization process too but also in IFs assembly while the tail is more specifically involved in the global organization of desmin IFs within the filamentous network presenting visco-elasticity properties [44-46]. Desmin is a highly insoluble protein that assembles though a multi-steps process: (i) two monomers of desmin dimerize within a parallel-oriented coiled-coil formation of the central rod domain; (ii) two coiled-coil dimers join together in an anti-parallel manner to form tetramer; and (iii) the lateral parallel assembly of tetramers leads to filaments of around 60 nm length and 16 nm diameter corresponding to unit-length filaments (ULFs) [8, 40, 47, 48]. The ULFs spontaneously assemble by annealing end-to-end to form incrementally longer filaments, leading at term to intermediate filaments of several hundred nanometres length and 10 nm width. Finally, these desmin IFs constitute a tridimensional filamentous network, anchoring a myriad of proteins within a complex interactome.

The desmin interactome is vast [49-52], desmin interacting with IFs and IFs-associated proteins, sarcomeric and membrane-associated proteins and also with heat shock proteins or signalling proteins [47, 49]. Thus, through specific interactions with a plethora of structural proteins, desmin forms a continuous transcytoplasmic network around Z-discs, maintaining the lateral alignment of myofibrils while tethering them to sarcolemma through costameres and organelles membrane, in particular nuclei, mitochondria and sarcoplasmic reticulum [3, 53]. This coupling of myofibrils to sarcolemma and mitochondria is essential for force transmission and mechanotransduction while maintaining the muscle cell integrity, and permits the optimization of energy use by myofibrils during the contraction

mechanism [3, 10, 40]. Thus, through the constitution of a tridimensional latticework and anchoring of myofibrils and organelles, desmin ensures the maintenance of cell shape and architecture, the preservation of muscle integrity, permitting efficient contractile activity and conferring resistance towards mechanical stress [49, 51, 54, 55]. Desmin IFs are also key actors of cell homeostasis and survival because of their implication in several cellular processes such as differentiation, repairing process, apoptosis, intracellular signalisation, mechanotransduction, vesicle trafficking, organelle biogenesis and/or positioning, calcium homeostasis, protein homeostasis, cell adhesion, metabolism and gene expression [3, 49, 50, 56-60]. Two independent desmin knock-out (KO) mice were obtained in 1996 by using exon 1 interruption strategy [61, 62]. These murine KO models support the essential role of desmin in muscle physiology. Indeed, in desmin null mice, the absence of desmin in muscle leads to the disruption of muscle architecture with strong abnormalities in myofibers characterized by a misalignment of myofibrils. As consequence, myofibrils integrity is lost, associated to a perturbation of sarcolemmal anchoring of myofibrils, abnormal mitochondrial localization and function, apoptosis and degeneration while endurance and muscle force decreased [59, 62-65]. Surprisingly, the desmin null mice are viable and fertile, and myofibrillogenesis and early stages of differentiation occur properly; however, during regeneration, the proliferation and the fusion delay while the second wave of myofibrillogenesis is abortive [58, 59, 64, 66, 67]. Since desmin is also found in cardiac intercalated disks and in skeletal muscle myotendinous and neuromuscular junctions, an abnormal morphology of intercalated disks and neuromuscular junction are also observed in desmin null mice [47, 63, 66]. Moreover, recent studies have assigned new roles to the desmin filaments as regulators of cell adhesion [60] and modifiers of dystrophic muscle [68].

2.2. Desmin network abnormalities and associated muscular and cardiac disorders

Mutations or impaired expression of desmin (primary desmin alteration) are closely associated to dramatic myofibrillar dysfunction and desmin is strongly associated to the aetiology of muscle pathologies, especially heart (*e.g.* dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy) and skeletal muscle diseases, in particular myofibrillar myopathies, a class of rare striated muscles diseases [3, 11, 49, 50, 54, 55, 69, 70]. It should also be noticed that desmin IFs remodelling (corresponding to secondary desmin alteration) is associated to aging and various disorders such as obesity, type II diabetes, sleep apnoea, asthma, dysphagia, hypoxia-induced pulmonary hypertension, muscle wasting, LMNA cardiomyopathy and Friedreich Ataxia, leading to cytoskeleton abnormalities and changes in muscle structure and/or function [48, 71-78]. Several case reports link desmin immunoreactivity abnormalities to diverse muscle pathologies such as congenital myopathy, developmental myopathies, adult onset myotubular myopathy, spheroid body myopathy, dystrophinopathies, cardiomyopathies or granulo-filamentous body myopathy, desmin being often localized toward cytoplasmic bodies and aggregates [79-90]. At the end of 1990s, Goldfarb et al.

described three missense mutations (A337P, A360P and N393I) in desmin gene associated with familial mild cardiac and adult-onset skeletal myopathy [91]. Several missense mutations, splice site or frame-shift mutations or deletions in *DES* gene were identified thereafter [92-105] (for review, see [47, 48, 50, 55, 106]). Importantly, these mutations could have repercussions on desmin structure, IFs assembly and/or organization and by extension on desmin IFs architecture [107]. A meta-analysis performed on 40 different mutations of *DES* gene (159 mutation carriers) revealed that 74% of patients presented myopathy or muscle weakness, 49% a combination of skeletal and cardiac signs and 26% suffer also from respiratory insufficiency [106]. The smooth muscle defects such as dysfunction of intestine or bladder are observed in some patients carrying desmin mutations [108, 109]. It is worth to note that the majority of these *DES* mutations occur predominantly in 2B domain, essential for IFs assembly, in particular in patients with neurological signs whereas predominant cardiological phenotype is rather linked to head and tail domains mutations [106]. These desmin-related myopathies (OMIM 601419), also referring as desminopathies, a subset of myofibrillar myopathies (MFMs), are characterized by strong morphological changes in striated muscle resulting from myofibril disintegration and abnormal accumulation of desmin among other structural and sarcomeric proteins (*e.g.* myotilin, filamin C, plectin, synemin, HSP27, αB-crystallin, dystrophin) [47]. Even if some mutations of *DES* gene are not characterized by abnormal protein aggregation [48], these ectopic desmin aggregates presenting subsarcolemmal and/or sarcoplasmic location are a hallmark of desminopathies and in larger extent, MFMs [110, 111]. As a consequence, desmin function is lost while toxic aggregates, that are seeding-competent amyloid aggregates of desmin, accumulate and persist within muscle fibres [112, 113]. The desmin network disorganization and destructuration have dramatic cellular repercussions since they are closely associated to improper mitochondrial function, loss of cell adhesion and cell-cell communication, fibrosis and inflammation [47, 50, 114]. Thus, desmin mutations lead to disruption of desmin cytoskeleton and mitochondrial abnormalities in terms of distribution, shape, number and function [115-117]. Finally, due to the role of desmin as scaffold for plethora of myofibrillar and signalling proteins, mutations of desmin could have repercussions on the function of the associated proteins that interact or co-interact within the desmin interactome. Indeed, when desmin aggregates in MFMs, numerous myofibrillar proteins co-aggregate such as αB-crystallin, filamin C, actinin, vimentin, synemin or myopalladin among others, leading to their mislocalization and/or the loss of their function [118-120]. Consequently, desmin mutants could affect several cellular processes depending on the mutation, such as proteasomal activity and autophagy (and in larger extent, protein homeostasis); in addition, cell stiffness changes due to the loss of interaction with nebulin and actin filaments [56, 121-125]. Thus, desmin-related myopathies (*i.e.* desminopathies) result from mutation in the desmin gene, but could also be consecutive to desmin cleavage and/or post-translational modifications (PTMs) changes leading to a dysfunctional desmin network [50, 105, 126-128].

2.3. The post-translational modifications of desmin

Desmin is the target of several PTMs [40, 71], the well-known and the most studied being phosphorylation. Desmin phosphorylation was firstly described four decades ago [129, 130], and phosphorylation of the head domain **(figure 1)** is often associated to IFs disassembly and solubilisation [131]. In addition, the change of the charge environment due to the addition of one or more negative charge(s) could also modify the interaction between desmin and its partner(s). Desmin is phosphorylated by several kinases, connecting desmin to different cellular processes such as cell division, myoblast differentiation or muscle contraction [71].

Among these kinases, Rho-associated kinase (also termed ROK or $p160^{ROCK}$), a member of the Rho family GTPase-dependant kinase, is involved in the regulation of muscle metabolism and differentiation while its activity increases after exercise [132-134]. Rho kinase phosphorylates desmin on threonines 17, 76 and 77 [135, 136], the phosphorylated desmin losing its ability to form 10 nm filaments. Similar observation was done when desmin is incubated with PAK (p21-Activated Kinase) that phosphorylates desmin mainly on the head domain [137]. PAK is a Ser/Thr kinase regulated by the Ras-related small G-proteins Cdc42/Rac1 involved in the regulation of cell cycle, cell survival, differentiation, cytoskeleton dynamics, muscle contractility and muscle regeneration [138-141]. However, even if similar consequences are observed on desmin depolymerisation when phosphorylated by ROK or PAK, modified sites are not the same since PAK phosphorylates serine residues whereas Rho kinase targets threonine residues [137]. These data support that specific kinases targeting different sites could impact the desmin function in a similar manner, increasing thus the regulatory potential for desmin organization and remodelling in response to specific cellular signals.

Desmin is also targeted by kinases involved in cell cycle regulation; among them, Aurora kinase B and Cdk1 phosphorylate desmin on Ser12/Thr17/Ser60 and Ser7/Ser28/Ser32, respectively [136, 142-144]. Interestingly, using phosphorylation site- and state-specific antibodies [145-147], Makihara and co-workers showed a spatio-temporal regulation of desmin phosphorylation on Ser32 during cell cycle in muscle cells. More specifically, they observed that phosphorylation on Ser32 occurs in the whole cytoplasm during the prometaphase to metaphase transition, leading to efficient separation of desmin IFs during mitosis [142]. They also demonstrated that desmin phosphorylation on Ser60 by Aurora-B and on Thr76 by Rho kinase occurs during late mitosis (from anaphase to telophase) specifically at the cleavage furrow [142], suggesting a fine spatio-temporal regulation of desmin IFs through the differential and coordinated recruitment of kinases. It is worth to note that hyperphosphorylation of Ser32 resulting from hyperactivation of Cdk-1 in Drp/MC mice (a model of dynamin-related protein 1 overexpression in skeletal muscle) modifies desmin network, leading to mechanotransduction impairment while biogenesis and maintenance of mitochondria are altered [144].

The non-helical N-terminal domain is also phosphorylated by PKC (calcium/phospholipid-dependant protein kinase) and PKA (cAMP-dependent protein kinase) [148-150]. Several sites, more

specifically on Ser13, Ser30, Ser39 and Ser57 (chicken sequence) were identified to be phosphorylated by PKC, corresponding to Ser13, Ser48 and Ser68 on human desmin [71, 149], while PKA phosphorylates desmin on Ser30, Ser36 and Ser51, corresponding to Ser45 and Ser60 on human desmin [71, 148]. The PKC family is a major mediator of signalling pathways regulating a large panel of cell functions (*e.g.* proliferation, differentiation, apoptosis) and is involved in detrimental consequences of several striated muscle diseases, particularly in heart (heart failure, myocardial infarction, atherosclerosis, cardiac hypertrophy or laminopathies) [151-156]. When PKC is activated, it phosphorylates desmin, leading to IFs disassembly while proliferation and differentiation are inhibited [157-159]. The desmin IFs turnover is also strongly impacted by protein kinase A through inhibition of polymerization; interestingly, the fusion of myoblasts into myotubes decreases [148, 160]. Lastly, CamKII was also reported to phosphorylate desmin, but nor the impact on desmin nor the modified site are known [71, 161, 162].

Phosphorylation is a reversible PTM; unsurprisingly, protein phosphatases contribute to the regulation of desmin phosphorylation and are involved in the organization and reorganization of IFs. Indeed, it was demonstrated that protein phosphatases inhibitors dramatically alter IFs, leading to the loss of cytoskeletal integrity [163, 164]. In contrast to phosphorylation inducing filaments disassembly, phosphatase treatment leads to the reassembly of the desmin [150]. In the same way, it was shown that PP1 (type 1 protein phosphatase) antagonizes with Rho kinase to finely regulate the phosphorylation turnover on desmin filaments, and in larger extent, the exchange of desmin subunits between the soluble pool and the filamentous desmin [165].

In addition to phosphorylation, assembly-disassembly of desmin filaments is regulated by ADP-ribosylation. Desmin is a substrate for ADP-ribosyl transferase and the modification occurs in the head domain (Arg48 and 68 on turkey desmin, corresponding to Arg58 and 73 on human desmin). Once ADP-ribosylated, desmin does not form the typical 10 nm-diameter filaments [71, 166-168]. Interestingly, it was shown that ADP-ribosylation is a mechanism modulating phosphorylation by PKA and is involved in muscle cells differentiation [166, 169].

At least, desmin is also post-translationally modified by an atypical glycosylation: the O-N-acetyl-β-D-glucosaminylation (O-GlcNAcylation) [170]. O-GlcNAcylation corresponds to the transfer of a unique monosaccharide, the N-acetyl-D-glucosamine, on serine or threonine hydroxyl group of a protein; O-GlcNAcylation is highly dynamic and reversible, presenting a dynamic interplay with phosphorylation. It is highly abundant on cytoskeletal proteins, and among them, desmin is glycosylated on Ser460 in tail domain [171-173]; probably other glycosylation sites exist on desmin but remain to be discovered. Even though it was demonstrated that O-GlcNAcylation is involved in organization and reorganization of skeletal muscle sarcomere, partly through the modulation of interaction of desmin and its molecular chaperone, the αB-crystallin, the precise role of O-GlcNAcylation remains uncharacterized [174]. However, since O-GlcNAcylation was demonstrated to modulate the phosphorylation level of IFs [162, 175, 176] and increases keratins solubility [14, 177], ubiquitination

and proteasomal degradation of these IFs proteins [178], it is legitimate to consider that O-GlcNAcylation could exert a key role in the regulation of desmin network organization. In this way, the link between O-GlcNAcylation and desmin network was recently established. Indeed, it was shown that global change of O-GlcNAcylation level in C2C12 skeletal muscle cells is associated to a differential partition of desmin toward cytoskeleton; interestingly, the correlation with desmin phosphorylation was clearly established, suggesting that a dynamic and complex interplay may occur on desmin to modulated its behaviour [162].

2.4. Aberrant modifications of desmin: a link between PTMs and the physiopathology of muscle disorders?

Desmin could be non-enzymatically modified in detrimental physiological conditions; in this way, it was shown that desmin is a preferential target of advanced glycation end (AGE) products in dilated cardiomyopathy [179]. Furthermore, oxidative stress strongly affects desmin, leading to desmin cytoskeleton reorganisation and aggregation [69, 180] **(figure 2)**. Desmin has been observed to be oxidized and nitrated within protein aggregates [111, 181, 182], and interestingly, antioxidant treatment prevents aggregation of desmin in cellular models of desminopathies submitted to various stresses [183]. It was suggested that these aberrant modifications make desmin untargeted by the ubiquitin-proteasome system, leading to the impairment of abnormal desmin degradation and at terms to desmin aggregation [111]. On another note, misregulated ubiquitination of desmin is associated to desmin degradation and is involved in the physiopathology of skeletal muscle atrophy, abnormal phosphorylation preceding the ubiquitination by TRIM32 [184, 185]. In this way, it was demonstrated that phosphorylation by GSK-3β, a kinase activated in fasting conditions [186], is the initial step for desmin IFs degradation in muscle atrophy. Once activated, GSK-3β phosphorylates desmin on Ser32, permitting subsequently its ubiquitination and degradation by calpain-1 [143, 184, 185, 187]. It is worth to note that additional site of phosphorylation linked to detrimental conditions for heart diseases was identified in head domain on the Ser28 [127, 179, 188] **(figure 2)**.

While some desmin mutations linked to desmin-related myopathies correspond to phosphorylated sites, such as S6F or S12F in the head domain [55], abnormal desmin phosphorylation was linked to several cardiac diseases [126, 179, 188, 189] **(figure 2)**. In this way, the phosphorylated form of desmin could be consider as a tissue marker of heart failure, and this phosphorylation increase is linked to desmin aggregation and cleavage by calpain or caspase [126, 127, 143, 190]. Importantly, the Ser32 phosphorylation was identified to be pivotal in the priming nucleation process leading to the formation of preamyloid oligomers [143]. As mentioned previously, Ser32 is also targeted by cyclin-dependant kinases [142, 144]. Interestingly, overexpression of several cyclin-dependant kinases is noticed in MFMs biopsies [191-193], suggesting that desmin hyperphosphorylation and the resulting IFs disassembly could be involved in the pathogenesis of desmin-related myopathies. In the same way, PKC

activity increase is described in a model of cardiomyopathic hamster heart, a model of myocardial disease resulting in chronic congestive heart failure [157]. In addition, desmin hyperphosphorylation occurs in some desminopathies [194, 195] while certain kinase isoforms expression increases in muscle fibres from patients suffering from myofibrillar myopathies [193, 196]; the phosphorylated fragments of desmin are closely associated with the amyloid-like oligomers deposition [188] **(figure 2)**. However, no hypothesis concerning the role of the increase of desmin phosphorylation has been proposed, and it is now clear that the impact of desmin PTMs remains underexploited in myofibrillar myopathies.

Finally, the O-GlcNAc site on desmin corresponds to a mutated site closely associated to the development of desminopathies [173]. Furthermore, it is worth to note that in heart failure, a dynamic interplay was observed between phosphorylation and O-GlcNAcylation on desmin, phosphorylation increasing while O-GlcNAcylation decreases [190] **(figure 2)**.

3. αB-CRYSTALLIN, THE MOLECULAR CHAPERONE OF DESMIN

3.1. Structure and properties of the αB-crystallin

The crystallins, regrouping α-, β- and γ-crystallin, were identified over a century ago as the major proteins in eye lens (around 90% of total protein content of the ocular lens) [197]. Among the different classes of crystallins, the α-crystallins regroup the αA- and αB-crystallins, encoded by two genes coming from a gene duplication event and presenting 57% sequence homology [198]. While the αA-crystallin is mainly expressed in eye lens, the αB-crystallin (encoded by the *CRYAB* gene located at the locus 11q23.1) is widespread expressed in various non-lenticular tissue, in particular heart, skeletal muscle (more specifically in the high oxidative type I fibres) and brain. Moreover, it has a significantly higher concentration in adult than in foetal tissues as demonstrated in rat [199-204]. They are for a long time classified as small Heat Shock Proteins (sHSP) due to their capacity to suppress aggregation of proteins, permitting the protection of eye lens from severe and deleterious consequences of protein aggregation [205, 206]. Although members of this protein superfamily differ according to their sequence and size, they share common characteristics, in particular: (i) a low molecular weight between 15 and 40 kDa; (ii) a tripartite structure with the "α-crystallin" domain (ACD), a signature consensus sequence; (iii) the association with up to 50 subunits within polydisperse homo- and hetero-oligomers of about 10-25 nm diameter; (iv) a dynamic quaternary structure; (v) their induction consecutively to various cellular stresses; and (vi) their chaperone activity permitting the suppression of protein aggregation [199, 207-210].

The αB-crystallin (UniProtKB/Swiss-Prot entry: P02511 for human α-crystallin B chain) presents a common tripartite structure, composed of a conserved and central ACD, the hallmark of sHSP family, flanked with variable N-terminal domain (NTD) and a short C-terminal extension (CTE) [211, 212] **(Table 1, figure 3)**. The ACD of αB-crystallin, covering around 80 amino acids, is characterized by a

predominance of β-strands that permit to form rapidly a stable dimer [197, 213-216]; this dimer is sufficient for *in vitro* chaperone activity, supporting that the multimeric state of αB-crystallin is not required for chaperone activity [214, 217]. In physiological conditions, soluble multimeric αB-crystallin complexes are formed; in contrast, in stress conditions, the αB-crystallin multimers dissociate to form smaller oligomers while the NTD and the CTE become available for recognition of the client proteins and the binding of the unfolded proteins (see below) [218]. For example, when pH varies from 7.5 to 6.8 (during cardiac ischemia, acidosis occurs), the ACD undergoes a transition from dimeric status to monomeric one, permitting so the αB-crystallin to act optimally [219]; at pH 6.8, the affinity of αB-crystallin for desmin increases, allowing so the preservation of IFs integrity in detrimental conditions for cardiac cells. The NTD is around 60 amino acids, particularly rich in hydrophobic amino acids [211]; the propensity of NTD to aggregate when expressed alone suggests that NTD hydrophobicity might be involved in the recognition of exposed hydrophobic domains of unfolded proteins, facilitating their capture [208]. Lastly, due to its modification by phosphorylation, the NTD contributes to conformational changes of αB-crystallin and the regulation of the chaperone activity; this point will be addressed hereinafter. Furthermore, the CTE is a short unstructured sequence of around 20 amino acids highly flexible, hydrophilic and accessible to solvent; consequently, the CTE contributes to the solubility of αB-crystallin under chaperone and non-chaperone conditions [197, 220-222]. The CTE contains the highly conserved IXI/V motif (Ile-Pro-Ile for αB-crystallin) that could interact with the neighbouring ACD domain; it is also involved in the formation and the solubility of oligomers [197, 211, 212, 223, 224]. Supporting the key role of CTE, it was demonstrated that its truncation or mutation leads to myofibrillar myopathies [225]. Importantly, the flanking NTD and CTE are required for solubility and stability of αB-crystallin, delay the amyloid fibril formation and contribute to the interaction with target proteins during the chaperone activity [221, 226]. Thus, although the ACD bears the chaperone activity, the N- and C-terminal regions of αB-crystallin are also involved in fibril disaggregation [227].

3.2. The cellular functions of αB-crystallin

Proteome is inherently metastable since the protein folding is intrinsically error-prone, and its integrity absolutely requires to be maintained; this corresponds to protein homeostasis or proteostasis [228-231]. A fundamental aspect of proteostasis is the maintenance of protein solubility; if not, proteins aggregate consecutively to the exposure and the interaction of hydrophobic amino acids/domains that are normally buried within proteins [228, 229, 232-234]. As a consequence, proteotoxicity results from abnormal accumulation of protein aggregates (extracellular amyloid deposits or intracellular inclusions); highly deleterious for cell and tissues, proteotoxicity is involved in a wide range of proteinopathies, sometimes termed as conformational diseases [233-238].

To ensure this protein equilibrium, cells use interconnected factors within the proteostasis network [231]; among them, molecular chaperones are critical players and guardians of the proteome's stability

and integrity. They are defined as “any protein that interacts with and aids in the folding or assembly of another protein without being part of its final structure” [229]; moreover, besides their role in *de novo* protein folding, molecular chaperones also contribute to aggregates unbundling and the refolding of stress-denaturated proteins. Many of molecular chaperones are logically heat shock proteins since they are synthesized under stress conditions that destabilize a subset of proteins [229]. The chaperone network regroups members fulfilling three main activities: (i) the “foldase” activity, assisting the protein refolding; (ii) the “holdase” activity, forming stable complexes with misfolded proteins and preventing protein aggregation; and (iii) the “translocase” activity, permitting the correct location of proteins [230, 239-241]. A further classification could also be considered, based on the energy dependence of the molecular chaperones: (i) the ATP-dependant chaperones, usually “foldases” such as HSP60, HSP70, HSP90, DnaK and GroEL, that need ATP hydrolysis for recognition and refolding of the targeted proteins; and (ii) the ATP-independent chaperone, usually “holdases”, preventing protein aggregation in an energy-independent way [239]. Archetypical “holdases” are sHSP that recognize misfolded proteins before cooperating with “foldase” chaperones to refold proteins or disintegrate the protein aggregates [211, 212, 230, 241-244]. Acting as the first line of defence against protein aggregation, they are qualified as the “paramedics” of the cell [216].

The αB-crystallin is an integral part of proteostasis system. Under various stresses leading to destabilization of proteins (oxidation, heat increase, pH changes, etc…), it interacts in an ATP-independent manner with the unfolded proteins to correct their conformation and can disrupt the unfolding process through the stabilization of the unfolded target proteins while facilitating their refolding thanks to its chaperone activity [221]. Importantly, it was demonstrated that the αB-crystallin interacts with amyloid oligomers, prevents the fibrillation of several target proteins, and mediates the amyloid dissolution and the depolymerisation of aggregation-prone proteins such as α-synuclein, β2-microglobulin or amyloid β-peptide [240, 241, 245-249]. To ensure its molecular chaperone function, a key step is the recognition and the interaction with target proteins. Several interactive sequences are identified in αB-crystallin, two of them being located into the NTD, four in the ACD, and one in the CTE **(figure 3)** [250]. Substantially, these interactive sequences exert dual roles since they could mediate the subunit-subunit interactions involved in αB-crystallin assembly and also the interactions with client proteins [251]. However, several data support that the interaction between the chaperone and the target proteins involves several interaction domains while an interaction domain could contribute to the interaction of αB-crystallin with various proteins target **(figure 3)**. For instance, the NTD or the ACD are the preferred interaction sites in some cases while in some other, both domains are needed for the chaperone activity [222, 250-257].

The αB-crystallin recognizes a broad spectrum of cellular proteins including proteins involved in apoptosis, cell-cell adhesion and cytoskeleton organization [242, 254, 258-260]. Consequently, over its role as guardian of proteome stability, the αB-crystallin also plays a critical role in the regulation and the modulation of several cellular functions such as cell integrity, apoptosis, autophagy, differentiation,

mitochondria function, aggresome formation, and cytoskeleton stabilization [261-265]; this last point will be explored thereafter. Thus, the αB-crystallin exerts anti-apoptotic activity through inhibition of caspase-3 and PARP, and by preventing the translocation of Bax and Bcl-2 and the activation of the RAS pathway [264, 266-272]. This anti-apoptotic effect of αB-crystallin is also demonstrated in the C2C12 skeletal muscle cell line and in neonatal mouse cardiomyocytes [273, 274]; in the same way, the overexpression of αB-crystallin in transgenic mice is closely associated to decrease of apoptosis and necrosis in cardiomyocytes [275]. Cytoprotective effects of αB-crystallin are also noticed in C2C12 myoblasts exposed to TNF-α [276]. Over its cytoprotective effects, the αB-crystallin seems to be involved in myogenic process since its expression ten-fold increases during skeletal muscle development and differentiation [277, 278] while its expression decreases in aging, closely linked to impaired proteostasis [279]. It modulates the activity of MyoD and delays the myogenic differentiation [280, 281] while C2C12 myoblasts deficient in αB-crystallin fail to form myotubes [282]. Finally, it should be mentioned that αB-crystallin is also detected in extracellular fluids where it binds inflammatory molecules and platelets [283], and it is demonstrated that the chaperone releasing occurs through exosomes under specific stress conditions [284].

3.3. αB-crystallin and cytoskeleton protection: focus on desmin network

As mentioned previously, sarcomere is a highly complex and dynamic structure requiring continuous protein turnover and assembly. The "sarcostat", a protein control quality system of the sarcomere, relies on two main components, one of them being the UPS (ubiquitin proteasome system) permitting to target specific proteins for their degradation [285-287]. In addition, to ensure sarcomere homeostasis and its protection against stressors such as the contraction (*i.e.* mechanical stress), the prime function of striated muscle, chaperones dynamically associate with target proteins through a dynamic interplay [285, 286, 288]. Several chaperones are known to interact with the sarcomere, ensuring its assembly and its stabilization, and among them, the αB-crystallin interacts with actin [289, 290], myosin [291], titin [292, 293], and importantly with desmin [285, 290]. It should also be mentioned that actin for example, that is subject to both polymerization and aggregation, is the target of several chaperones that overlap (GimC, TRiC, HSP27, and αB-crystallin), suggesting a cooperative interplay between several chaperones [285]. It is worth to note that the αB-crystallin also interacts with the ubiquitin ligase FBX4, a F-box-containing protein component of the SCF complex (SKP1/Cul1/F-box) [294]. This suggests that, in addition to its role in the prevention of protein misfolding, the αB-crystallin also interplays with the UPS for the degradation of target proteins [285].

Through its involvement in microtubules and IFs dynamics, the αB-crystallin remains essential to cell shape maintenance and in mechano-biology [295], permitting the muscle cells protection toward mechanical stress [288, 296]. It is worth to note that αB-crystallin displays sarcomeric localization, in

particular on Z-disks and I-bands of skeletal muscle and cardiac sarcomeres where proteins are continuously submitted to mechanical stress [278, 297-299]; these interactions occur in both basal and stress conditions [288]. It should be mentioned that over its cytosolic distribution, αB-crystallin could be also located in subnuclear compartment [300]. Importantly, it is shown that αB-crystallin maintains the myosin enzymatic activity while preventing its aggregation under heat stress, suggesting that over its role in myofibrillogenesis and the maintenance of cytoskeleton integrity, the small molecular chaperone also sustains muscle performance [291]. Moreover, physical activity, considered as a physiological stressor, leads to a strong increase of different HSPs permitting the protection of muscle toward heat, oxidative and mechanical stresses resulting from exercise [301]. It is demonstrated that accumulation of the αB-crystallin preferentially occurred to Z-disks, to membrane scaffolding proteins and to desmin IFs [302, 303]. In addition, the increased expression of αB-crystallin facilitates the remodelling of trained skeletal muscle (*i.e.* protein synthesis and the resulting hypertrophy, and metabolic adaptation, in particular mitochondrial activity) [301]. This could explain why the expression of the αB-crystallin depends on the muscle phenotype, of the type of contraction (eccentric, concentric or isometric) and also depends on the training protocol (resistance *versus* endurance) [303-309].

As for microtubules and microfilaments, the IFs organization depends on the competence of the sHSP [285, 310]. Indeed, since these large complex structures have a propensity to misfold and/or aggregate, they need to be chaperoned. Interestingly, it is shown that the molecular chaperone could interact both with IFs and with soluble subunits, suggesting that it could be involved in the modulation of IFs assembly and remodelling as well as in the inter-filament interactions [310-314]. Thus, upon stress, the IFs network dynamically remodels while the αB-crystallin is concomitantly recruited on IFs proteins [311, 315]. The αB-crystallin interacts with desmin to inhibit both its assembly and its aggregation [311], and the assembly of desmin as well as the formation of desmin network requires the αB-crystallin [316, 317]. Over the role in assembly and stabilization of desmin IFs, the interplay between desmin and αB-crystallin is involved in the mitochondria homeostasis and cell viability [119, 318]. Interestingly, the morphology of desmin filaments impacts the binding of the αB-crystallin which mainly occurs on the C-terminal domain of desmin (442-453 amino acids sequence), underlining the sensor properties of αB-crystallin that is able to detect changes in the surface topology of desmin IFs [314]. Importantly, desmin mutants in the C-terminal domain, harbouring critical binding sites for αB-crystallin, have opposing effects on the binding of the molecular chaperone. Thus, the mutation I451M leads to a decreased αB-crystallin binding while the sample viscosity increased, supporting that the filament-filament interaction is enhanced. In contrast, the mutation R454W (a mutant causing desminopathy such as the I451M mutant) is correlated with an increase of the binding of αB-crystallin along the surface of the filament [314].

The αB-crystallin presents several bioactive interactive sequences modulating the sensitivity, the selectivity and in larger extent the activity of the molecular chaperone [319]. Using protein pin array,

Ghosh and co-workers identified interactive sequences on the αB-crystallin depending on its protein partners. They have identified seven interactive sequences involved in chaperone activity; five of them overlap with interactive sequences involved in subunit-subunit interaction, suggesting a dual function for some interactive sequences in multimerization of αB-crystallin and in its chaperone activity **(figure 3)** [250]. Several interactive sequences are involved in the regulation of αB-crystallin activity and in the recognition of protein targets [254]. These interactive sequences could have different repercussion on the interacting proteins. As example, five interactive sequences are involved in the interaction with tubulin **(figure 3)**; two of them promote microtubule assembly while inhibiting their disassembly, one of them inhibits both microtubule assembly and disassembly, and the two remaining sequences have little or no effect on microtubule assembly and disassembly [320]. In fact, the effect of the molecular chaperone on microtubule assembly depends on the ratio of αB-crystallin to tubulin: favourable ratio (1:4<ratio<2:1) promotes microtubule assembly while unfavourable ratio (<1:4 or >2:1 corresponding so to low or high concentration of the molecular chaperone) inhibits the filament assembly. A similar effect was observed for actin [321]. All these data suggest that in unstressed conditions, the αB-crystallin could interact with filaments for their stabilization; in contrast, upon stress conditions, the molecular chaperone dissociates from filaments to interact with the unfolded proteins. Finally, for desmin, several interactive sequences are identified [321, 322]; among them, the peptide ^{113}FISREFHR^{120} has a strong affinity for desmin. This point is reinforced by the fact that the R120G mutant of αB-crystallin, presenting abnormal interaction with the target protein, leads to protein aggregation and disorganisation of desmin network in cardiomyopathy and in desmin-related myopathy [317, 323, 324].

While modulating the desmin network viscosity, the main function of the αB-crystallin is to prevent the improper self-assembly of desmin IFs that could lead to desmin filaments aggregation [119, 322]. Supporting this role of αB-crystallin in preventing desmin IFs aggregation, Elliott and co-workers have demonstrated that αB-crystallin alleviates desmin aggregation *in vitro* [119]. It is worth to note that if the molecular chaperone is missing, or if the recognition between desmin and its molecular chaperone is altered, desmin forms stable misfolded oligomers that accumulate within the cell [112, 314, 325]. The most relevant finding supporting the essential role of sHSP and IFs interaction is illustrated by the phenotype resulting from sHSP mutation. Indeed, the mutation of sHSP mimics the IFs aggregation phenotype related to IFs diseases [312]. Interestingly, some post-translationally modified sites are located into or close to some of the interactive domains **(figure 3)**, suggesting a key role of PTMs in the modulation of the molecular chaperone functions. This important point will be also considered and discussed below.

3.4. The post-translational modifications of αB-crystallin

Three major phosphorylation sites are described on αB-crystallin: the serines 19, 45 and 59 that are localized into the NTD. While the Ser45 and the Ser59 are phosphorylated by p42/44 MAPK and

MAPKAP2/3, respectively, the kinase responsible of the Ser19 phosphorylation remains to be identified [326-328]. As mentioned previously, the αB-crystallin forms large polydisperse oligomers assemblies in equilibrium with smaller-assembly species, the oligomers containing a variable number of subunits; the NTD is mainly responsible of their assembly and their dynamic distribution [223, 277]. It is reported that serine phosphorylation is involved in the shift of higher-order oligomers toward smaller activated ones, in correlation with the enhancement of substrate binding [197, 224]. Once p38 MAPK stress transduction pathways activated, the N-terminal domain is phosphorylated and sHSP disassemble; interestingly, this is correlated with partition of the chaperone toward insoluble protein materials [286, 289, 329-331]. The αB-crystallin phosphorylation varies according to cellular demands or stress conditions, leading to activity profile changes [328]. Thus, several *in cellulo* studies have reported an increase of phosphorylation of the αB-crystallin following stresses [276, 289, 332-335]. However, phosphorylation changes are observed consecutively to several pathologies such as ischemia-reperfusion, chronic hyperglycaemia, congestive heart failure, cardioplegia or myocardial infarction [286, 336-342] or during skeletal muscle healing [343].

In fact, the phosphorylation of αB-crystallin has beneficial outcomes to counteract stress; however, if stress occurs for a long-time duration, the phosphorylation, which becomes irreversible, induces deleterious effects [262]. Among the seven interactive sequences of the αB-crystallin **(figure 2)**, the ^{57}APSWFDTG^{64} peptide which has a strong interaction with actin harbours the Ser59 that is known to be phosphorylated in stress conditions, increasing the interaction between the αB-crystallin and cytoskeleton [321]. In the same way, several studies have reported that upon stress conditions, Ser59 is involved in the colocalization of αB-crystallin with actin microfilaments, microtubules and intermediates filaments, permitting the stabilization and the preservation of the cytoskeleton [289, 328, 332, 334, 337]. Through its involvement in microtubules and IFs dynamics, the αB-crystallin remains essential for cell shape maintenance and in mechano-biology [295], permitting the muscle cells protection toward mechanical stress [288, 296]. As mentioned previously, αB-crystallin displays a sarcomeric localization (in particular on Z-disks and I-bands) where proteins are continuously submitted to mechanical stress. Thus, it makes sense that phosphorylation of αB-crystallin is increased during exercise in myocardium as well as in skeletal muscle [301, 304, 334, 344]. However, while lengthening contraction is often correlated to increase of αB-crystallin phosphorylation, it is shown that the cytoskeleton translocation is independent of the phosphorylation of the molecular chaperone [308]. In this way, while preconditioning and cardiac ischemia lead to αB-crystallin phosphorylation on Ser45 and Ser59 and translocation to contractile apparatus, reperfusion is linked to the dissociation of αB-crystallin from the contractile apparatus but without any correlation with the dephosphorylation of the chaperone [336, 341, 345]. This suggests that phosphorylation alone could not explain the translocation of the chaperone toward the cytoskeleton. In the same way, it is reported that both unphosphorylated

and phosphorylated forms of αB-crystallin are equally efficient to prevent the assembly of some IFs proteins, in particular GFAP and vimentin [310].

It is worth to note that numerous studies exclusively focused on Ser59 phosphorylation without considering simultaneously all the aforementioned sites. However, the relationship between the phosphorylation of αB-crystallin and its molecular chaperone activity is sometimes contradictory. It seems that the modulation of the chaperone activity and the interaction with the target protein depend on the phosphorylation pattern [346, 347]. Supporting this complex interplay between phosphosites, a study of Singh et al. shows a differential kinetic of phosphorylation for Ser45 and Ser59. Indeed, they observed that upon heat stress of H9c2 cardiac cells line, the phosphorylated Ser59 remains constant the first 30 minutes of stress and increases thereafter; interestingly, they observed a peak of phosphorylation on Ser59 in the soluble fraction up to 30 minutes and a decrease afterwards [289]. In contrast, the phosphorylation of Ser45 shows a gradual decrease in the soluble fraction while it increases in the insoluble fraction up to 60 minutes after which it decreases. While these data support the correlation between αB-crystallin phosphorylation, interaction with actin fibres and the partition of the chaperone toward insoluble material in stress conditions, they also suggest that phosphorylation differentially occurs at different sites which may have an impact on the interaction with actin fibres [289]. The phosphorylation of αB-crystallin on a given site could also affect the subcellular localization of the chaperone. In this way, in human myocardium after cardioplegia and cardiopulmonary bypass, Clements and coworkers observed a preferential localization of Ser59 phosphorylated αB-crystallin on Z-disks and I-bands, while the phosphorylated forms on Ser45 and Ser19 are preferentially localized to cell periphery/membrane and intercalated discs, respectively [340]. Lastly, while the phosphorylation of αB-crystallin is closely linked to cytoskeleton translocation, certain studies have shown that the phosphorylated αB-crystallin localized into the mitochondria in myocardium in models of ischemia or myocardial infarction [339, 348, 349]. It should be mentioned that phosphorylation occurs once αB-crystallin is translocated into mitochondria.

The αB-crystallin is also modified by O-GlcNAcylation, the turnover of the monosaccharide on the protein backbone being highly dynamic [350, 351]. Initially identified to be O-GlcNAcylated in lens, the O-GlcNAcylation of the αB-crystallin is known in heart and in skeletal muscle since 1996 and 2004, respectively [351, 352]. The main O-GlcNAcylation site of the molecular chaperone is found on the CTE, especially on the Thr170 [351]; additional site is described on Thr162 in C2C12 skeletal muscle cells line [173]. In this cell line, it was demonstrated that O-GlcNAcylation is involved in the remodelling of sarcomeric cytoskeleton through the modulation of protein-protein interactions including the interaction between desmin and the αB-crystallin [174]. It is now well admitted that O-GlcNAcylation mediates the regulation of protein-protein interactions [353, 354], reinforcing the potential role of O-GlcNAcylation in the binding of αB-crystallin on desmin. In this way, the O-GlcNAcylation sites are located closed to or into the ^{163}REEKPAVTAAPK^{174} interactive sequence with desmin **(figure 3)**; it is thus legitimate to propose the O-GlcNAcylation as a modulator of desmin/αB-

crystallin interaction. Interestingly, it is demonstrated in cardiomyocytes that O-GlcNAcylation of the αB-crystallin is involved in stress-induced translocation to cytoskeleton and in cytoprotection [355]. More specifically, in stressed cardiomyocytes, the O-GlcNAcylation of αB-crystallin increases while the O-GlcNAcylated αB-crystallin translocates to insoluble material; in contrast, the T170A mutant partially translocates while the cell survival decreases, supporting the pivotal role of Thr170 O-GlcNAcylation [355]. While O-GlcNAcylation occurs on both phosphorylated and non-phosphorylated αB-crystallin [351], Krishnamoorthy et al. showed that the T170A mutant is robustly phosphorylated on Ser45 and Ser59 compared with the wild-type αB-crystallin while, surprisingly, the mutant translocates less when phosphorylated [355]. Finally, over its role in the αB-crystallin translocation and interaction with protein partners, additional key roles could be devoted to O-GlcNAcylation of the sHSP. In particular, O-GlcNAcylation which modifies αB-crystallin close to the regulatory IXI/V domain, could also modulate its chaperone activity; in this way, Balana et al. demonstrated that O-GlcNAcylation could enhance the anti-amyloid chaperone activity of αB-crystallin toward α-synuclein [356]. Lastly, αB-crystallin is released in extracellular compartment through exosomes [357, 358] and it seems that O-GlcNAcylation, linked to the non-phosphorylation of αB-crystallin, regulates the exosomal secretion of the molecular chaperone [359]. This is demonstrated in glioma cells, but to our knowledge, there is no data about the secretion of phosphorylated and/or O-GlcNAcylated forms of αB-crystallin in striated muscle cells/tissue.

In addition to phosphorylation and O-GlcNAcylation, the αB-crystallin also brings other PTMs. Thus, non-enzymatic deamidation could occur on Asn78 and Asn146, affecting the chaperone activity of αB-crystallin, in particular for the N146D [360]. Deamidation leads to the appearance of a negative charge in place of a neutral amide group. Consequently, the stability and the solubility of αB-crystallin change, the extent of deamidated αB-crystallin increasing in the water-insoluble fraction [360, 361]. While this post-translational change is mainly described in lens and in the physiopathology of cataract, the deamidation of αB-crystallin is also reported in ischemic myocardium [342, 362]. It should be noticed that the αB-crystallin could be also modified by succinylation, acetylation, glycation, oxidation or carbamylation, and it could be truncated [363-368]; to our knowledge it has not been determined whether these PTMs could modify the αB-crystallin in skeletal muscle and in heart. Moreover, while the main sites are nowadays well-characterized and prominent in the literature, other sites could be modified on the αB-crystallin. Thus, 9 sites of lysine acetylation, 4 O-GlcNAc sites and 13 phosphorylation sites are identified on standard bovine αB-crystallin [369], and a multitude of sites that could be post-translationally modified also exist on αB-crystallin, in particular through phosphorylation [368, 370]. This plethora of potentially modified sites dramatically increases the complexity of the PTMs forms of αB-crystallin.

3.5. The αB-crystallin in physiopathological conditions

The αB-crystallin accumulates in several diseases, particularly in those involving abnormal protein aggregation. Moreover, a dysfunction of the chaperone is closely linked to the physiopathology of several disorders such as cardiovascular pathologies (desmin-related and dilated cardiomyopathies, ischemia/reperfusion), neurodegenerative disorders (Alzheimer's, Huntington's and amyotrophic lateral sclerosis among others), cancer, cataract, myofibrillar myopathies and inflammation related diseases [211, 371-374]. It was also established that the sHSP expression and/or subcellular localization change in several muscle diseases such as GNE myopathy (GNE: UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine-kinase), core myopathies, dystrophinopathies, or myofibrillar myopathies [375-378]. Numerous mutations of αB-crystallin are identified in skeletal muscle and/or heart diseases: the R120G mutation in desmin-related myopathy (myofibrillar myopathy and hypertrophic cardio-myopathy), the R157H in dilated cardiomyopathy, the Q151X and the 464delCT in myofibrillar myopathy, the 343delT in early-onset skeletal myopathy, the G154S in the late-onset distal myopathy and dilated cardiomyopathy, the D109H and the D109A in myofibrillar myopathy and dilated cardiomyopathy, the D109G in axial myopathy and restrictive cardiomyopathy, the 176Wext*19 in dilated cardiomyopathy, and the M1x and the S21Ala*24 in infantile myofibrillar myopathies [225, 277, 323, 324, 368, 379-390]. The mutations could have repercussions on skeletal muscle and/or myocardium, often together with cataract. Pathologies resulting from αB-crystallin mutation correspond to αB-crystallinopathies, presenting the typical characteristics of myofibrillar myopathies with the hallmark of protein aggregates including desmin and αB-crystallin, myofibrillar disorganization and the presence of vacuoles [277, 391-396]. In some case, hyperphosphorylation of αB-crystallin is reported, as well as changes in chaperone activity (gain-of-function or loss-of-function), oligomerization of the chaperone and/or change in its distribution (for review, see [374, 389, 390, 394, 397]). Concerning PTMs, it is worth to note that phosphorylation changes are observed consecutively to several pathologies such as ischemia-reperfusion, chronic hyperglycaemia, congestive heart failure, cardioplegia or myocardial infarction [286, 336-342]. In contrast, while phosphorylation of HSP27 was proposed to be a diagnostic tool to differentiate primary desminopathies from myofibrillar myopathies, no phosphorylation changes were observed in biopsies of patients for αB-crystallin [398].

Importantly and as mentioned previously, the mutation of sHSP mimics the IFs aggregation phenotype related to IFs diseases [312]. Thus, the mutation in the *CRYAB* gene which results from the replacement of arginine residue at the position 120 (a residue essential for the quaternary structure and function of αB-crystallin [399]) by a glycine residue (mutation R120G) leads to a desmin-related myopathy, an inherited disease characterized by desmin aggregation in skeletal and cardiac muscles [324]. This disease is closely linked to limb, neck, trunk and facial muscle weakness associated to cardiac dysfunction leading to cardiomyopathy [324, 400]. In addition, all protective functions dedicated to the wild-type αB-crystallin are lost when the mutant expresses, such as differentiation, apoptosis, aggresome formation, mitochondrial function and ubiquitin-proteasome system while desmin filaments are affected and aggregate leading to impaired myofibrils alignment [317, 325, 401-404]. It is also

demonstrated that R120G mutant is hyperphosphorylated while its interaction with other HSP is modified; this hyperphosphorylation appears as an important aspect of the pathogenicity of the mutant [330, 405, 406].

4. CONCLUDING REMARKS

In light of the role of αB-crystallin in the maintenance of protein homeostasis, modulation of expression and/or activity of molecular chaperone emerges to prevent, alleviate or cure the conformational diseases not only in striated muscle but also in neurological disorders or in cancer [407, 408]. *In vitro* studies have demonstrated that the sHSP could exert protective effects on skeletal muscle cells and cardiomyocytes submitted to various stresses [276, 334, 409-417]. Importantly, expression of αB-crystallin with the R120G mutant promotes the protein aggregation in C2C12 cells while overexpression of αB-crystallin in a mouse model of desminopathies counteracts the desmin function loss since it restores the mitochondrial homeostasis and rescues cardiomyocytes from death [318, 418]. In the same way, the development of dilated cardiomyopathy is attenuated when αB-crystallin is overexpressed in a mouse model presenting a mutation in the *LMNA* gene [77]. The protective role of αB-crystallin is highlighted with experiments demonstrating that its overexpression alleviates muscular dystrophy and other wasting conditions while heart has a better recovery after ischemia [275, 419]. Thus, αB-crystallin emerges as a new great therapeutic tool against protein aggregation and the resulting proteotoxicity. Interestingly, physical activity is shown to have beneficial effects to prevent skeletal muscle weakness, partially through the protective effect of αB-crystallin on myofibrils in models of adjuvant-induced arthritis, idiopathic inflammatory myopathies and muscle atrophy [420-422]. The beneficial effects of exercise are also observed in R120G desmin-related myopathy [423]. As mentioned in the herein paper, exercise modulates expression and/or phosphorylation of αB-crystallin in relation to the translocation of αB-crystallin to cytoskeleton and the cytoprotective effects; the expression/ phosphorylation of αB-crystallin in correlation with the type of exercise is extensively reviewed by Dimauro and Caporossi, as well as the beneficial effects induced by exercise to alleviate muscle diseases [424].

In addition, tuning the phosphorylation of αB-crystallin in a spatio-temporal way could provide a powerful therapeutic strategy to counteract proteotoxicity and restore proteostasis [328, 425, 426]. Moreover, compounds which modulate αB-crystallin phosphorylation have been tested and proposed as a putative attractive therapeutic approach in neurodegenerative disorders [426]. Furthermore, since the interactive sequences could exert specific effect on cellular processes, for example microtubule assembly, the αB-crystallin peptides could be considered as new therapeutics for cancer, Alzeihmer's disease and taupathies [320]. In this way, it is demonstrated that bioactive peptides synthetized from the interactive sequences of αB-crystallin target the toxic intermediates of amyloidogenic proteins and

decrease their fibrillation [427]. However, the precise framework of αB-crystallin PTMs needs to be clarified. Indeed, dynamic interplay should exist between PTMs, and it remains essential to determine precisely their role on αB-crystallin functions, in particular chaperone function and/or proteins targeting.

In addition, it remains also essential to better characterize the PTMs pattern and/or changes on the proteins targeted by αB-crystallin, in particular desmin. Indeed, as discussed hereinbefore, the desmin, preserving the muscle integrity, is fundamental for contractile activity and muscle function [3, 40]. Supporting this fundamental role of desmin in muscle physiology when mutated (nowadays, around 50 mutations are identified on desmin gene), the cytoskeletal network turns extremely disorganized while protein aggregates (including desmin) accumulate in myofibrils. These desmin-related disorders result from mutation in the desmin gene, cleavage of desmin, and/or changes on PTMs (in particular phosphorylation and/or kinases dysregulation) [50, 55, 128, 143]. In addition, desmin is O-GlcNAcylated on a serine of the C-terminal domain; however, it is not excluded that other O-GlcNAc sites could exist on desmin. Interestingly, a modification in the number or the linkage of O-GlcNAc moieties are closely associated to the physiopathology of several diseases, and the involvement of O-GlcNAcylation in neurodegenerative disorders, cancer, cardiovascular diseases or type II diabetes have been clearly demonstrated [428-431]. Importantly O-GlcNAcylation and neuromuscular pathologies are also closely linked, in particular in type I spinal amyotrophy, polymyositis, dermatomyositis, sporadic inclusion body myositis, muscular dystrophies, neurogenic muscular atrophy, rhabdomyolysis, and distal myopathy with rimmed vacuoles; the O-GlcNAc modification is also demonstrated to be involved in skeletal muscle atrophy [432-435]. Thus, it would be of interest to investigate whether O-GlcNAcylation could change on desmin or its chaperone in skeletal muscle and heart diseases.

Lastly, it was demonstrated that O-GlcNAcylation could be involved in the modulation of the desmin/αB-crystallin interaction [173, 174], but the dynamic interplay between phosphorylation and O-GlcNAcylation on desmin and its molecular chaperone remains misunderstood nowadays. Deciphering finely this interplay on two essential proteins of striated muscle cytoskeleton will bring new insights for a better understanding of the physiology of striated muscle and the physiopathology of disorders such as desmin-related diseases. Moreover, considering PTMs is a great challenge nowadays and opens a new research field in the world of molecular chaperone and their target proteins; it could permit the emergence of new therapeutic interventions for striated muscle diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS CONTRIBUTION

Conceptualization, C.C.B. and O.A.; writing-original draft preparation, C.C.B., C.C., N.B.; review and editing, C.C.B., C.C., N.B., O.A., B.B. All authors are the guarantors of the article jointly and have read and agreed to the published version of the manuscript.

FIGURES LEGEND

Figure 1: Representative scheme of desmin structure. Are indicated the head, the α-helical rod and the tail domains of the desmin. The N-terminal domain is magnified with the indication of the amino acid sequences of human desmin (UniProtKB/Swiss-Prot entry: P17661, Homo sapiens), mouse desmin (UniProtKB/Swiss-Prot entry: P31001, Mus musculus) and chicken desmin (UniProtKB/Swiss-Prot entry: P02542, Gallus gallus). The amino acids in red correspond to phosphorylation sites, those in green to ADP-ribosylation sites. The O-GlcNAcylation site in the C-terminal domain is indicated in blue.

Figure 2: Aberrant post-translational modifications of desmin and αB-crystallin in the physiopathology of striated muscle disorders. The structural organization of the sarcomere and desmin IFs of healthy muscle is depicted at the centre of the recapitulative scheme. Main aberrant PTMs are represented in diseased muscle and also their involvement in the physiopathology of several striated muscle pathologies and their consequences on the structural organization of sarcomere and desmin IFs. For diseased muscle, the scheme is divided in four parts for diseased muscle, corresponding to the link between muscle disorders and a default of desmin phosphorylation (in blue) and/or O-GlcNAcylation (in pink), desmin non-enzymatic modifications (in green), or hyperphosphorylation of αB-crystallin (in yellow).

Figure 3: Representative scheme of the structure of αB-crystallin. Are indicated the N-terminal domain, the α-crystallin domain, the IXI motif and the C-terminal extension. The phosphorylated sites are indicated in red, the O-GlcNAcylated sites in blue. The seven interactive sequences are represented in green, and those involved in the interaction of αB-crystallin with tubulin, desmin and actin are represented in blue, red and yellow, respectively. Note the overlap of the interactive sequences between themselves (black dotted lines), and the position of post-translational modifications within these sequences (red dotted lines).

Table 1: Main characteristics of human desmin and its molecular chaperone, the αB-crystallin.

Characteristics	Desmin		αB-crystallin	
UniProtKB/Swiss-Prot entry	P17661		P02511	
Gene	*DES*		*CRYAB*	
Chromosome	2q35		11q23.1	
Molecular weight	53.5 kDa		20.1 kDa	
Number of amino acids	470 AA		175 AA	
Protein class	Class III intermediate filament protein		sHSP	
Major role	Cytoskeleton organization; filamentous 3D network	[3, 44-46, 49, 51, 53-55]	Proteostasis; molecular chaperone	[228-231]
Other cellular functions	Differentiation, apoptosis, intracellular signalisation, mechano-transduction, vesicle trafficking, organelle biogenesis and/or positioning, calcium homeostasis, protein homeostasis, cell adhesion, metabolism, gene expression	[3, 49, 50, 56-60]	Cell integrity, cell shape maintenance, apoptosis, autophagy, differentiation, mitochondria function, aggresome formation, and cytoskeleton stabilization	[242, 254, 258-265]
Main post-translational modifications	Phosphorylation, O-GlcNAcylation, ADP-ribosylation, glycation, oxidation, nitration, ubiquitination	See Table 2 for more details and references	Phosphorylation, O-GlcNAcylation, deamidation, succinylation, acetylation, glycation, truncation, oxidation, carbamylation	See Table 2 for more details and references
Associated Pathologies	***Primary desmin alteration:*** Dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, restrictive cardiomyopathy, desmin-related myopathies, myofibrillar	[3, 11, 49, 50, 54, 55, 69, 70, 79-90]	***Striated muscle diseases:*** Restrictive cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, ischemia-reperfusion, myofibrillar myopathies, αB-crystallinopathies, desmin-related myopathy, GNE myopathy, core	[225, 277, 323, 324, 368, 375-396]

	myopathies, desminopathies		myopathies, dystrophinopathies, early-onset skeletal myopathy, late-onset distal myopathy, axial myopathy, infantile myofibrillar myopathies.	
	Secondary desmin alteration: Aging, heart failure, obesity, type II diabetes, sleep apnoea, asthma, dysphagia, hypoxia-induced pulmonary hypertension, muscle wasting, LMNA cardiomyopathy, Friedreich Ataxia	[48, 71-78]	***Other diseases:*** Neurodegenerative disorders (Alzheimer's, Huntington's and amyotrophic lateral sclerosis among others), cancer, cataract, inflammation related diseases	[211, 371-374]

Table 2: Main post-translational modifications on human desmin. The involved enzymes and the amino acid(s) bearing the modification are indicated, as well as the effect of the modification on the desmin. Non-enzymatic modifications are also mentioned. For each reference, it is indicated whether data result from *in vitro* (#), *in cellulo* (§) and *in vivo* (*) experiments, or from studies of human biopsies (‡)

Enzyme	Abbreviation	PTM sites	Modification	Effect on desmin	Ref
ADP-ribosyl transferase	ADPRT	Arg58, Arg73	ADP-ribosylation	Desmin IFs dynamics; depolymerisation. Modulation of phosphorylation by PKA; involvement in differentiation	[166#, 167#, 168#]
Aurora kinase B	Aurora-B	Ser12, Thr17, Ser60	Phosphorylation	Desmin IFs dynamics during cell cycle	[136#§]
Calcium-calmodulin-dependent protein kinase II	CamKII	Unknown	Phosphorylation	Unknown	[161#, 162§]
Calcium / phospholipid-dependant kinase	PKC, Protein kinase C	Ser13, Ser48, Ser68	Phosphorylation	Desmin IFs dynamics; depolymerisation. Inhibition of proliferation and differentiation	[149#]
cAMP-dependent protein kinase	PKA, Protein kinase A	Ser45, Ser60	Phosphorylation	Desmin IFs dynamics; depolymerisation. Inhibition of differentiation	[148#]
Cyclin-dependant kinase 1	Cdk1	Ser7, Ser28, Ser32	Phosphorylation	Desmin IFs dynamics; separation of desmin IFs. Hyperphosphorylation on Ser32 leads to desmin IFs alteration	[142#*, 144*]
E3 ubiquitin ligase TRIM32	TRIM32	Unknown	Ubiquitination	Desmin turnover; muscle atrophy	[185*]
Glycogen synthase kinase-3 beta	GSK-3β	Ser32	Phosphorylation	Initial step for desmin IFs degradation; precedes ubiquitination	[143§*, 185*, 187*]
N-acetyl-β-D-glucosaminidase	OGA, O-GlcNAcase	/	Deglycosylation	Regulation of O-GlcNAc moieties turnover	[170*]
p21-Activated Kinase	PAK	Head domain	Phosphorylation	Desmin IFs dynamics; depolymerisation	[137#]
Protein phosphatase 1	PP1	/	Dephosphorylation	Reassembly of desmin IFs; fine regulation of phosphorylation turnover	[165#]

Rho-associated kinase	ROK	Thr 17, Thr76, Thr77	Phosphorylation	Desmin IFs dynamics; depolymerisation	[135[#], 136[#§]]
Uridine diphospho-N-acetylglucosamine polypeptide β-N-acetylglucosaminyl-transferase	OGT, O-GlcNAc transferase	Ser460	O-GlcNAcylation	Unknown; modulation of interaction with protein partners?	[162[§], 170[*], 173[§], 174[§]]
Non-enzymatic modification		Unknown	Glycoxidation (Advanced glycation end products)	Dilated cardiomyopathy	[179[*]]
		Unknown	Oxidation	Cytoskeleton reorganization and desmin aggregation	[181[*], 182[*]]
		Unknown	Nitration	Cytoskeleton reorganization and desmin aggregation	[181[*], 182[*]]

The modified aminoacid(s) was(were) numbered including the starting methionine in protein sequence.

Table 3: Main post-translational modifications on human αB-crystallin. The involved enzymes and the amino acid(s) bearing the modification are indicated, as well as the effect of the modification on the αb-crystallin. Non-enzymatic modifications are also mentioned. For each reference, it is indicated whether data result from *in vitro* (#), *in cellulo* (§) and *in vivo* (*) experiments, or from studies of human biopsies (⁑).

Enzyme	Abbreviation	PTM sites	Modification	Effect on αB-crystallin	Ref
Lysine acetyl transferase	KAT	Lys92	Acetylation†	Modulation of structure and function of the chaperone	[364#§]
MAPK activated protein kinase 2/3	MAPKAP2/3	Ser59	Phosphorylation	Phosphorylated in stress conditions; interaction with cytoskeleton; partition toward insoluble fraction	[289§, 332§, 334#*, 337*]
N-acetyl-β-D-glucosaminidase	OGA, O-GlcNAcase	Thr162, Thr170	Deglycosylation	Regulation of O-GlcNAc moieties turnover	[174§]
p42/44 Mitogen activated protein kinase	P42/44 MAPK	Ser45	Phosphorylation	Phosphorylated in stress conditions; interaction with cytoskeleton; partition toward insoluble fraction	[289§, 336*, 341*, 345*]
Acyltransferase	Acyl CoA transferase	Lys72, Lys90, Lys92, K166, K175	Succinylation†	Modulation of chaperone activity. Note that non-enzymatic succinylation may occur on lysine	[363⁑]
Unknown	/	Ser19	Phosphorylation	Subcellular localization?	[340⁑]
Uridine diphospho-N-acetylglucosamine polypeptide β-N-acetylglucosaminyl-transferase	OGT, O-GlcNAc transferase	Thr162, Thr170	O-GlcNAcylation	Partition toward insoluble material; modulation of chaperone activity; exosomal secretion; modulation of interaction with protein partners?	[173§, 174§, 350*⁑, 351§*, 352*, 355§, 356#⁑, 359§]
Non-enzymatic modification		Gln26, Asn78, Gln108, Asn146	Deamidation	Changes of stability, solubility and chaperone activity	[342*, 360#, 361⁑, 362*, 368]
		Lys92, Glu164, Lys166, Lys175	Carbamylation†	Modification of protein conformation and aggregation. *In vivo* carbamylase?	[367⁑, 368]

† *Indicates PTMs described on αB-crystallin, but it is unknown whether they occur in heart and/or skeletal muscle. Note that several other PTMs are described on the molecular chaperone but not indicated in the herein table (for review, see [368]).*

REFERENCES

[1] Clark, KA, McElhinny, AS, Beckerle, MC and Gregorio, CC (2002). *Striated muscle cytoarchitecture: an intricate web of form and function.* Annu. Rev. Cell Dev. Biol, 18: 637-706. DOI: 10.1146/annurev.cellbio.18.012502.105840.

[2] Gautel, M (2011). *The sarcomeric cytoskeleton: who picks up the strain?* Curr. Opin. Cell Biol, 23(1): 39-46. DOI: 10.1016/j.ceb.2010.12.001.

[3] Henderson, CA, Gomez, CG, Novak, SM, Mi-Mi, L and Gregorio, CC (2017). *Overview of the Muscle Cytoskeleton.* Compr Physiol, 7(3): 891-944. DOI: 10.1002/cphy.c160033.

[4] Kontrogianni-Konstantopoulos, A, Ackermann, MA, Bowman, AL, Yap, SV and Bloch, RJ (2009). *Muscle giants: molecular scaffolds in sarcomerogenesis.* Physiol Rev, 89(4): 1217-1267. DOI: 10.1152/physrev.00017.2009.

[5] Herrmann, H, Hesse, M, Reichenzeller, M, Aebi, U and Magin, TM (2003). *Functional complexity of intermediate filament cytoskeletons: from structure to assembly to gene ablation.* Int Rev Cytol, 223: 83-175. DOI: 10.1016/s0074-7696(05)23003-6.

[6] Goldmann, WH (2018). *Intermediate filaments and cellular mechanics.* Cell Biol Int, 42(2): 132-138. DOI: 10.1002/cbin.10879.

[7] Huber, F, Boire, A, Lopez, MP and Koenderink, GH (2015). *Cytoskeletal crosstalk: when three different personalities team up.* Curr Opin Cell Biol, 32: 39-47. DOI: 10.1016/j.ceb.2014.10.005.

[8] Herrmann, H, Strelkov, SV, Burkhard, P and Aebi, U (2009). *Intermediate filaments: primary determinants of cell architecture and plasticity.* J. Clin. Invest, 119(7): 1772-1783. DOI: 10.1172/JCI38214.

[9] Schwarz, N and Leube, RE (2016). *Intermediate Filaments as Organizers of Cellular Space: How They Affect Mitochondrial Structure and Function.* Cells, 5(3). DOI: 10.3390/cells5030030.

[10] Mado, K, Chekulayev, V, Shevchuk, I, Puurand, M, Tepp, K and Kaambre, T (2019). *On the role of tubulin, plectin, desmin, and vimentin in the regulation of mitochondrial energy fluxes in muscle cells.* Am J Physiol Cell Physiol, 316(5): C657-C667. DOI: 10.1152/ajpcell.00303.2018.

[11] Etienne-Manneville, S (2018). *Cytoplasmic Intermediate Filaments in Cell Biology.* Annu Rev Cell Dev Biol, 34: 1-28. DOI: 10.1146/annurev-cellbio-100617-062534.

[12] Sanghvi-Shah, R and Weber, GF (2017). *Intermediate Filaments at the Junction of Mechanotransduction, Migration, and Development.* Front Cell Dev Biol, 5: 81. DOI: 10.3389/fcell.2017.00081.

[13] Brunner, E, Ahrens, CH, Mohanty, S, Baetschmann, H, Loevenich, S, Potthast, F, Deutsch, EW, Panse, C, de, LU, Rinner, O, Lee, H, Pedrioli, PG, Malmstrom, J, Koehler, K, Schrimpf, S, Krijgsveld, J, Kregenow, F, Heck, AJ, Hafen, E, Schlapbach, R and Aebersold, R (2007). *A high-quality catalog of the Drosophila melanogaster proteome.* Nat. Biotechnol, 25(5): 576-583. DOI: 10.1038/nbt1300.

[14] Srikanth, B, Vaidya, MM and Kalraiya, RD (2010). *O-GlcNAcylation determines the solubility, filament organization, and stability of keratins 8 and 18.* J. Biol. Chem, 285(44): 34062-34071. DOI: 10.1074/jbc.M109.098996.

[15] Tarbet, HJ, Dolat, L, Smith, TJ, Condon, BM, O'Brien, ET, 3rd, Valdivia, RH and Boyce, M (2018). *Site-specific glycosylation regulates the form and function of the intermediate filament cytoskeleton.* Elife, 7. DOI: 10.7554/eLife.31807.

[16] Snider, NT and Omary, MB (2014). *Post-translational modifications of intermediate filament proteins: mechanisms and functions.* Nat. Rev. Mol. Cell Biol, 15(3): 163-177. DOI: 10.1038/nrm3753].

[17] Hyder, CL, Pallari, HM, Kochin, V and Eriksson, JE (2008). *Providing cellular signposts--post-translational modifications of intermediate filaments.* FEBS Lett, 582(14): 2140-2148. DOI: 10.1016/j.febslet.2008.04.064.

[18] Kim, S and Coulombe, PA (2007). *Intermediate filament scaffolds fulfill mechanical, organizational, and signaling functions in the cytoplasm.* Genes Dev, 21(13): 1581-97. DOI: 10.1101/gad.1552107.

[19] Li, Z, Parlakian, A, Coletti, D, Alonso-Martin, S, Hourde, C, Joanne, P, Gao-Li, J, Blanc, J, Ferry, A, Paulin, D, Xue, Z and Agbulut, O (2014). *Synemin acts as a regulator of signalling molecules during skeletal muscle hypertrophy.* J Cell Sci, 127(Pt 21): 4589-601. DOI: 10.1242/jcs.143164.

[20] Dey, P, Togra, J and Mitra, S (2014). *Intermediate filament: structure, function, and applications in cytology.* Diagn Cytopathol, 42(7): 628-35. DOI: 10.1002/dc.23132.

[21] Pallari, HM and Eriksson, JE (2006). *Intermediate filaments as signaling platforms.* Sci STKE, 2006(366): pe53. DOI: 10.1126/stke.3662006pe53.

[22] Cheng, F and Eriksson, JE (2017). *Intermediate Filaments and the Regulation of Cell Motility during Regeneration and Wound Healing.* Cold Spring Harb Perspect Biol, 9(9). DOI: 10.1101/cshperspect.a022046.

[23] Hyder, CL, Isoniemi, KO, Torvaldson, ES and Eriksson, JE (2011). *Insights into intermediate filament regulation from development to ageing.* J Cell Sci, 124(Pt 9): 1363-72. DOI: 10.1242/jcs.041244.

[24] Jones, JC, Kam, CY, Harmon, RM, Woychek, AV, Hopkinson, SB and Green, KJ (2017). *Intermediate Filaments and the Plasma Membrane.* Cold Spring Harb Perspect Biol, 9(1). DOI: 10.1101/cshperspect.a025866.

[25] Paulin, D, Lilienbaum, A, Kardjian, S, Agbulut, O and Li, Z (2022). *Vimentin: Regulation and pathogenesis.* Biochimie, 197: 96-112. DOI: 10.1016/j.biochi.2022.02.003.

[26] Patteson, AE, Vahabikashi, A, Goldman, RD and Janmey, PA (2020). *Mechanical and Non-Mechanical Functions of Filamentous and Non-Filamentous Vimentin.* Bioessays, 42(11): e2000078. DOI: 10.1002/bies.202000078.

[27] Li, Z, Paulin, D, Lacolley, P, Coletti, D and Agbulut, O (2020). *Vimentin as a target for the treatment of COVID-19.* BMJ Open Respir Res, 7(1). DOI: 10.1136/bmjresp-2020-000623.

[28] Suprewicz, L, Swoger, M, Gupta, S, Piktel, E, Byfield, FJ, Iwamoto, DV, Germann, D, Reszec, J, Marcinczyk, N, Carroll, RJ, Janmey, PA, Schwarz, JM, Bucki, R and Patteson, AE (2022). *Extracellular Vimentin as a Target Against SARS-CoV-2 Host Cell Invasion.* Small, 18(6): e2105640. DOI: 10.1002/smll.202105640.

[29] Szeverenyi, I, Cassidy, AJ, Chung, CW, Lee, BT, Common, JE, Ogg, SC, Chen, H, Sim, SY, Goh, WL, Ng, KW, Simpson, JA, Chee, LL, Eng, GH, Li, B, Lunny, DP, Chuon, D, Venkatesh, A, Khoo, KH, McLean, WH, Lim, YP and Lane, EB (2008). *The Human Intermediate Filament Database: comprehensive information on a gene family involved in many human diseases.* Hum Mutat, 29(3): 351-60. DOI: 10.1002/humu.20652.

[30] Lowery, J, Kuczmarski, ER, Herrmann, H and Goldman, RD (2015). *Intermediate Filaments Play a Pivotal Role in Regulating Cell Architecture and Function.* J. Biol. Chem. DOI: 10.1074/jbc.R115.640359.

[31] Omary, MB (2009). *"IF-pathies": a broad spectrum of intermediate filament-associated diseases.* J Clin Invest, 119(7): 1756-62. DOI: 10.1172/JCI39894.

[32] Nishimura, Y, Kasahara, K and Inagaki, M (2019). *Intermediate filaments and IF-associated proteins: from cell architecture to cell proliferation.* Proc Jpn Acad Ser B Phys Biol Sci, 95(8): 479-493. DOI: 10.2183/pjab.95.034.

[33] Price, MG (1984). *Molecular analysis of intermediate filament cytoskeleton--a putative load-bearing structure.* Am J Physiol, 246(4 Pt 2): H566-72. DOI: 10.1152/ajpheart.1984.246.4.H566.

[34] Small, JV and Gimona, M (1998). *The cytoskeleton of the vertebrate smooth muscle cell.* Acta Physiol Scand, 164(4): 341-8. DOI: 10.1046/j.1365-201X.1998.00441.x.

[35] Burt, AD, Robertson, JL, Heir, J and MacSween, RN (1986). *Desmin-containing stellate cells in rat liver; distribution in normal animals and response to experimental acute liver injury.* J Pathol, 150(1): 29-35. DOI: 10.1002/path.1711500106.

[36] Kjorell, U and Thornell, LE (1982). *Identification of a complex between alpha-actinin and the intermediate filament subunit skeletin in bovine heart Purkinje fibres.* Eur J Cell Biol, 28(1): 139-44.

[37] Hellstrom, M, Kalen, M, Lindahl, P, Abramsson, A and Betsholtz, C (1999). *Role of PDGF-B and PDGFR-beta in recruitment of vascular smooth muscle cells and pericytes during embryonic blood vessel formation in the mouse.* Development, 126(14): 3047-55. DOI: 10.1242/dev.126.14.3047.

[38] Rogatsch, H, Jezek, D, Hittmair, A, Mikuz, G and Feichtinger, H (1996). *Expression of vimentin, cytokeratin, and desmin in Sertoli cells of human fetal, cryptorchid, and tumour-adjacent testicular tissue.* Virchows Arch, 427(5): 497-502. DOI: 10.1007/BF00199510.

[39] Heinzelmann, K, Lehmann, M, Gerckens, M, Noskovicova, N, Frankenberger, M, Lindner, M, Hatz, R, Behr, J, Hilgendorff, A, Konigshoff, M and Eickelberg, O (2018). *Cell-surface phenotyping identifies CD36 and CD97 as novel markers of fibroblast quiescence in lung fibrosis.* Am J Physiol Lung Cell Mol Physiol, 315(5): L682-L696. DOI: 10.1152/ajplung.00439.2017.

[40] Agnetti, G, Herrmann, H and Cohen, S (2022). *New roles for desmin in the maintenance of muscle homeostasis.* FEBS J, 289(10): 2755-2770. DOI: 10.1111/febs.15864.

[41] Chernyatina, AA, Nicolet, S, Aebi, U, Herrmann, H and Strelkov, SV (2012). *Atomic structure of the vimentin central alpha-helical domain and its implications for intermediate filament assembly.* Proc Natl Acad Sci U S A, 109(34): 13620-5. DOI: 10.1073/pnas.1206836109.

[42] Vermeire, PJ, Lilina, AV, Hashim, HM, Dlabolova, L, Fiala, J, Beelen, S, Kukacka, Z, Harvey, JN, Novak, P and Strelkov, SV (2023). *Molecular structure of soluble vimentin tetramers.* Sci Rep, 13(1): 8841. DOI: 10.1038/s41598-023-34814-4.

[43] Vermeire, PJ, Stalmans, G, Lilina, AV, Fiala, J, Novak, P, Herrmann, H and Strelkov, SV (2021). *Molecular Interactions Driving Intermediate Filament Assembly.* Cells, 10(9). DOI: 10.3390/cells10092457.

[44] Charrier, EE and Janmey, PA (2016). *Mechanical Properties of Intermediate Filament Proteins.* Methods Enzymol, 568: 35-57. DOI: 10.1016/bs.mie.2015.09.009.

[45] Charrier, EE, Montel, L, Asnacios, A, Delort, F, Vicart, P, Gallet, F, Batonnet-Pichon, S and Henon, S (2018). *The desmin network is a determinant of the cytoplasmic stiffness of myoblasts.* Biol Cell, 110(4): 77-90. DOI: 10.1111/boc.201700040.

[46] Goldman, RD, Cleland, MM, Murthy, SN, Mahammad, S and Kuczmarski, ER (2012). *Inroads into the structure and function of intermediate filament networks.* J Struct Biol, 177(1): 14-23. DOI: 10.1016/j.jsb.2011.11.017.

[47] Clemen, CS, Herrmann, H, Strelkov, SV and Schroder, R (2013). *Desminopathies: pathology and mechanisms.* Acta Neuropathol, 125(1): 47-75. DOI: 10.1007/s00401-012-1057-6.

[48] Brodehl, A, Gaertner-Rommel, A and Milting, H (2018). *Molecular insights into cardiomyopathies associated with desmin (DES) mutations.* Biophys Rev, 10(4): 983-1006. DOI: 10.1007/s12551-018-0429-0.

[49] Hnia, K, Ramspacher, C, Vermot, J and Laporte, J (2014). *Desmin in muscle and associated diseases: beyond the structural function.* Cell Tissue Res. DOI: 10.1007/s00441-014-2016-4.

[50] Tsikitis, M, Galata, Z, Mavroidis, M, Psarras, S and Capetanaki, Y (2018). *Intermediate filaments in cardiomyopathy.* Biophys Rev, 10(4): 1007-1031. DOI: 10.1007/s12551-018-0443-2.

[51] Hol, EM and Capetanaki, Y (2017). *Type III Intermediate Filaments Desmin, Glial Fibrillary Acidic Protein (GFAP), Vimentin, and Peripherin.* Cold Spring Harb Perspect Biol, 9(12). DOI: 10.1101/cshperspect.a021642.

[52] Costa, ML, Escaleira, R, Cataldo, A, Oliveira, F and Mermelstein, CS (2004). *Desmin: molecular interactions and putative functions of the muscle intermediate filament protein.* Braz. J Med. Biol Res, 37(12): 1819-1830. DOI: S0100-879X2004001200007.

[53] Capetanaki, Y, Bloch, RJ, Kouloumenta, A, Mavroidis, M and Psarras, S (2007). *Muscle intermediate filaments and their links to membranes and membranous organelles.* Exp. Cell Res, 313(10): 2063-2076. DOI: 10.1016/j.yexcr.2007.03.033.

[54] Koutakis, P, Miserlis, D, Myers, SA, Kim, JK, Zhu, Z, Papoutsi, E, Swanson, SA, Haynatzki, G, Ha, DM, Carpenter, LA, McComb, RD, Johanning, JM, Casale, GP and Pipinos, II (2015). *Abnormal accumulation of desmin in gastrocnemius myofibers of patients with peripheral artery disease: associations with altered myofiber morphology and density, mitochondrial dysfunction and impaired limb function.* J. Histochem. Cytochem, 63(4): 256-269. DOI: 10.1369/0022155415569348.

[55] Capetanaki, Y, Papathanasiou, S, Diokmetzidou, A, Vatsellas, G and Tsikitis, M (2015). *Desmin related disease: a matter of cell survival failure.* Curr. Opin. Cell Biol, 32: 113-120. DOI: 10.1016/j.ceb.2015.01.004.

[56] Winter, L, Unger, A, Berwanger, C, Sporrer, M, Turk, M, Chevessier, F, Strucksberg, KH, Schlotzer-Schrehardt, U, Wittig, I, Goldmann, WH, Marcus, K, Linke, WA, Clemen, CS and Schroder, R (2019). *Imbalances in protein homeostasis caused by mutant desmin.* Neuropathol Appl Neurobiol, 45(5): 476-494. DOI: 10.1111/nan.12516.

[57] Carlsson, L and Thornell, LE (2001). *Desmin-related myopathies in mice and man.* Acta Physiol Scand, 171(3): 341-348.

[58] Smythe, GM, Davies, MJ, Paulin, D and Grounds, MD (2001). *Absence of desmin slightly prolongs myoblast proliferation and delays fusion in vivo in regenerating grafts of skeletal muscle.* Cell Tissue Res, 304(2): 287-94. DOI: 10.1007/s004410100366.

[59] Li, Z, Mericskay, M, Agbulut, O, Butler-Browne, G, Carlsson, L, Thornell, LE, Babinet, C and Paulin, D (1997). *Desmin is essential for the tensile strength and integrity of myofibrils but not for myogenic commitment, differentiation, and fusion of skeletal muscle.* J. Cell Biol, 139(1): 129-144.

[60] Hakibilen, C, Delort, F, Daher, MT, Joanne, P, Cabet, E, Cardoso, O, Bourgois-Rocha, F, Tian, C, Rivas, E, Madruga, M, Ferreiro, A, Lilienbaum, A, Vicart, P, Agbulut, O, Henon, S and Batonnet-Pichon, S (2022). *Desmin Modulates Muscle Cell Adhesion and Migration.* Front Cell Dev Biol, 10: 783724. DOI: 10.3389/fcell.2022.783724.

[61] Li, Z, Colucci-Guyon, E, Pincon-Raymond, M, Mericskay, M, Pournin, S, Paulin, D and Babinet, C (1996). *Cardiovascular lesions and skeletal myopathy in mice lacking desmin.* Dev Biol, 175(2): 362-6. DOI: 10.1006/dbio.1996.0122.

[62] Milner, DJ, Weitzer, G, Tran, D, Bradley, A and Capetanaki, Y (1996). *Disruption of muscle architecture and myocardial degeneration in mice lacking desmin.* J Cell Biol, 134(5): 1255-70. DOI: 10.1083/jcb.134.5.1255.

[63] Thornell, L, Carlsson, L, Li, Z, Mericskay, M and Paulin, D (1997). *Null mutation in the desmin gene gives rise to a cardiomyopathy.* J. Mol. Cell Cardiol, 29(8): 2107-2124.

[64] Capetanaki, Y, Milner, DJ and Weitzer, G (1997). *Desmin in muscle formation and maintenance: knockouts and consequences.* Cell Struct. Funct, 22(1): 103-116.

[65] Paulin, D and Li, Z (2004). *Desmin: a major intermediate filament protein essential for the structural integrity and function of muscle.* Exp. Cell Res, 301(1): 1-7. DOI: 10.1016/j.yexcr.2004.08.004.

[66] Agbulut, O, Li, Z, Perie, S, Ludosky, MA, Paulin, D, Cartaud, J and Butler-Browne, G (2001). *Lack of desmin results in abortive muscle regeneration and modifications in synaptic structure.* Cell Motil Cytoskeleton, 49(2): 51-66. DOI: 10.1002/cm.1020.

[67] Joanne, P, Hovhannisyan, Y, Bencze, M, Daher, MT, Parlakian, A, Toutirais, G, Gao-Li, J, Lilienbaum, A, Li, Z, Kordeli, E, Ferry, A and Agbulut, O (2021). *Absence of Desmin Results in Impaired Adaptive Response to Mechanical Overloading of Skeletal Muscle.* Front Cell Dev Biol, 9: 662133. DOI: 10.3389/fcell.2021.662133.

[68] Ferry, A, Messeant, J, Parlakian, A, Lemaitre, M, Roy, P, Delacroix, C, Lilienbaum, A, Hovhannisyan, Y, Furling, D, Klein, A, Li, Z and Agbulut, O (2020). *Desmin prevents muscle wasting, exaggerated weakness and fragility, and fatigue in dystrophic mdx mouse.* J Physiol, 598(17): 3667-3689. DOI: 10.1113/JP279282.

[69] Datta, K, Basak, T, Varshney, S, Sengupta, S and Sarkar, S (2017). *Quantitative proteomic changes during post myocardial infarction remodeling reveals altered cardiac metabolism and Desmin aggregation in the infarct region.* J Proteomics, 152: 283-299. DOI: 10.1016/j.jprot.2016.11.017.

[70] Coats, CJ (2018). *The vital role of exercise testing in hypertrophic cardiomyopathy.* Int J Cardiol, 271: 200-201. DOI: 10.1016/j.ijcard.2018.06.028.

[71] Winter, DL, Paulin, D, Mericskay, M and Li, Z (2014). *Posttranslational modifications of desmin and their implication in biological processes and pathologies.* Histochem. Cell Biol, 141(1): 1-16. DOI: 10.1007/s00418-013-1148-z.

[72] Shah, F, Franklin, KA, Holmlund, T, Levring Jaghagen, E, Berggren, D, Forsgren, S and Stal, P (2019). *Desmin and dystrophin abnormalities in upper airway muscles of snorers and patients with sleep apnea.* Respir Res, 20(1): 31. DOI: 10.1186/s12931-019-0999-9.

[73] Mohamed, JS, Hajira, A, Li, Z, Paulin, D and Boriek, AM (2011). *Desmin regulates airway smooth muscle hypertrophy through early growth-responsive protein-1 and microRNA-26a.* J Biol Chem, 286(50): 43394-404. DOI: 10.1074/jbc.M111.235127.

[74] Lemler, MS, Bies, RD, Frid, MG, Sastravaha, A, Zisman, LS, Bohlmeyer, T, Gerdes, AM, Reeves, JT and Stenmark, KR (2000). *Myocyte cytoskeletal disorganization and right heart*

failure in hypoxia-induced neonatal pulmonary hypertension. Am J Physiol Heart Circ Physiol, 279(3): H1365-76. DOI: 10.1152/ajpheart.2000.279.3.H1365.

[75] Hwang, H, Bowen, BP, Lefort, N, Flynn, CR, De Filippis, EA, Roberts, C, Smoke, CC, Meyer, C, Hojlund, K, Yi, Z and Mandarino, LJ (2010). *Proteomics analysis of human skeletal muscle reveals novel abnormalities in obesity and type 2 diabetes.* Diabetes, 59(1): 33-42. DOI: 10.2337/db09-0214.

[76] Koeppen, A, Rafique, R, Mazurkiewicz, J, Pelech, S, Sutter, C, Lin, Q and Qian, J (2021). *Friedreich cardiomyopathy is a secondary desminopathy.* Free Neuropathology, 2: 34. DOI: 10.17879/freeneuropathology-2021-3679.

[77] Galata, Z, Kloukina, I, Kostavasili, I, Varela, A, Davos, CH, Makridakis, M, Bonne, G and Capetanaki, Y (2018). *Amelioration of desmin network defects by alphaB-crystallin overexpression confers cardioprotection in a mouse model of dilated cardiomyopathy caused by LMNA gene mutation.* J Mol Cell Cardiol, 125: 73-86. DOI: 10.1016/j.yjmcc.2018.10.017.

[78] Russ, DW and Grandy, JS (2011). *Increased desmin expression in hindlimb muscles of aging rats.* J Cachexia Sarcopenia Muscle, 2(3): 175-180. DOI: 10.1007/s13539-011-0033-7.

[79] Osborn, M and Goebel, HH (1983). *The cytoplasmic bodies in a congenital myopathy can be stained with antibodies to desmin, the muscle-specific intermediate filament protein.* Acta Neuropathol, 62(1-2): 149-52. DOI: 10.1007/BF00684933.

[80] Sarnat, HB (1991). *Vimentin/desmin immunoreactivity of myofibres in developmental myopathies.* Acta Paediatr Jpn, 33(2): 238-46. DOI: 10.1111/j.1442-200x.1991.tb01549.x.

[81] Goebel, HH (1991). *Congenital myopathies.* Acta Paediatr Jpn, 33(2): 247-55. DOI: 10.1111/j.1442-200x.1991.tb01550.x.

[82] Goebel, HH (1997). *Desmin-related myopathies.* Curr Opin Neurol, 10(5): 426-9. DOI: 10.1097/00019052-199710000-00012.

[83] Misra, AK, Menon, NK and Mishra, SK (1992). *Abnormal distribution of desmin and vimentin in myofibers in adult onset myotubular myopathy.* Muscle Nerve, 15(11): 1246-52. DOI: 10.1002/mus.880151105.

[84] Prelle, A, Moggio, M, Comi, GP, Gallanti, A, Checcarelli, N, Bresolin, N, Ciscato, P, Fortunato, F and Scarlato, G (1992). *Congenital myopathy associated with abnormal accumulation of desmin and dystrophin.* Neuromuscul Disord, 2(3): 169-75. DOI: 10.1016/0960-8966(92)90003-o.

[85] Goebel, HH and Bornemann, A (1993). *Desmin pathology in neuromuscular diseases.* Virchows Arch B Cell Pathol Incl Mol Pathol, 64(3): 127-35. DOI: 10.1007/BF02915105.

[86] Pellissier, JF, Pouget, J, Charpin, C and Figarella, D (1989). *Myopathy associated with desmin type intermediate filaments. An immunoelectron microscopic study.* J Neurol Sci, 89(1): 49-61. DOI: 10.1016/0022-510x(89)90006-3.

[87] Caron, A, Viader, F, Lechevalier, B and Chapon, F (1995). *Cytoplasmic body myopathy: familial cases with accumulation of desmin and dystrophin. An immunohistochemical, immunoelectron microscopic and biochemical study.* Acta Neuropathol, 90(2): 150-7. DOI: 10.1007/BF00294314.

[88] Wolburg, H, Schlote, W, Langohr, HD, Peiffer, J, Reiher, KH and Heckl, RW (1982). *Slowly progressive congenital myopathy with cytoplasmic bodies--report of two cases and a review of the literature.* Clin Neuropathol, 1(2): 55-66.

[89] Porte, A, Stoeckel, ME, Sacrez, A and Batzenschlager, A (1980). *Unusual familial cardiomyopathy with storage of intermediate filaments in the cardiac muscular cells.* Virchows Arch A Pathol Anat Histol, 386(1): 43-58. DOI: 10.1007/BF00432643.

[90] Stoeckel, ME, Osborn, M, Porte, A, Sacrez, A, Batzenschlager, A and Weber, K (1981). *An unusual familial cardiomyopathy characterized by aberrant accumulations of desmin-type intermediate filaments.* Virchows Arch A Pathol Anat Histol, 393(1): 53-60. DOI: 10.1007/BF00430870.

[91] Goldfarb, LG, Park, KY, Cervenakova, L, Gorokhova, S, Lee, HS, Vasconcelos, O, Nagle, JW, Semino-Mora, C, Sivakumar, K and Dalakas, MC (1998). *Missense mutations in desmin associated with familial cardiac and skeletal myopathy.* Nat Genet, 19(4): 402-3. DOI: 10.1038/1300.

[92] Park, KY, Dalakas, MC, Goebel, HH, Ferrans, VJ, Semino-Mora, C, Litvak, S, Takeda, K and Goldfarb, LG (2000). *Desmin splice variants causing cardiac and skeletal myopathy.* J Med Genet, 37(11): 851-7. DOI: 10.1136/jmg.37.11.851.

[93] Munoz-Marmol, AM, Strasser, G, Isamat, M, Coulombe, PA, Yang, Y, Roca, X, Vela, E, Mate, JL, Coll, J, Fernandez-Figueras, MT, Navas-Palacios, JJ, Ariza, A and Fuchs, E (1998). *A dysfunctional desmin mutation in a patient with severe generalized myopathy.* Proc Natl Acad Sci U S A, 95(19): 11312-7. DOI: 10.1073/pnas.95.19.11312.

[94] Sjoberg, G, Saavedra-Matiz, CA, Rosen, DR, Wijsman, EM, Borg, K, Horowitz, SH and Sejersen, T (1999). *A missense mutation in the desmin rod domain is associated with autosomal dominant distal myopathy, and exerts a dominant negative effect on filament formation.* Hum Mol Genet, 8(12): 2191-8. DOI: 10.1093/hmg/8.12.2191.

[95] Bar, H, Goudeau, B, Walde, S, Casteras-Simon, M, Mucke, N, Shatunov, A, Goldberg, YP, Clarke, C, Holton, JL, Eymard, B, Katus, HA, Fardeau, M, Goldfarb, L, Vicart, P and Herrmann, H (2007). *Conspicuous involvement of desmin tail mutations in diverse cardiac and skeletal myopathies.* Hum Mutat, 28(4): 374-86. DOI: 10.1002/humu.20459.

[96] Bergman, JE, Veenstra-Knol, HE, van Essen, AJ, van Ravenswaaij, CM, den Dunnen, WF, van den Wijngaard, A and van Tintelen, JP (2007). *Two related Dutch families with a clinically variable presentation of cardioskeletal myopathy caused by a novel S13F mutation in the desmin gene.* Eur J Med Genet, 50(5): 355-66. DOI: 10.1016/j.ejmg.2007.06.003.

[97] Pica, EC, Kathirvel, P, Pramono, ZA, Lai, PS and Yee, WC (2008). *Characterization of a novel S13F desmin mutation associated with desmin myopathy and heart block in a Chinese family.* Neuromuscul. Disord, 18(2): 178-182. DOI: 10.1016/j.nmd.2007.09.011.

[98] van Tintelen, JP, Van Gelder, IC, Asimaki, A, Suurmeijer, AJ, Wiesfeld, AC, Jongbloed, JD, van den Wijngaard, A, Kuks, JB, van Spaendonck-Zwarts, KY, Notermans, N, Boven, L, van den Heuvel, F, Veenstra-Knol, HE, Saffitz, JE, Hofstra, RM and van den Berg, MP (2009). *Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene.* Heart Rhythm, 6(11): 1574-83. DOI: 10.1016/j.hrthm.2009.07.041.

[99] Otten, E, Asimaki, A, Maass, A, van Langen, IM, van der Wal, A, de Jonge, N, van den Berg, MP, Saffitz, JE, Wilde, AA, Jongbloed, JD and van Tintelen, JP (2010). *Desmin mutations as a cause of right ventricular heart failure affect the intercalated disks.* Heart Rhythm, 7(8): 1058-64. DOI: 10.1016/j.hrthm.2010.04.023.

[100] Hedberg, C, Melberg, A, Kuhl, A, Jenne, D and Oldfors, A (2012). *Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy 7 is caused by a DES mutation.* Eur J Hum Genet, 20(9): 984-5. DOI: 10.1038/ejhg.2012.39.

[101] Cetin, N, Balci-Hayta, B, Gundesli, H, Korkusuz, P, Purali, N, Talim, B, Tan, E, Selcen, D, Erdem-Ozdamar, S and Dincer, P (2013). *A novel desmin mutation leading to autosomal recessive limb-girdle muscular dystrophy: distinct histopathological outcomes compared with desminopathies.* J Med Genet, 50(7): 437-43. DOI: 10.1136/jmedgenet-2012-101487.

[102] Riley, LG, Waddell, LB, Ghaoui, R, Evesson, FJ, Cummings, BB, Bryen, SJ, Joshi, H, Wang, MX, Brammah, S, Kritharides, L, Corbett, A, MacArthur, DG and Cooper, ST (2019). *Recessive DES cardio/myopathy without myofibrillar aggregates: intronic splice variant silences one allele leaving only missense L190P-desmin.* Eur J Hum Genet, 27(8): 1267-1273. DOI: 10.1038/s41431-019-0393-6.

[103] Bermudez-Jimenez, FJ, Carriel, V, Brodehl, A, Alaminos, M, Campos, A, Schirmer, I, Milting, H, Abril, BA, Alvarez, M, Lopez-Fernandez, S, Garcia-Giustiniani, D, Monserrat, L, Tercedor, L and Jimenez-Jaimez, J (2018). *Novel Desmin Mutation p.Glu401Asp Impairs Filament Formation, Disrupts Cell Membrane Integrity, and Causes Severe Arrhythmogenic Left Ventricular Cardiomyopathy/Dysplasia.* Circulation, 137(15): 1595-1610. DOI: 10.1161/CIRCULATIONAHA.117.028719.

[104] Li, D, Tapscoft, T, Gonzalez, O, Burch, PE, Quinones, MA, Zoghbi, WA, Hill, R, Bachinski, LL, Mann, DL and Roberts, R (1999). *Desmin mutation responsible for idiopathic dilated cardiomyopathy.* Circulation, 100(5): 461-4. DOI: 10.1161/01.cir.100.5.461.

[105] Dalakas, MC, Park, KY, Semino-Mora, C, Lee, HS, Sivakumar, K and Goldfarb, LG (2000). *Desmin myopathy, a skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene.* N Engl J Med, 342(11): 770-80. DOI: 10.1056/NEJM200003163421104.

[106] van Spaendonck-Zwarts, KY, van Hessem, L, Jongbloed, JD, de Walle, HE, Capetanaki, Y, van der Kooi, AJ, van Langen, IM, van den Berg, MP and van Tintelen, JP (2011). *Desmin-related myopathy.* Clin Genet, 80(4): 354-66. DOI: 10.1111/j.1399-0004.2010.01512.x.

[107] Bar, H, Strelkov, SV, Sjoberg, G, Aebi, U and Herrmann, H (2004). *The biology of desmin filaments: how do mutations affect their structure, assembly, and organisation?* J. Struct. Biol, 148(2): 137-152. DOI: 10.1016/j.jsb.2004.04.003.

[108] Ariza, A, Coll, J, Fernandez-Figueras, MT, Lopez, MD, Mate, JL, Garcia, O, Fernandez-Vasalo, A and Navas-Palacios, JJ (1995). *Desmin myopathy: a multisystem disorder involving skeletal, cardiac, and smooth muscle.* Hum Pathol, 26(9): 1032-7. DOI: 10.1016/0046-8177(95)90095-0.

[109] Herrmann, H, Cabet, E, Chevalier, NR, Moosmann, J, Schultheis, D, Haas, J, Schowalter, M, Berwanger, C, Weyerer, V, Agaimy, A, Meder, B, Muller, OJ, Katus, HA, Schlotzer-Schrehardt, U, Vicart, P, Ferreiro, A, Dittrich, S, Clemen, CS, Lilienbaum, A and Schroder, R (2020). *Dual Functional States of R406W-Desmin Assembly Complexes Cause Cardiomyopathy With Severe Intercalated Disc Derangement in Humans and in Knock-In Mice.* Circulation, 142(22): 2155-2171. DOI: 10.1161/CIRCULATIONAHA.120.050218.

[110] Selcen, D (2011). *Myofibrillar myopathies.* Neuromuscul. Disord, 21(3): 161-171. DOI: 10.1016/j.nmd.2010.12.007.

[111] Ferrer, I and Olive, M (2008). *Molecular pathology of myofibrillar myopathies.* Expert Rev Mol Med, 10: e25. DOI: 10.1017/S1462399408000793.

[112] Kedia, N, Arhzaouy, K, Pittman, SK, Sun, Y, Batchelor, M, Weihl, CC and Bieschke, J (2019). *Desmin forms toxic, seeding-competent amyloid aggregates that persist in muscle fibers.* Proc Natl Acad Sci U S A, 116(34): 16835-16840. DOI: 10.1073/pnas.1908263116.

[113] Singh, SR and Robbins, J (2018). *Desmin and Cardiac Disease: An Unfolding Story*. Circ Res, 122(10): 1324-1326. DOI: 10.1161/CIRCRESAHA.118.312965.

[114] Joanne, P, Chourbagi, O, Hourde, C, Ferry, A, Butler-Browne, G, Vicart, P, Dumonceaux, J and Agbulut, O (2013). *Viral-mediated expression of desmin mutants to create mouse models of myofibrillar myopathy.* Skelet. Muscle, 3(1): 4. DOI: 10.1186/2044-5040-3-4.

[115] Winter, L, Wittig, I, Peeva, V, Eggers, B, Heidler, J, Chevessier, F, Kley, RA, Barkovits, K, Strecker, V, Berwanger, C, Herrmann, H, Marcus, K, Kornblum, C, Kunz, WS, Schroder, R and Clemen, CS (2016). *Mutant desmin substantially perturbs mitochondrial morphology, function and maintenance in skeletal muscle tissue.* Acta Neuropathol, 132(3): 453-73. DOI: 10.1007/s00401-016-1592-7.

[116] Henderson, M, De Waele, L, Hudson, J, Eagle, M, Sewry, C, Marsh, J, Charlton, R, He, L, Blakely, EL, Horrocks, I, Stewart, W, Taylor, RW, Longman, C, Bushby, K and Barresi, R (2013). *Recessive desmin-null muscular dystrophy with central nuclei and mitochondrial abnormalities.* Acta Neuropathol, 125(6): 917-9. DOI: 10.1007/s00401-013-1113-x.

[117] Smolina, N, Bruton, J, Sjoberg, G, Kostareva, A and Sejersen, T (2014). *Aggregate-prone desmin mutations impair mitochondrial calcium uptake in primary myotubes.* Cell Calcium, 56(4): 269-75. DOI: 10.1016/j.ceca.2014.08.001.

[118] Maerkens, A, Kley, RA, Olive, M, Theis, V, van der Ven, PF, Reimann, J, Milting, H, Schreiner, A, Uszkoreit, J, Eisenacher, M, Barkovits, K, Guttsches, AK, Tonillo, J, Kuhlmann, K, Meyer, HE, Schroder, R, Tegenthoff, M, Furst, DO, Muller, T, Goldfarb, LG, Vorgerd, M and Marcus, K (2013). *Differential proteomic analysis of abnormal intramyoplasmic aggregates in desminopathy.* J. Proteomics, 90: 14-27. DOI: 10.1016/j.jprot.2013.04.026.

[119] Elliott, JL, Der, PM, Prescott, AR, Jansen, KA, Koenderink, GH and Quinlan, RA (2013). *The specificity of the interaction between alphaB-crystallin and desmin filaments and its impact on filament aggregation and cell viability.* Philos. Trans. R. Soc. Lond B Biol. Sci, 368(1617): 20120375. DOI: 10.1098/rstb.2012.0375.

[120] Chourbagi, O, Bruston, F, Carinci, M, Xue, Z, Vicart, P, Paulin, D and Agbulut, O (2011). *Desmin mutations in the terminal consensus motif prevent synemin-desmin heteropolymer filament assembly.* Exp. Cell Res, 317(6): 886-897. DOI: 10.1016/j.yexcr.2011.01.013.

[121] Conover, GM, Henderson, SN and Gregorio, CC (2009). *A myopathy-linked desmin mutation perturbs striated muscle actin filament architecture.* Mol. Biol. Cell, 20(3): 834-845. DOI: 10.1091/mbc.E08-07-0753.

[122] Even, C, Abramovici, G, Delort, F, Rigato, AF, Bailleux, V, de Sousa Moreira, A, Vicart, P, Rico, F, Batonnet-Pichon, S and Briki, F (2017). *Mutation in the Core Structure of Desmin Intermediate Filaments Affects Myoblast Elasticity*. Biophys J, 113(3): 627-636. DOI: 10.1016/j.bpj.2017.06.020.

[123] Kreplak, L and Bar, H (2009). *Severe myopathy mutations modify the nanomechanics of desmin intermediate filaments.* J Mol Biol, 385(4): 1043-51. DOI: 10.1016/j.jmb.2008.10.095.

[124] Charrier, EE, Asnacios, A, Milloud, R, De Mets, R, Balland, M, Delort, F, Cardoso, O, Vicart, P, Batonnet-Pichon, S and Henon, S (2016). *Desmin Mutation in the C-Terminal Domain Impairs Traction Force Generation in Myoblasts.* Biophys J, 110(2): 470-480. DOI: 10.1016/j.bpj.2015.11.3518.

[125] Bonakdar, N, Luczak, J, Lautscham, L, Czonstke, M, Koch, TM, Mainka, A, Jungbauer, T, Goldmann, WH, Schroder, R and Fabry, B (2012). *Biomechanical characterization of a desminopathy in primary human myoblasts.* Biochem Biophys Res Commun, 419(4): 703-7. DOI: 10.1016/j.bbrc.2012.02.083.

[126] Panagopoulou, P, Davos, CH, Milner, DJ, Varela, E, Cameron, J, Mann, DL and Capetanaki, Y (2008). *Desmin mediates TNF-alpha-induced aggregate formation and intercalated disk reorganization in heart failure.* J. Cell Biol, 181(5): 761-775. DOI: 10.1083/jcb.200710049.

[127] Bouvet, M, Dubois-Deruy, E, Alayi, TD, Mulder, P, El Amranii, M, Beseme, O, Amouyel, P, Richard, V, Tomavo, S and Pinet, F (2016). *Increased level of phosphorylated desmin and its degradation products in heart failure.* Biochem Biophys Rep, 6: 54-62. DOI: 10.1016/j.bbrep.2016.02.014.

[128] Delort, F, Segard, BD, Hakibilen, C, Bourgois-Rocha, F, Cabet, E, Vicart, P, Huang, ME, Clary, G, Lilienbaum, A, Agbulut, O and Batonnet-Pichon, S (2019). *Alterations of redox dynamics and desmin post-translational modifications in skeletal muscle models of desminopathies.* Exp Cell Res, 383(2): 111539. DOI: 10.1016/j.yexcr.2019.111539.

[129] Gard, DL, Bell, PB and Lazarides, E (1979). *Coexistence of desmin and the fibroblastic intermediate filament subunit in muscle and nonmuscle cells: identification and comparative peptide analysis.* Proc Natl Acad Sci U S A, 76(8): 3894-8. DOI: 10.1073/pnas.76.8.3894.

[130] O'Connor, CM, Balzer, DR, Jr. and Lazarides, E (1979). *Phosphorylation of subunit proteins of intermediate filaments from chicken muscle and nonmuscle cells.* Proc Natl Acad Sci U S A, 76(2): 819-23. DOI: 10.1073/pnas.76.2.819.

[131] Inagaki, M, Nishi, Y, Nishizawa, K, Matsuyama, M and Sato, C (1987). *Site-specific phosphorylation induces disassembly of vimentin filaments in vitro.* Nature, 328(6131): 649-52. DOI: 10.1038/328649a0.

[132] Landry, T, Shookster, D and Huang, H (2020). *Tissue-Specific Approaches Reveal Diverse Metabolic Functions of Rho-Kinase 1.* Front Endocrinol (Lausanne), 11: 622581. DOI: 10.3389/fendo.2020.622581.

[133] Castellani, L, Salvati, E, Alema, S and Falcone, G (2006). *Fine regulation of RhoA and Rock is required for skeletal muscle differentiation.* J Biol Chem, 281(22): 15249-57. DOI: 10.1074/jbc.M601390200.

[134] Munoz, VR, Gaspar, RC, Esteca, MV, Baptista, IL, Vieira, RFL, da Silva, ASR, de Moura, LP, Cintra, DE, Ropelle, ER and Pauli, JR (2020). *Physical exercise increases ROCK activity in the skeletal muscle of middle-aged rats.* Mech Ageing Dev, 186: 111213. DOI: 10.1016/j.mad.2020.111213.

[135] Inada, H, Goto, H, Tanabe, K, Nishi, Y, Kaibuchi, K and Inagaki, M (1998). *Rho-associated kinase phosphorylates desmin, the myogenic intermediate filament protein, at unique amino-terminal sites.* Biochem Biophys Res Commun, 253(1): 21-5. DOI: 10.1006/bbrc.1998.9732.

[136] Kawajiri, A, Yasui, Y, Goto, H, Tatsuka, M, Takahashi, M, Nagata, K and Inagaki, M (2003). *Functional significance of the specific sites phosphorylated in desmin at cleavage furrow: Aurora-B may phosphorylate and regulate type III intermediate filaments during cytokinesis coordinatedly with Rho-kinase.* Mol Biol Cell, 14(4): 1489-500. DOI: 10.1091/mbc.e02-09-0612.

[137] Ohtakara, K, Inada, H, Goto, H, Taki, W, Manser, E, Lim, L, Izawa, I and Inagaki, M (2000). *p21-activated kinase PAK phosphorylates desmin at sites different from those for Rho-associated kinase.* Biochem Biophys Res Commun, 272(3): 712-6. DOI: 10.1006/bbrc.2000.2854.

[138] Wang, Y, Wang, S, Lei, M, Boyett, M, Tsui, H, Liu, W and Wang, X (2018). *The p21-activated kinase 1 (Pak1) signalling pathway in cardiac disease: from mechanistic study to therapeutic exploration.* Br J Pharmacol, 175(8): 1362-1374. DOI: 10.1111/bph.13872.

[139] Joseph, GA, Lu, M, Radu, M, Lee, JK, Burden, SJ, Chernoff, J and Krauss, RS (2017). *Group I Paks Promote Skeletal Myoblast Differentiation In Vivo and In Vitro.* Mol Cell Biol, 37(4). DOI: 10.1128/MCB.00222-16.

[140] Cerquone Perpetuini, A, Re Cecconi, AD, Chiappa, M, Martinelli, GB, Fuoco, C, Desiderio, G, Castagnoli, L, Gargioli, C, Piccirillo, R and Cesareni, G (2018). *Group I Paks support muscle regeneration and counteract cancer-associated muscle atrophy.* J Cachexia Sarcopenia Muscle, 9(4): 727-746. DOI: 10.1002/jcsm.12303.

[141] Sheehan, KA, Ke, Y, Wolska, BM and Solaro, RJ (2009). *Expression of active p21-activated kinase-1 induces Ca2+ flux modification with altered regulatory protein phosphorylation in cardiac myocytes.* Am J Physiol Cell Physiol, 296(1): C47-58. DOI: 10.1152/ajpcell.00012.2008.

[142] Makihara, H, Inaba, H, Enomoto, A, Tanaka, H, Tomono, Y, Ushida, K, Goto, M, Kurita, K, Nishida, Y, Kasahara, K, Goto, H and Inagaki, M (2016). *Desmin phosphorylation by Cdk1 is required for efficient separation of desmin intermediate filaments in mitosis and detected in murine embryonic/newborn muscle and human rhabdomyosarcoma tissues.* Biochem Biophys Res Commun, 478(3): 1323-9. DOI: 10.1016/j.bbrc.2016.08.122.

[143] Rainer, PP, Dong, P, Sorge, M, Fert-Bober, J, Holewinski, RJ, Wang, Y, Foss, CA, An, SS, Baracca, A, Solaini, G, Glabe, CG, Pomper, MG, Van Eyk, JE, Tomaselli, GF, Paolocci, N and Agnetti, G (2018). *Desmin Phosphorylation Triggers Preamyloid Oligomers Formation and Myocyte Dysfunction in Acquired Heart Failure.* Circ Res, 122(10): e75-e83. DOI: 10.1161/CIRCRESAHA.117.312082.

[144] Giovarelli, M, Zecchini, S, Martini, E, Garre, M, Barozzi, S, Ripolone, M, Napoli, L, Coazzoli, M, Vantaggiato, C, Roux-Biejat, P, Cervia, D, Moscheni, C, Perrotta, C, Parazzoli, D, Clementi, E and De Palma, C (2020). *Drp1 overexpression induces desmin disassembling and drives kinesin-1 activation promoting mitochondrial trafficking in skeletal muscle.* Cell Death Differ, 27(8): 2383-2401. DOI: 10.1038/s41418-020-0510-7.

[145] Nagata, K, Izawa, I and Inagaki, M (2001). *A decade of site- and phosphorylation state-specific antibodies: recent advances in studies of spatiotemporal protein phosphorylation.* Genes Cells, 6(8): 653-64. DOI: 10.1046/j.1365-2443.2001.00454.x.

[146] Inagaki, M, Inagaki, N, Takahashi, T and Takai, Y (1997). *Phosphorylation-dependent control of structures of intermediate filaments: a novel approach using site- and phosphorylation state-specific antibodies.* J Biochem, 121(3): 407-14. DOI: 10.1093/oxfordjournals.jbchem.a021603.

[147] Izawa, I and Inagaki, M (2006). *Regulatory mechanisms and functions of intermediate filaments: a study using site- and phosphorylation state-specific antibodies.* Cancer Sci, 97(3): 167-74. DOI: 10.1111/j.1349-7006.2006.00161.x.

[148] Geisler, N and Weber, K (1988). *Phosphorylation of desmin in vitro inhibits formation of intermediate filaments; identification of three kinase A sites in the aminoterminal head domain.* EMBO J, 7(1): 15-20.

[149] Kitamura, S, Ando, S, Shibata, M, Tanabe, K, Sato, C and Inagaki, M (1989). *Protein kinase C phosphorylation of desmin at four serine residues within the non-alpha-helical head domain.* J Biol Chem, 264(10): 5674-8.

[150] Inagaki, M, Gonda, Y, Matsuyama, M, Nishizawa, K, Nishi, Y and Sato, C (1988). *Intermediate filament reconstitution in vitro. The role of phosphorylation on the assembly-disassembly of desmin.* J Biol Chem, 263(12): 5970-8.

[151] Singh, RM, Cummings, E, Pantos, C and Singh, J (2017). *Protein kinase C and cardiac dysfunction: a review.* Heart Fail Rev, 22(6): 843-859. DOI: 10.1007/s10741-017-9634-3.

[152] Kooij, V, Stienen, GJM and van der Velden, J (2011). *The role of protein kinase C-mediated phosphorylation of sarcomeric proteins in the heart-detrimental or beneficial?* Biophys Rev, 3(3): 107. DOI: 10.1007/s12551-011-0050-y.

[153] Newton, AC, Antal, CE and Steinberg, SF (2016). *Protein kinase C mechanisms that contribute to cardiac remodelling.* Clin Sci (Lond), 130(17): 1499-510. DOI: 10.1042/CS20160036.

[154] Boczan, J, Boros, S, Mechler, F, Kovacs, L and Biro, T (2000). *Differential expressions of protein kinase C isozymes during proliferation and differentiation of human skeletal muscle cells in vitro.* Acta Neuropathol, 99(2): 96-104. DOI: 10.1007/pl00007429.

[155] Czifra, G, Toth, IB, Marincsak, R, Juhasz, I, Kovacs, I, Acs, P, Kovacs, L, Blumberg, PM and Biro, T (2006). *Insulin-like growth factor-I-coupled mitogenic signaling in primary cultured human skeletal muscle cells and in C2C12 myoblasts. A central role of protein kinase Cdelta.* Cell Signal, 18(9): 1461-72. DOI: 10.1016/j.cellsig.2005.11.007.

[156] Nicolas, HA, Bertrand, AT, Labib, S, Mohamed-Uvaize, M, Bolongo, PM, Wu, WY, Bilinska, ZT, Bonne, G, Akimenko, MA and Tesson, F (2020). *Protein Kinase C Alpha Cellular Distribution, Activity, and Proximity with Lamin A/C in Striated Muscle Laminopathies.* Cells, 9(11). DOI: 10.3390/cells9112388.

[157] Huang, X, Li, J, Foster, D, Lemanski, SL, Dube, DK, Zhang, C and Lemanski, LF (2002). *Protein kinase C-mediated desmin phosphorylation is related to myofibril disarray in cardiomyopathic hamster heart.* Exp. Biol. Med. (Maywood.), 227(11): 1039-1046.

[158] Mermelstein Cdos, S, Costa, ML, Chagas Filho, C and Moura Neto, V (1996). *Intermediate filament proteins in TPA-treated skeletal muscle cells in culture.* J Muscle Res Cell Motil, 17(2): 199-206. DOI: 10.1007/BF00124242.

[159] Boczan, J, Biro, T, Czifra, G, Lazar, J, Papp, H, Bardos, H, Adany, R, Mechler, F and Kovacs, L (2001). *Phorbol ester treatment inhibits proliferation and differentiation of cultured human skeletal muscle satellite cells by differentially acting on protein kinase C isoforms.* Acta Neuropathol, 102(1): 55-62. DOI: 10.1007/s004010000347.

[160] Tao, JX and Ip, W (1991). *Site-specific antibodies block kinase A phosphorylation of desmin in vitro and inhibit incorporation of myoblasts into myotubes.* Cell Motil Cytoskeleton, 19(2): 109-20. DOI: 10.1002/cm.970190206.

[161] Tokui, T, Yamauchi, T, Yano, T, Nishi, Y, Kusagawa, M, Yatani, R and Inagaki, M (1990). *Ca2(+)-calmodulin-dependent protein kinase II phosphorylates various types of non-epithelial intermediate filament proteins.* Biochem Biophys Res Commun, 169(3): 896-904. DOI: 10.1016/0006-291x(90)91977-z.

[162] Claeyssen, C, Bastide, B and Cieniewski-Bernard, C (2022). *Global O-GlcNAcylation changes impact desmin phosphorylation and its partition toward cytoskeleton in C2C12 skeletal muscle cells differentiated into myotubes.* Sci Rep, 12(1): 9831. DOI: 10.1038/s41598-022-14033-z.

[163] Eriksson, JE, Brautigan, DL, Vallee, R, Olmsted, J, Fujiki, H and Goldman, RD (1992). *Cytoskeletal integrity in interphase cells requires protein phosphatase activity.* Proc Natl Acad Sci U S A, 89(22): 11093-7. DOI: 10.1073/pnas.89.22.11093.

[164] Toivola, DM, Goldman, RD, Garrod, DR and Eriksson, JE (1997). *Protein phosphatases maintain the organization and structural interactions of hepatic keratin intermediate filaments.* J Cell Sci, 110 (Pt 1): 23-33.

[165] Inada, H, Togashi, H, Nakamura, Y, Kaibuchi, K, Nagata, K and Inagaki, M (1999). *Balance between activities of Rho kinase and type 1 protein phosphatase modulates turnover of phosphorylation and dynamics of desmin/vimentin filaments.* J Biol Chem, 274(49): 34932-9. DOI: 10.1074/jbc.274.49.34932.

[166] Huang, HY, Graves, DJ, Robson, RM and Huiatt, TW (1993). *ADP-ribosylation of the intermediate filament protein desmin and inhibition of desmin assembly in vitro by muscle ADP-ribosyltransferase.* Biochem Biophys Res Commun, 197(2): 570-7. DOI: 10.1006/bbrc.1993.2517.

[167] Zhou, H, Huiatt, TW, Robson, RM, Sernett, SW and Graves, DJ (1996). *Characterization of ADP-ribosylation sites on desmin and restoration of desmin intermediate filament assembly by de-ADP-ribosylation.* Arch Biochem Biophys, 334(2): 214-22. DOI: 10.1006/abbi.1996.0449.

[168] Yuan, J, Huiatt, TW, Liao, CX, Robson, RM and Graves, DJ (1999). *The effects of mono-ADP-ribosylation on desmin assembly-disassembly.* Arch Biochem Biophys, 363(2): 314-22. DOI: 10.1006/abbi.1998.1096.

[169] Graves, DJ, Huiatt, TW, Zhou, H, Huang, HY, Sernett, SW, Robson, RM and McMahon, KK (1997). *Regulatory role of arginine-specific mono(ADP-ribosyl)transferase in muscle cells.* Adv Exp Med Biol, 419: 305-13. DOI: 10.1007/978-1-4419-8632-0_40.

[170] Cieniewski-Bernard, C, Dupont, E, Richard, E and Bastide, B (2014). *Phospho-GlcNAc modulation of slow MLC2 during soleus atrophy through a multienzymatic and sarcomeric complex.* Pflugers Arch, 466(11): 2139-2151. DOI: 10.1007/s00424-014-1453-y.

[171] Lambert, M, Claeyssen, C, Bastide, B and Cieniewski-Bernard, C (2020). *O-GlcNAcylation as a regulator of the functional and structural properties of the sarcomere in skeletal muscle: An update review.* Acta Physiol (Oxf), 228(1): e13301. DOI: 10.1111/apha.13301.

[172] Cieniewski-Bernard, C, Montel, V, Berthoin, S and Bastide, B (2012). *Increasing O-GlcNAcylation Level on Organ Culture of Soleus Modulates the Calcium Activation Parameters of Muscle Fibers.* PLoS. One, 7(10): e48218. DOI: 10.1371/journal.pone.0048218.

[173] Deracinois, B, Camoin, L, Lambert, M, Boyer, JB, Dupont, E, Bastide, B and Cieniewski-Bernard, C (2018). *O-GlcNAcylation site mapping by (azide-alkyne) click chemistry and mass spectrometry following intensive fractionation of skeletal muscle cells proteins.* J Proteomics, 186: 83-97. DOI: 10.1016/j.jprot.2018.07.005.

[174] Lambert, M, Richard, E, Duban-Deweer, S, Krzewinski, F, Deracinois, B, Dupont, E, Bastide, B and Cieniewski-Bernard, C (2016). *O-GlcNAcylation is a key modulator of skeletal muscle sarcomeric morphometry associated to modulation of protein-protein interactions.* Biochim. Biophys. Acta - General Subjects, 1860(9): 2017-2030. DOI: 10.1016/j.bbagen.2016.06.011.

[175] Farach, AM and Galileo, DS (2008). *O-GlcNAc modification of radial glial vimentin filaments in the developing chick brain.* Brain Cell Biol, 36(5-6): 191-202. DOI: 10.1007/s11068-008-9036-5.

[176] Slawson, C, Lakshmanan, T, Knapp, S and Hart, GW (2008). *A mitotic GlcNAcylation/phosphorylation signaling complex alters the posttranslational state of the cytoskeletal protein vimentin.* Mol. Biol. Cell, 19(10): 4130-4140. DOI: 10.1091/mbc.E07-11-1146.

[177] Rotty, JD, Hart, GW and Coulombe, PA (2010). *Stressing the role of O-GlcNAc: linking cell survival to keratin modification.* Nat. Cell Biol, 12(9): 847-849. DOI: 10.1038/ncb0910-847.

[178] Ruan, HB, Nie, Y and Yang, X (2013). *Regulation of protein degradation by O-GlcNAcylation: crosstalk with ubiquitination.* Mol. Cell Proteomics, 12(12): 3489-3497. DOI: 10.1074/mcp.R113.029751.

[179] Diguet, N, Mallat, Y, Ladouce, R, Clodic, G, Prola, A, Tritsch, E, Blanc, J, Larcher, JC, Delcayre, C, Samuel, JL, Friguet, B, Bolbach, G, Li, Z and Mericskay, M (2011). *Muscle creatine kinase deficiency triggers both actin depolymerization and desmin disorganization by advanced glycation end products in dilated cardiomyopathy.* J Biol Chem, 286(40): 35007-19. DOI: 10.1074/jbc.M111.252395.

[180] Ahmed, MI, Guichard, JL, Soorappan, RN, Ahmad, S, Mariappan, N, Litovsky, S, Gupta, H, Lloyd, SG, Denney, TS, Powell, PC, Aban, I, Collawn, J, Davies, JE, McGiffin, DC and Dell'Italia, LJ (2016). *Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function.* J Thorac Cardiovasc Surg, 152(4): 1059-1070 e2. DOI: 10.1016/j.jtcvs.2016.06.017.

[181] Janue, A, Odena, MA, Oliveira, E, Olive, M and Ferrer, I (2007). *Desmin is oxidized and nitrated in affected muscles in myotilinopathies and desminopathies.* J. Neuropathol. Exp. Neurol, 66(8): 711-723. DOI: 10.1097/nen.0b013e3181256b4c.

[182] Janue, A, Olive, M and Ferrer, I (2007). *Oxidative stress in desminopathies and myotilinopathies: a link between oxidative damage and abnormal protein aggregation.* Brain Pathol, 17(4): 377-388. DOI: 10.1111/j.1750-3639.2007.00087.x.

[183] Segard, BD, Delort, F, Bailleux, V, Simon, S, Leccia, E, Gausseres, B, Briki, F, Vicart, P and Batonnet-Pichon, S (2013). *N-acetyl-L-cysteine prevents stress-induced desmin aggregation in cellular models of desminopathy.* PLoS One, 8(10): e76361. DOI: 10.1371/journal.pone.0076361.

[184] Cohen, S (2020). *Role of calpains in promoting desmin filaments depolymerization and muscle atrophy.* Biochim Biophys Acta Mol Cell Res, 1867(10): 118788. DOI: 10.1016/j.bbamcr.2020.118788.

[185] Cohen, S, Zhai, B, Gygi, SP and Goldberg, AL (2012). *Ubiquitylation by Trim32 causes coupled loss of desmin, Z-bands, and thin filaments in muscle atrophy.* J Cell Biol, 198(4): 575-89. DOI: 10.1083/jcb.201110067.

[186] Mirzoev, TM, Sharlo, KA and Shenkman, BS (2021). *The Role of GSK-3beta in the Regulation of Protein Turnover, Myosin Phenotype, and Oxidative Capacity in Skeletal Muscle under Disuse Conditions.* Int J Mol Sci, 22(10). DOI: 10.3390/ijms22105081.

[187] Aweida, D, Rudesky, I, Volodin, A, Shimko, E and Cohen, S (2018). *GSK3-beta promotes calpain-1-mediated desmin filament depolymerization and myofibril loss in atrophy.* J Cell Biol, 217(10): 3698-3714. DOI: 10.1083/jcb.201802018.

[188] Agnetti, G, Halperin, VL, Kirk, JA, Chakir, K, Guo, Y, Lund, L, Nicolini, F, Gherli, T, Guarnieri, C, Caldarera, CM, Tomaselli, GF, Kass, DA and Van Eyk, JE (2014). *Desmin modifications associate with amyloid-like oligomers deposition in heart failure.* Cardiovasc Res, 102(1): 24-34. DOI: 10.1093/cvr/cvu003.

[189] Nakano, SJ, Walker, JS, Walker, LA, Li, X, Du, Y, Miyamoto, SD, Sucharov, CC, Garcia, AM, Mitchell, MB, Ambardekar, AV and Stauffer, BL (2019). *Increased myocyte calcium sensitivity in end-stage pediatric dilated cardiomyopathy.* Am J Physiol Heart Circ Physiol, 317(6): H1221-H1230. DOI: 10.1152/ajpheart.00409.2019.

[190] Mercier, T, Bouvet, M, Dubois-Deruy, E, Dechaumes, A, Beseme, O, Richard, V, Mulder, P and Pinet, F (2018). *Interplay Between Phosphorylation and O-GlcNAcylation of Sarcomeric Proteins in Ischemic Heart Failure.* Front Endocrinol (Lausanne), 9: 598. DOI: 10.3389/fendo.2018.00598.

[191] Wanschit, J, Nakano, S, Goudeau, B, Strobel, T, Rinner, W, Wimmer, G, Resch, H, Jaksch, M, Akiguchi, I, Vicart, P and Budka, H (2002). *Myofibrillar (desmin-related) myopathy: clinico-pathological spectrum in 3 cases and review of the literature.* Clin Neuropathol, 21(5): 220-31.

[192] Prelle, A, Sciacco, M, Comi, GP, Messina, S, Carpo, M, Ciscato, P, Nobile Orazio, E, Fortunato, F, Mora, G, Bignotti, V, Fagiolari, G, Moggio, M and Scarlato, G (2000). *A sporadic, atypical case of desminopathy: morphological and immunological characterization.* Clin Neuropathol, 19(4): 208-12.

[193] Nakano, S, Engel, AG, Akiguchi, I and Kimura, J (1997). *Myofibrillar myopathy. III. Abnormal expression of cyclin-dependent kinases and nuclear proteins.* J Neuropathol Exp Neurol, 56(8): 850-6. DOI: 10.1097/00005072-199708000-00002.

[194] Caron, A and Chapon, F (1999). *Desmin phosphorylation abnormalities in cytoplasmic body and desmin-related myopathies.* Muscle Nerve, 22(8): 1122-1125.

[195] Rappaport, L, Contard, F, Samuel, JL, Delcayre, C, Marotte, F, Tome, F and Fardeau, M (1988). *Storage of phosphorylated desmin in a familial myopathy.* FEBS Lett, 231(2): 421-425.

[196] Vattemi, G, Tonin, P, Mora, M, Filosto, M, Morandi, L, Savio, C, Dal Pra, I, Rizzuto, N and Tomelleri, G (2004). *Expression of protein kinase C isoforms and interleukin-1beta in myofibrillar myopathy.* Neurology, 62(10): 1778-82. DOI: 10.1212/01.wnl.0000125197.70310.8e.

[197] Haslbeck, M, Peschek, J, Buchner, J and Weinkauf, S (2016). *Structure and function of alpha-crystallins: Traversing from in vitro to in vivo.* Biochim. Biophys. Acta, 1860(1 Pt B): 149-166. DOI: 10.1016/j.bbagen.2015.06.008.

[198] Van Der Ouderaa, FJ, De Jong, WW, Hilderink, A and Bloemendal, H (1974). *The amino-acids sequence of the alphaB2 chain of bovine alpha-crystallin.* Eur J Biochem, 49(1): 157-68. DOI: 10.1111/j.1432-1033.1974.tb03821.x.

[199] Bhat, SP and Nagineni, CN (1989). *alpha B subunit of lens-specific protein alpha-crystallin is present in other ocular and non-ocular tissues.* Biochem Biophys Res Commun, 158(1): 319-25. DOI: 10.1016/s0006-291x(89)80215-3.

[200] Dubin, RA, Wawrousek, EF and Piatigorsky, J (1989). *Expression of the murine alpha B-crystallin gene is not restricted to the lens.* Mol Cell Biol, 9(3): 1083-91. DOI: 10.1128/mcb.9.3.1083-1091.1989.

[201] Iwaki, T, Kume-Iwaki, A, Liem, RK and Goldman, JE (1989). *Alpha B-crystallin is expressed in non-lenticular tissues and accumulates in Alexander's disease brain.* Cell, 57(1): 71-8. DOI: 10.1016/0092-8674(89)90173-6.

[202] Kato, K, Shinohara, H, Kurobe, N, Inaguma, Y, Shimizu, K and Ohshima, K (1991). *Tissue distribution and developmental profiles of immunoreactive alpha B crystallin in the rat determined with a sensitive immunoassay system.* Biochim Biophys Acta, 1074(1): 201-8. DOI: 10.1016/0304-4165(91)90062-l.

[203] Brady, JP, Garland, DL, Green, DE, Tamm, ER, Giblin, FJ and Wawrousek, EF (2001). *AlphaB-crystallin in lens development and muscle integrity: a gene knockout approach.* Invest Ophthalmol Vis Sci, 42(12): 2924-34.

[204] Atomi, Y, Toro, K, Masuda, T and Hatta, H (2000). *Fiber-type-specific alphaB-crystallin distribution and its shifts with T(3) and PTU treatments in rat hindlimb muscles.* J Appl Physiol (1985), 88(4): 1355-64. DOI: 10.1152/jappl.2000.88.4.1355.

[205] Klemenz, R, Frohli, E, Steiger, RH, Schafer, R and Aoyama, A (1991). *Alpha B-crystallin is a small heat shock protein.* Proc Natl Acad Sci U S A, 88(9): 3652-6. DOI: 10.1073/pnas.88.9.3652.

[206] Horwitz, J (1992). *Alpha-crystallin can function as a molecular chaperone.* Proc Natl Acad Sci U S A, 89(21): 10449-53. DOI: 10.1073/pnas.89.21.10449.

[207] Horwitz, J (2003). *Alpha-crystallin.* Exp Eye Res, 76(2): 145-53. DOI: 10.1016/s0014-4835(02)00278-6.

[208] de Jong, WW, Caspers, GJ and Leunissen, JA (1998). *Genealogy of the alpha-crystallin--small heat-shock protein superfamily.* Int J Biol Macromol, 22(3-4): 151-62. DOI: 10.1016/s0141-8130(98)00013-0.

[209] Haslbeck, M, Franzmann, T, Weinfurtner, D and Buchner, J (2005). *Some like it hot: the structure and function of small heat-shock proteins.* Nat. Struct. Mol Biol, 12(10): 842-846. DOI: 10.1038/nsmb993.

[210] Jee, H (2016). *Size dependent classification of heat shock proteins: a mini-review.* J Exerc Rehabil, 12(4): 255-9. DOI: 10.12965/jer.1632642.321.

[211] Riedl, M, Strauch, A, Catici, DAM and Haslbeck, M (2020). *Proteinaceous Transformers: Structural and Functional Variability of Human sHsps.* Int J Mol Sci, 21(15). DOI: 10.3390/ijms21155448.

[212] Hayashi, J and Carver, JA (2020). *The multifaceted nature of alphaB-crystallin.* Cell Stress Chaperones, 25(4): 639-654. DOI: 10.1007/s12192-020-01098-w.

[213] Laganowsky, A, Benesch, JL, Landau, M, Ding, L, Sawaya, MR, Cascio, D, Huang, Q, Robinson, CV, Horwitz, J and Eisenberg, D (2010). *Crystal structures of truncated alphaA and alphaB crystallins reveal structural mechanisms of polydispersity important for eye lens function.* Protein Sci, 19(5): 1031-43. DOI: 10.1002/pro.380.

[214] Feil, IK, Malfois, M, Hendle, J, van Der Zandt, H and Svergun, DI (2001). *A novel quaternary structure of the dimeric alpha-crystallin domain with chaperone-like activity.* J Biol Chem, 276(15): 12024-9. DOI: 10.1074/jbc.M010856200.

[215] Bagneris, C, Bateman, OA, Naylor, CE, Cronin, N, Boelens, WC, Keep, NH and Slingsby, C (2009). *Crystal structures of alpha-crystallin domain dimers of alphaB-crystallin and Hsp20.* J Mol Biol, 392(5): 1242-52. DOI: 10.1016/j.jmb.2009.07.069.

[216] Hilton, GR, Lioe, H, Stengel, F, Baldwin, AJ and Benesch, JL (2013). *Small heat-shock proteins: paramedics of the cell.* Top Curr Chem, 328: 69-98. DOI: 10.1007/128_2012_324.

[217] Saha, S and Das, KP (2004). *Relationship between chaperone activity and oligomeric size of recombinant human alphaA- and alphaB-crystallin: a tryptic digestion study.* Proteins, 57(3): 610-7. DOI: 10.1002/prot.20230.

[218] Liu, L, Ghosh, JG, Clark, JI and Jiang, S (2006). *Studies of alphaB crystallin subunit dynamics by surface plasmon resonance.* Anal. Biochem, 350(2): 186-195. DOI: 10.1016/j.ab.2005.12.019.

[219] Jehle, S, van Rossum, B, Stout, JR, Noguchi, SM, Falber, K, Rehbein, K, Oschkinat, H, Klevit, RE and Rajagopal, P (2009). *alphaB-crystallin: a hybrid solid-state/solution-state NMR investigation reveals structural aspects of the heterogeneous oligomer.* J Mol Biol, 385(5): 1481-97. DOI: 10.1016/j.jmb.2008.10.097.

[220] Carver, JA and Lindner, RA (1998). *NMR spectroscopy of alpha-crystallin. Insights into the structure, interactions and chaperone action of small heat-shock proteins.* Int J Biol Macromol, 22(3-4): 197-209. DOI: 10.1016/s0141-8130(98)00017-8.

[221] Carver, JA, Grosas, AB, Ecroyd, H and Quinlan, RA (2017). *The functional roles of the unstructured N- and C-terminal regions in alphaB-crystallin and other mammalian small heat-shock proteins.* Cell Stress Chaperones, 22(4): 627-638. DOI: 10.1007/s12192-017-0789-6.
[222] Treweek, TM, Rekas, A, Walker, MJ and Carver, JA (2010). *A quantitative NMR spectroscopic examination of the flexibility of the C-terminal extensions of the molecular chaperones, alphaA- and alphaB-crystallin.* Exp Eye Res, 91(5): 691-9. DOI: 10.1016/j.exer.2010.08.015.
[223] Delbecq, SP and Klevit, RE (2013). *One size does not fit all: the oligomeric states of alphaB crystallin.* FEBS Lett, 587(8): 1073-80. DOI: 10.1016/j.febslet.2013.01.021.
[224] Peschek, J, Braun, N, Rohrberg, J, Back, KC, Kriehuber, T, Kastenmuller, A, Weinkauf, S and Buchner, J (2013). *Regulated structural transitions unleash the chaperone activity of alphaB-crystallin.* Proc Natl Acad Sci U S A, 110(40): E3780-9. DOI: 10.1073/pnas.1308898110.
[225] Selcen, D and Engel, AG (2003). *Myofibrillar myopathy caused by novel dominant negative alpha B-crystallin mutations.* Ann Neurol, 54(6): 804-10. DOI: 10.1002/ana.10767.
[226] Asomugha, CO, Gupta, R and Srivastava, OP (2011). *Structural and functional roles of deamidation of N146 and/or truncation of NH2- or COOH-termini in human alphaB-crystallin.* Mol Vis, 17: 2407-20.
[227] Selig, EE, Zlatic, CO, Cox, D, Mok, YF, Gooley, PR, Ecroyd, H and Griffin, MDW (2020). *N- and C-terminal regions of alphaB-crystallin and Hsp27 mediate inhibition of amyloid nucleation, fibril binding, and fibril disaggregation.* J Biol Chem, 295(29): 9838-9854. DOI: 10.1074/jbc.RA120.012748.
[228] Balchin, D, Hayer-Hartl, M and Hartl, FU (2016). *In vivo aspects of protein folding and quality control.* Science, 353(6294): aac4354. DOI: 10.1126/science.aac4354.
[229] Kim, YE, Hipp, MS, Bracher, A, Hayer-Hartl, M and Hartl, FU (2013). *Molecular chaperone functions in protein folding and proteostasis.* Annu Rev Biochem, 82: 323-55. DOI: 10.1146/annurev-biochem-060208-092442.
[230] Hipp, MS, Park, SH and Hartl, FU (2014). *Proteostasis impairment in protein-misfolding and -aggregation diseases.* Trends Cell Biol, 24(9): 506-14. DOI: 10.1016/j.tcb.2014.05.003.
[231] Jayaraj, GG, Hipp, MS and Hartl, FU (2020). *Functional Modules of the Proteostasis Network.* Cold Spring Harb Perspect Biol, 12(1). DOI: 10.1101/cshperspect.a033951.
[232] Ciryam, P, Tartaglia, GG, Morimoto, RI, Dobson, CM and Vendruscolo, M (2013). *Widespread aggregation and neurodegenerative diseases are associated with supersaturated proteins.* Cell Rep, 5(3): 781-790. DOI: 10.1016/j.celrep.2013.09.043.
[233] Chiti, F and Dobson, CM (2006). *Protein misfolding, functional amyloid, and human disease.* Annu Rev Biochem, 75: 333-66. DOI: 10.1146/annurev.biochem.75.101304.123901.
[234] Priya, S, Sharma, SK and Goloubinoff, P (2013). *Molecular chaperones as enzymes that catalytically unfold misfolded polypeptides.* FEBS Lett, 587(13): 1981-7. DOI: 10.1016/j.febslet.2013.05.014.
[235] Gregersen, N (2006). *Protein misfolding disorders: pathogenesis and intervention.* J. Inherit. Metab Dis, 29(2-3): 456-470. DOI: 10.1007/s10545-006-0301-4.
[236] Ecroyd, H and Carver, JA (2008). *Unraveling the mysteries of protein folding and misfolding.* IUBMB Life, 60(12): 769-74. DOI: 10.1002/iub.117.
[237] Hartl, FU (2017). *Protein Misfolding Diseases.* Annu Rev Biochem, 86: 21-26. DOI: 10.1146/annurev-biochem-061516-044518.
[238] Calamini, B, Silva, MC, Madoux, F, Hutt, DM, Khanna, S, Chalfant, MA, Saldanha, SA, Hodder, P, Tait, BD, Garza, D, Balch, WE and Morimoto, RI (2011). *Small-molecule proteostasis regulators for protein conformational diseases.* Nat. Chem. Biol, 8(2): 185-196. DOI: 10.1038/nchembio.763.
[239] Suss, O and Reichmann, D (2015). *Protein plasticity underlines activation and function of ATP-independent chaperones.* Front Mol Biosci, 2: 43. DOI: 10.3389/fmolb.2015.00043.
[240] Mattoo, RU and Goloubinoff, P (2014). *Molecular chaperones are nanomachines that catalytically unfold misfolded and alternatively folded proteins.* Cell Mol Life Sci, 71(17): 3311-25. DOI: 10.1007/s00018-014-1627-y.
[241] Cox, D, Carver, JA and Ecroyd, H (2014). *Preventing alpha-synuclein aggregation: the role of the small heat-shock molecular chaperone proteins.* Biochim. Biophys. Acta, 1842(9): 1830-1843. DOI: 10.1016/j.bbadis.2014.06.024.

[242] Fu, X (2014). *Chaperone function and mechanism of small heat-shock proteins.* Acta Biochim Biophys Sin (Shanghai), 46(5): 347-56. DOI: 10.1093/abbs/gmt152.

[243] Haslbeck, M, Weinkauf, S and Buchner, J (2019). *Small heat shock proteins: Simplicity meets complexity.* J Biol Chem, 294(6): 2121-2132. DOI: 10.1074/jbc.REV118.002809.

[244] Carra, S, Alberti, S, Arrigo, PA, Benesch, JL, Benjamin, IJ, Boelens, W, Bartelt-Kirbach, B, Brundel, B, Buchner, J, Bukau, B, Carver, JA, Ecroyd, H, Emanuelsson, C, Finet, S, Golenhofen, N, Goloubinoff, P, Gusev, N, Haslbeck, M, Hightower, LE, Kampinga, HH, Klevit, RE, Liberek, K, McHaourab, HS, McMenimen, KA, Poletti, A, Quinlan, R, Strelkov, SV, Toth, ME, Vierling, E and Tanguay, RM (2017). *The growing world of small heat shock proteins: from structure to functions.* Cell Stress Chaperones, 22(4): 601-611. DOI: 10.1007/s12192-017-0787-8.

[245] Raman, B, Ban, T, Sakai, M, Pasta, SY, Ramakrishna, T, Naiki, H, Goto, Y and Rao Ch, M (2005). *AlphaB-crystallin, a small heat-shock protein, prevents the amyloid fibril growth of an amyloid beta-peptide and beta2-microglobulin.* Biochem J, 392(Pt 3): 573-81. DOI: 10.1042/BJ20050339.

[246] Rekas, A, Adda, CG, Andrew Aquilina, J, Barnham, KJ, Sunde, M, Galatis, D, Williamson, NA, Masters, CL, Anders, RF, Robinson, CV, Cappai, R and Carver, JA (2004). *Interaction of the molecular chaperone alphaB-crystallin with alpha-synuclein: effects on amyloid fibril formation and chaperone activity.* J Mol Biol, 340(5): 1167-83. DOI: 10.1016/j.jmb.2004.05.054.

[247] Shammas, SL, Waudby, CA, Wang, S, Buell, AK, Knowles, TP, Ecroyd, H, Welland, ME, Carver, JA, Dobson, CM and Meehan, S (2011). *Binding of the molecular chaperone alphaB-crystallin to Abeta amyloid fibrils inhibits fibril elongation.* Biophys J, 101(7): 1681-9. DOI: 10.1016/j.bpj.2011.07.056.

[248] Waudby, CA, Knowles, TP, Devlin, GL, Skepper, JN, Ecroyd, H, Carver, JA, Welland, ME, Christodoulou, J, Dobson, CM and Meehan, S (2010). *The interaction of alphaB-crystallin with mature alpha-synuclein amyloid fibrils inhibits their elongation.* Biophys J, 98(5): 843-51. DOI: 10.1016/j.bpj.2009.10.056.

[249] Cox, D and Ecroyd, H (2017). *The small heat shock proteins alphaB-crystallin (HSPB5) and Hsp27 (HSPB1) inhibit the intracellular aggregation of alpha-synuclein.* Cell Stress Chaperones, 22(4): 589-600. DOI: 10.1007/s12192-017-0785-x.

[250] Ghosh, JG, Estrada, MR and Clark, JI (2005). *Interactive domains for chaperone activity in the small heat shock protein, human alphaB crystallin.* Biochemistry, 44(45): 14854-69. DOI: 10.1021/bi0503910.

[251] Freilich, R, Arhar, T, Abrams, JL and Gestwicki, JE (2018). *Protein-Protein Interactions in the Molecular Chaperone Network.* Acc Chem Res, 51(4): 940-949. DOI: 10.1021/acs.accounts.8b00036.

[252] Hochberg, GK, Ecroyd, H, Liu, C, Cox, D, Cascio, D, Sawaya, MR, Collier, MP, Stroud, J, Carver, JA, Baldwin, AJ, Robinson, CV, Eisenberg, DS, Benesch, JL and Laganowsky, A (2014). *The structured core domain of alphaB-crystallin can prevent amyloid fibrillation and associated toxicity.* Proc. Natl. Acad. Sci. U. S. A, 111(16): E1562-E1570. DOI: 10.1073/pnas.1322673111.

[253] Mainz, A, Peschek, J, Stavropoulou, M, Back, KC, Bardiaux, B, Asami, S, Prade, E, Peters, C, Weinkauf, S, Buchner, J and Reif, B (2015). *The chaperone alphaB-crystallin uses different interfaces to capture an amorphous and an amyloid client.* Nat Struct Mol Biol, 22(11): 898-905. DOI: 10.1038/nsmb.3108.

[254] Ghosh, JG, Shenoy, AK, Jr. and Clark, JI (2007). *Interactions between important regulatory proteins and human alphaB crystallin.* Biochemistry, 46(21): 6308-17. DOI: 10.1021/bi700149h.

[255] Sharma, KK, Kumar, GS, Murphy, AS and Kester, K (1998). *Identification of 1,1'-bi(4-anilino)naphthalene-5,5'-disulfonic acid binding sequences in alpha-crystallin.* J Biol Chem, 273(25): 15474-8. DOI: 10.1074/jbc.273.25.15474.

[256] Banerjee, PR, Pande, A, Shekhtman, A and Pande, J (2015). *Molecular mechanism of the chaperone function of mini-alpha-crystallin, a 19-residue peptide of human alpha-crystallin.* Biochemistry, 54(2): 505-15. DOI: 10.1021/bi5014479.

[257] Bhattacharyya, J, Padmanabha Udupa, EG, Wang, J and Sharma, KK (2006). *Mini-alphaB-crystallin: a functional element of alphaB-crystallin with chaperone-like activity.* Biochemistry, 45(9): 3069-76. DOI: 10.1021/bi0518141.

[258] Quinlan, RA and Ellis, RJ (2013). *Chaperones: needed for both the good times and the bad times.* Philos. Trans. R. Soc. Lond B Biol. Sci, 368(1617): 20130091. DOI: 10.1098/rstb.2013.0091.

[259] Mymrikov, EV, Daake, M, Richter, B, Haslbeck, M and Buchner, J (2017). *The Chaperone Activity and Substrate Spectrum of Human Small Heat Shock Proteins.* J Biol Chem, 292(2): 672-684. DOI: 10.1074/jbc.M116.760413.

[260] Basha, E, Lee, GJ, Breci, LA, Hausrath, AC, Buan, NR, Giese, KC and Vierling, E (2004). *The identity of proteins associated with a small heat shock protein during heat stress in vivo indicates that these chaperones protect a wide range of cellular functions.* J Biol Chem, 279(9): 7566-75. DOI: 10.1074/jbc.M310684200.

[261] Treweek, TM, Meehan, S, Ecroyd, H and Carver, JA (2015). *Small heat-shock proteins: important players in regulating cellular proteostasis.* Cell Mol Life Sci, 72(3): 429-451. DOI: 10.1007/s00018-014-1754-5.

[262] Bakthisaran, R, Tangirala, R and Rao, C (2015). *Small heat shock proteins: Role in cellular functions and pathology.* Biochim. Biophys. Acta, 1854(4): 291-319. DOI: 10.1016/j.bbapap.2014.12.019.

[263] Raju, I, Kumarasamy, A and Abraham, EC (2011). *Multiple aggregates and aggresomes of C-terminal truncated human alphaA-crystallins in mammalian cells and protection by alphaB-crystallin.* PLoS One, 6(5): e19876. DOI: 10.1371/journal.pone.0019876.

[264] Acunzo, J, Katsogiannou, M and Rocchi, P (2012). *Small heat shock proteins HSP27 (HspB1), alphaB-crystallin (HspB5) and HSP22 (HspB8) as regulators of cell death.* Int. J. Biochem. Cell Biol, 44(10): 1622-1631. DOI: 10.1016/j.biocel.2012.04.002.

[265] Zeng, L, Tan, J, Lu, W, Lu, T and Hu, Z (2013). *The potential role of small heat shock proteins in mitochondria.* Cell Signal, 25(11): 2312-9. DOI: 10.1016/j.cellsig.2013.07.027.

[266] Sreekumar, PG, Kannan, R, Kitamura, M, Spee, C, Barron, E, Ryan, SJ and Hinton, DR (2010). *alphaB crystallin is apically secreted within exosomes by polarized human retinal pigment epithelium and provides neuroprotection to adjacent cells.* PLoS. One, 5(10): e12578. DOI: 10.1371/journal.pone.0012578.

[267] Kamradt, MC, Chen, F and Cryns, VL (2001). *The small heat shock protein alpha B-crystallin negatively regulates cytochrome c- and caspase-8-dependent activation of caspase-3 by inhibiting its autoproteolytic maturation.* J Biol Chem, 276(19): 16059-63. DOI: 10.1074/jbc.C100107200.

[268] Kamradt, MC, Lu, M, Werner, ME, Kwan, T, Chen, F, Strohecker, A, Oshita, S, Wilkinson, JC, Yu, C, Oliver, PG, Duckett, CS, Buchsbaum, DJ, LoBuglio, AF, Jordan, VC and Cryns, VL (2005). *The small heat shock protein alpha B-crystallin is a novel inhibitor of TRAIL-induced apoptosis that suppresses the activation of caspase-3.* J Biol Chem, 280(12): 11059-66. DOI: 10.1074/jbc.M413382200.

[269] Mao, YW, Liu, JP, Xiang, H and Li, DW (2004). *Human alphaA- and alphaB-crystallins bind to Bax and Bcl-X(S) to sequester their translocation during staurosporine-induced apoptosis.* Cell Death Differ, 11(5): 512-26. DOI: 10.1038/sj.cdd.4401384.

[270] Liu, JP, Schlosser, R, Ma, WY, Dong, Z, Feng, H, Liu, L, Huang, XQ, Liu, Y and Li, DW (2004). *Human alphaA- and alphaB-crystallins prevent UVA-induced apoptosis through regulation of PKCalpha, RAF/MEK/ERK and AKT signaling pathways.* Exp Eye Res, 79(3): 393-403. DOI: 10.1016/j.exer.2004.06.015.

[271] Li, DW, Liu, JP, Mao, YW, Xiang, H, Wang, J, Ma, WY, Dong, Z, Pike, HM, Brown, RE and Reed, JC (2005). *Calcium-activated RAF/MEK/ERK signaling pathway mediates p53-dependent apoptosis and is abrogated by alpha B-crystallin through inhibition of RAS activation.* Mol Biol Cell, 16(9): 4437-53. DOI: 10.1091/mbc.e05-01-0010.

[272] Dou, G, Sreekumar, PG, Spee, C, He, S, Ryan, SJ, Kannan, R and Hinton, DR (2012). *Deficiency of alphaB crystallin augments ER stress-induced apoptosis by enhancing mitochondrial dysfunction.* Free Radic Biol Med, 53(5): 1111-22. DOI: 10.1016/j.freeradbiomed.2012.06.042.

[273] Liu, S, Li, J, Tao, Y and Xiao, X (2007). *Small heat shock protein alphaB-crystallin binds to p53 to sequester its translocation to mitochondria during hydrogen peroxide-induced apoptosis.* Biochem Biophys Res Commun, 354(1): 109-14. DOI: 10.1016/j.bbrc.2006.12.152.

[274] Bousette, N, Chugh, S, Fong, V, Isserlin, R, Kim, KH, Volchuk, A, Backx, PH, Liu, P, Kislinger, T, MacLennan, DH, Emili, A and Gramolini, AO (2010). *Constitutively active calcineurin*

induces cardiac endoplasmic reticulum stress and protects against apoptosis that is mediated by alpha-crystallin-B. Proc Natl Acad Sci U S A, 107(43): 18481-6. DOI: 10.1073/pnas.1013555107.

[275] Ray, PS, Martin, JL, Swanson, EA, Otani, H, Dillmann, WH and Das, DK (2001). *Transgene overexpression of alphaB crystallin confers simultaneous protection against cardiomyocyte apoptosis and necrosis during myocardial ischemia and reperfusion.* FASEB J, 15(2): 393-402. DOI: 10.1096/fj.00-0199com.

[276] Adhikari, AS, Singh, BN, Rao, KS and Rao Ch, M (2011). *alphaB-crystallin, a small heat shock protein, modulates NF-kappaB activity in a phosphorylation-dependent manner and protects muscle myoblasts from TNF-alpha induced cytotoxicity.* Biochim Biophys Acta, 1813(8): 1532-42. DOI: 10.1016/j.bbamcr.2011.04.009.

[277] Dimauro, I, Antonioni, A, Mercatelli, N and Caporossi, D (2018). *The role of alphaB-crystallin in skeletal and cardiac muscle tissues.* Cell Stress Chaperones, 23(4): 491-505. DOI: 10.1007/s12192-017-0866-x.

[278] Wojtowicz, I, Jablonska, J, Zmojdzian, M, Taghli-Lamallem, O, Renaud, Y, Junion, G, Daczewska, M, Huelsmann, S, Jagla, K and Jagla, T (2015). *Drosophila small heat shock protein CryAB ensures structural integrity of developing muscles, and proper muscle and heart performance.* Development, 142(5): 994-1005. DOI: 10.1242/dev.115352.

[279] Fernando, R, Drescher, C, Nowotny, K, Grune, T and Castro, JP (2019). *Impaired proteostasis during skeletal muscle aging.* Free Radic Biol Med, 132: 58-66. DOI: 10.1016/j.freeradbiomed.2018.08.037.

[280] Singh, BN, Rao, KS and Rao Ch, M (2010). *Ubiquitin-proteasome-mediated degradation and synthesis of MyoD is modulated by alphaB-crystallin, a small heat shock protein, during muscle differentiation.* Biochim Biophys Acta, 1803(2): 288-99. DOI: 10.1016/j.bbamcr.2009.11.009.

[281] Ikeda, R, Yoshida, K, Ushiyama, M, Yamaguchi, T, Iwashita, K, Futagawa, T, Shibayama, Y, Oiso, S, Takeda, Y, Kariyazono, H, Furukawa, T, Nakamura, K, Akiyama, S, Inoue, I and Yamada, K (2006). *The small heat shock protein alphaB-crystallin inhibits differentiation-induced caspase 3 activation and myogenic differentiation.* Biol Pharm Bull, 29(9): 1815-9.

[282] Sakurai, T, Fujita, Y, Ohto, E, Oguro, A and Atomi, Y (2005). *The decrease of the cytoskeleton tubulin follows the decrease of the associating molecular chaperone alphaB-crystallin in unloaded soleus muscle atrophy without stretch.* FASEB J, 19(9): 1199-201. DOI: 10.1096/fj.04-3060fje.

[283] Enomoto, Y, Adachi, S, Matsushima-Nishiwaki, R, Niwa, M, Tokuda, H, Akamatsu, S, Doi, T, Kato, H, Yoshimura, S, Ogura, S, Iwama, T and Kozawa, O (2009). *alphaB-crystallin extracellularly suppresses ADP-induced granule secretion from human platelets.* FEBS Lett, 583(15): 2464-8. DOI: 10.1016/j.febslet.2009.06.036.

[284] Gangalum, RK, Atanasov, IC, Zhou, ZH and Bhat, SP (2011). *AlphaB-crystallin is found in detergent-resistant membrane microdomains and is secreted via exosomes from human retinal pigment epithelial cells.* J. Biol. Chem, 286(5): 3261-3269. DOI: 10.1074/jbc.M110.160135.

[285] Willis, MS, Schisler, JC, Portbury, AL and Patterson, C (2009). *Build it up-Tear it down: protein quality control in the cardiac sarcomere.* Cardiovasc Res, 81(3): 439-48. DOI: 10.1093/cvr/cvn289.

[286] Islam, M, Diwan, A and Mani, K (2020). *Come Together: Protein Assemblies, Aggregates and the Sarcostat at the Heart of Cardiac Myocyte Homeostasis.* Front Physiol, 11: 586. DOI: 10.3389/fphys.2020.00586.

[287] Carlisle, C, Prill, K and Pilgrim, D (2017). *Chaperones and the Proteasome System: Regulating the Construction and Demolition of Striated Muscle.* Int J Mol Sci, 19(1). DOI: 10.3390/ijms19010032.

[288] Collier, MP and Benesch, JLP (2020). *Small heat-shock proteins and their role in mechanical stress.* Cell Stress Chaperones, 25(4): 601-613. DOI: 10.1007/s12192-020-01095-z.

[289] Singh, BN, Rao, KS, Ramakrishna, T, Rangaraj, N and Rao Ch, M (2007). *Association of alphaB-crystallin, a small heat shock protein, with actin: role in modulating actin filament dynamics in vivo.* J Mol Biol, 366(3): 756-67. DOI: 10.1016/j.jmb.2006.12.012.

[290] Bennardini, F, Wrzosek, A and Chiesi, M (1992). *Alpha B-crystallin in cardiac tissue. Association with actin and desmin filaments.* Circ Res, 71(2): 288-94. DOI: 10.1161/01.res.71.2.288.

[291] Melkani, GC, Cammarato, A and Bernstein, SI (2006). *alphaB-crystallin maintains skeletal muscle myosin enzymatic activity and prevents its aggregation under heat-shock stress.* J Mol Biol, 358(3): 635-45. DOI: 10.1016/j.jmb.2006.02.043.

[292] Bullard, B, Ferguson, C, Minajeva, A, Leake, MC, Gautel, M, Labeit, D, Ding, L, Labeit, S, Horwitz, J, Leonard, KR and Linke, WA (2004). *Association of the chaperone alphaB-crystallin with titin in heart muscle.* J Biol Chem, 279(9): 7917-24. DOI: 10.1074/jbc.M307473200.

[293] Golenhofen, N, Arbeiter, A, Koob, R and Drenckhahn, D (2002). *Ischemia-induced association of the stress protein alpha B-crystallin with I-band portion of cardiac titin.* J Mol Cell Cardiol, 34(3): 309-19. DOI: 10.1006/jmcc.2001.1513.

[294] den Engelsman, J, Keijsers, V, de Jong, WW and Boelens, WC (2003). *The small heat-shock protein alpha B-crystallin promotes FBX4-dependent ubiquitination.* J Biol Chem, 278(7): 4699-704. DOI: 10.1074/jbc.M211403200.

[295] Shimizu, M, Tanaka, M and Atomi, Y (2016). *Small Heat Shock Protein alphaB-Crystallin Controls Shape and Adhesion of Glioma and Myoblast Cells in the Absence of Stress.* PLoS One, 11(12): e0168136. DOI: 10.1371/journal.pone.0168136.

[296] Hohfeld, J, Benzing, T, Bloch, W, Furst, DO, Gehlert, S, Hesse, M, Hoffmann, B, Hoppe, T, Huesgen, PF, Kohn, M, Kolanus, W, Merkel, R, Niessen, CM, Pokrzywa, W, Rinschen, MM, Wachten, D and Warscheid, B (2021). *Maintaining proteostasis under mechanical stress.* EMBO Rep, 22(8): e52507. DOI: 10.15252/embr.202152507.

[297] Atomi, Y, Yamada, S, Strohman, R and Nonomura, Y (1991). *Alpha B-crystallin in skeletal muscle: purification and localization.* J Biochem, 110(5): 812-22. DOI: 10.1093/oxfordjournals.jbchem.a123665.

[298] van de Klundert, FA, Gijsen, ML, van den, IPR, Snoeckx, LH and de Jong, WW (1998). *alpha B-crystallin and hsp25 in neonatal cardiac cells--differences in cellular localization under stress conditions.* Eur J Cell Biol, 75(1): 38-45. DOI: 10.1016/s0171-9335(98)80044-7.

[299] Ohto-Fujita, E, Hayasaki, S, Atomi, A, Fujiki, S, Watanabe, T, Boelens, WC, Shimizu, M and Atomi, Y (2020). *Dynamic localization of alphaB-crystallin at the microtubule cytoskeleton network in beating heart cells.* J Biochem, 168(2): 125-137. DOI: 10.1093/jb/mvaa025.

[300] Adhikari, AS, Sridhar Rao, K, Rangaraj, N, Parnaik, VK and Mohan Rao, C (2004). *Heat stress-induced localization of small heat shock proteins in mouse myoblasts: intranuclear lamin A/C speckles as target for alphaB-crystallin and Hsp25.* Exp Cell Res, 299(2): 393-403. DOI: 10.1016/j.yexcr.2004.05.032.

[301] D'Amico, D, Fiore, R, Caporossi, D, Di Felice, VD, Cappello, F, Dimauro, I and Barone, R (2021). *Function and Fiber-Type Specific Distribution of Hsp60 and alphaB-Crystallin in Skeletal Muscles: Role of Physical Exercise.* Biology (Basel), 10(2). DOI: 10.3390/biology10020077.

[302] Koh, TJ and Escobedo, J (2004). *Cytoskeletal disruption and small heat shock protein translocation immediately after lengthening contractions.* Am J Physiol Cell Physiol, 286(3): C713-22. DOI: 10.1152/ajpcell.00341.2003.

[303] Paulsen, G, Lauritzen, F, Bayer, ML, Kalhovde, JM, Ugelstad, I, Owe, SG, Hallen, J, Bergersen, LH and Raastad, T (2009). *Subcellular movement and expression of HSP27, alphaB-crystallin, and HSP70 after two bouts of eccentric exercise in humans.* J Appl Physiol (1985), 107(2): 570-82. DOI: 10.1152/japplphysiol.00209.2009.

[304] Jacko, D, Bersiner, K, Hebchen, J, de Marees, M, Bloch, W and Gehlert, S (2019). *Phosphorylation of alphaB-crystallin and its cytoskeleton association differs in skeletal myofiber types depending on resistance exercise intensity and volume.* J Appl Physiol (1985), 126(6): 1607-1618. DOI: 10.1152/japplphysiol.01038.2018.

[305] Dimauro, I, Antonioni, A, Mercatelli, N, Grazioli, E, Fantini, C, Barone, R, Macaluso, F, Di Felice, V and Caporossi, D (2019). *The early response of alphaB-crystallin to a single bout of aerobic exercise in mouse skeletal muscles depends upon fiber oxidative features.* Redox Biol, 24: 101183. DOI: 10.1016/j.redox.2019.101183.

[306] Folkesson, M, Mackey, AL, Langberg, H, Oskarsson, E, Piehl-Aulin, K, Henriksson, J and Kadi, F (2013). *The expression of heat shock protein in human skeletal muscle: effects of muscle fibre phenotype and training background.* Acta Physiol (Oxf), 209(1): 26-33. DOI: 10.1111/apha.12124.

[307] Neufer, PD and Benjamin, IJ (1996). *Differential expression of B-crystallin and Hsp27 in skeletal muscle during continuous contractile activity. Relationship to myogenic regulatory factors.* J Biol Chem, 271(39): 24089-95. DOI: 10.1074/jbc.271.39.24089.

[308] Frankenberg, NT, Lamb, GD, Overgaard, K, Murphy, RM and Vissing, K (2014). *Small heat shock proteins translocate to the cytoskeleton in human skeletal muscle following eccentric exercise independently of phosphorylation.* J. Appl. Physiol (1985.), 116(11): 1463-1472. DOI: 10.1152/japplphysiol.01026.2013.

[309] Wiig, H, Cumming, KT, Handegaard, V, Stabell, J, Spencer, M and Raastad, T (2022). *Muscular heat shock protein response and muscle damage after semi-professional football match.* Scand J Med Sci Sports, 32(6): 984-996. DOI: 10.1111/sms.14148.

[310] Nicholl, ID and Quinlan, RA (1994). *Chaperone activity of alpha-crystallins modulates intermediate filament assembly.* EMBO J, 13(4): 945-53.

[311] Perng, MD, Cairns, L, van den, IJ, Prescott, A, Hutcheson, AM and Quinlan, RA (1999). *Intermediate filament interactions can be altered by HSP27 and alphaB-crystallin.* J. Cell Sci, 112 (Pt 13): 2099-2112.

[312] Wettstein, G, Bellaye, PS, Micheau, O and Bonniaud, P (2012). *Small heat shock proteins and the cytoskeleton: an essential interplay for cell integrity?* Int. J. Biochem. Cell Biol, 44(10): 1680-1686. DOI: 10.1016/j.biocel.2012.05.024.

[313] Landsbury, A, Perng, MD, Pohl, E and Quinlan, RA, *Functional symbiosis between the intermediate filament cytoskeleton and small heat shock proteins.*, in *In S. Simon & A. P. Arigo (Eds.), New York: Nova Science*. 2010. p. 55-87.

[314] Sharma, S, Conover, GM, Elliott, JL, Der Perng, M, Herrmann, H and Quinlan, RA (2017). *alphaB-crystallin is a sensor for assembly intermediates and for the subunit topology of desmin intermediate filaments.* Cell Stress Chaperones, 22(4): 613-626. DOI: 10.1007/s12192-017-0788-7.

[315] Djabali, K, de Nechaud, B, Landon, F and Portier, MM (1997). *AlphaB-crystallin interacts with intermediate filaments in response to stress.* J Cell Sci, 110 (Pt 21): 2759-69. DOI: 10.1242/jcs.110.21.2759.

[316] Perng, MD, Muchowski, PJ, van Den, IP, Wu, GJ, Hutcheson, AM, Clark, JI and Quinlan, RA (1999). *The cardiomyopathy and lens cataract mutation in alphaB-crystallin alters its protein structure, chaperone activity, and interaction with intermediate filaments in vitro.* J Biol Chem, 274(47): 33235-43. DOI: 10.1074/jbc.274.47.33235.

[317] Perng, MD, Wen, SF, van den, IP, Prescott, AR and Quinlan, RA (2004). *Desmin aggregate formation by R120G alphaB-crystallin is caused by altered filament interactions and is dependent upon network status in cells.* Mol Biol Cell, 15(5): 2335-46. DOI: 10.1091/mbc.E03-12-0893.

[318] Diokmetzidou, A, Soumaka, E, Kloukina, I, Tsikitis, M, Makridakis, M, Varela, A, Davos, CH, Georgopoulos, S, Anesti, V, Vlahou, A and Capetanaki, Y (2016). *Desmin and alphaB-crystallin interplay in the maintenance of mitochondrial homeostasis and cardiomyocyte survival.* J Cell Sci, 129(20): 3705-3720. DOI: 10.1242/jcs.192203.

[319] Clark, JI (2016). *Functional sequences in human alphaB crystallin.* Biochim Biophys Acta, 1860(1 Pt B): 240-5. DOI: 10.1016/j.bbagen.2015.08.014.

[320] Ghosh, JG, Houck, SA and Clark, JI (2007). *Interactive domains in the molecular chaperone human alphaB crystallin modulate microtubule assembly and disassembly.* PLoS One, 2(6): e498. DOI: 10.1371/journal.pone.0000498.

[321] Ghosh, JG, Houck, SA and Clark, JI (2007). *Interactive sequences in the stress protein and molecular chaperone human alphaB crystallin recognize and modulate the assembly of filaments.* Int J Biochem Cell Biol, 39(10): 1804-15. DOI: 10.1016/j.biocel.2007.04.027.

[322] Houck, SA, Landsbury, A, Clark, JI and Quinlan, RA (2011). *Multiple sites in alphaB-crystallin modulate its interactions with desmin filaments assembled in vitro.* PLoS. One, 6(11): e25859. DOI: 10.1371/journal.pone.0025859.

[323] Inagaki, N, Hayashi, T, Arimura, T, Koga, Y, Takahashi, M, Shibata, H, Teraoka, K, Chikamori, T, Yamashina, A and Kimura, A (2006). *Alpha B-crystallin mutation in dilated cardiomyopathy.* Biochem Biophys Res Commun, 342(2): 379-86. DOI: 10.1016/j.bbrc.2006.01.154.

[324] Vicart, P, Caron, A, Guicheney, P, Li, Z, Prevost, MC, Faure, A, Chateau, D, Chapon, F, Tome, F, Dupret, JM, Paulin, D and Fardeau, M (1998). *A missense mutation in the alphaB-crystallin*

chaperone gene causes a desmin-related myopathy. Nat. Genet, 20(1): 92-95. DOI: 10.1038/1765.

[325] Wang, X, Osinska, H, Klevitsky, R, Gerdes, AM, Nieman, M, Lorenz, J, Hewett, T and Robbins, J (2001). *Expression of R120G-alphaB-crystallin causes aberrant desmin and alphaB-crystallin aggregation and cardiomyopathy in mice.* Circ Res, 89(1): 84-91. DOI: 10.1161/hh1301.092688.

[326] Kato, K, Ito, H, Kamei, K, Inaguma, Y, Iwamoto, I and Saga, S (1998). *Phosphorylation of alphaB-crystallin in mitotic cells and identification of enzymatic activities responsible for phosphorylation.* J Biol Chem, 273(43): 28346-54. DOI: 10.1074/jbc.273.43.28346.

[327] Ito, H, Okamoto, K, Nakayama, H, Isobe, T and Kato, K (1997). *Phosphorylation of alphaB-crystallin in response to various types of stress.* J Biol Chem, 272(47): 29934-41. DOI: 10.1074/jbc.272.47.29934.

[328] Bakthisaran, R, Akula, KK, Tangirala, R and Rao, C (2016). *Phosphorylation of alphaB-crystallin: Role in stress, aging and patho-physiological conditions.* Biochim. Biophys. Acta, 1860(1 Pt B): 167-182. DOI: 10.1016/j.bbagen.2015.09.017.

[329] Ito, H, Kamei, K, Iwamoto, I, Inaguma, Y and Kato, K (2001). *Regulation of the levels of small heat-shock proteins during differentiation of C2C12 cells.* Exp Cell Res, 266(2): 213-21. DOI: 10.1006/excr.2001.5220.

[330] Simon, S, Fontaine, JM, Martin, JL, Sun, X, Hoppe, AD, Welsh, MJ, Benndorf, R and Vicart, P (2007). *Myopathy-associated alphaB-crystallin mutants: abnormal phosphorylation, intracellular location, and interactions with other small heat shock proteins.* J Biol Chem, 282(47): 34276-87. DOI: 10.1074/jbc.M703267200.

[331] den Engelsman, J, Bennink, EJ, Doerwald, L, Onnekink, C, Wunderink, L, Andley, UP, Kato, K, de Jong, WW and Boelens, WC (2004). *Mimicking phosphorylation of the small heat-shock protein alphaB-crystallin recruits the F-box protein FBX4 to nuclear SC35 speckles.* Eur J Biochem, 271(21): 4195-203. DOI: 10.1111/j.1432-1033.2004.04359.x.

[332] Launay, N, Goudeau, B, Kato, K, Vicart, P and Lilienbaum, A (2006). *Cell signaling pathways to alphaB-crystallin following stresses of the cytoskeleton.* Exp. Cell Res, 312(18): 3570-3584. DOI: 10.1016/j.yexcr.2006.07.025.

[333] Morrison, LE, Hoover, HE, Thuerauf, DJ and Glembotski, CC (2003). *Mimicking phosphorylation of alphaB-crystallin on serine-59 is necessary and sufficient to provide maximal protection of cardiac myocytes from apoptosis.* Circ Res, 92(2): 203-11. DOI: 10.1161/01.res.0000052989.83995.a5.

[334] Antonioni, A, Dimauro, I, Fantini, C, Barone, R, Macaluso, F, Di Felice, V and Caporossi, D (2020). *alphaB-crystallin response to a pro-oxidant non-cytotoxic environment in murine cardiac cells: An "in vitro" and "in vivo" study.* Free Radic Biol Med, 152: 301-312. DOI: 10.1016/j.freeradbiomed.2020.03.013.

[335] Hoover, HE, Thuerauf, DJ, Martindale, JJ and Glembotski, CC (2000). *alpha B-crystallin gene induction and phosphorylation by MKK6-activated p38. A potential role for alpha B-crystallin as a target of the p38 branch of the cardiac stress response.* J Biol Chem, 275(31): 23825-33. DOI: 10.1074/jbc.M003864200.

[336] Golenhofen, N, Ness, W, Koob, R, Htun, P, Schaper, W and Drenckhahn, D (1998). *Ischemia-induced phosphorylation and translocation of stress protein alpha B-crystallin to Z lines of myocardium.* Am J Physiol, 274(5): H1457-64. DOI: 10.1152/ajpheart.1998.274.5.H1457.

[337] Reddy, VS, Kumar Ch, U, Raghu, G and Reddy, GB (2014). *Expression and induction of small heat shock proteins in rat heart under chronic hyperglycemic conditions.* Arch Biochem Biophys, 558: 1-9. DOI: 10.1016/j.abb.2014.06.008.

[338] Dohke, T, Wada, A, Isono, T, Fujii, M, Yamamoto, T, Tsutamoto, T and Horie, M (2006). *Proteomic analysis reveals significant alternations of cardiac small heat shock protein expression in congestive heart failure.* J Card Fail, 12(1): 77-84. DOI: 10.1016/j.cardfail.2005.07.006.

[339] Marunouchi, T, Abe, Y, Murata, M, Inomata, S, Sanbe, A, Takagi, N and Tanonaka, K (2013). *Changes in small heat shock proteins HSPB1, HSPB5 and HSPB8 in mitochondria of the failing heart following myocardial infarction in rats.* Biol Pharm Bull, 36(4): 529-39.

[340] Clements, RT, Sodha, NR, Feng, J, Mieno, S, Boodhwani, M, Ramlawi, B, Bianchi, C and Sellke, FW (2007). *Phosphorylation and translocation of heat shock protein 27 and alphaB-crystallin in*

human myocardium after cardioplegia and cardiopulmonary bypass. J Thorac Cardiovasc Surg, 134(6): 1461-70. DOI: 10.1016/j.jtcvs.2007.06.026.

[341] Eaton, P, Fuller, W, Bell, JR and Shattock, MJ (2001). *AlphaB crystallin translocation and phosphorylation: signal transduction pathways and preconditioning in the isolated rat heart.* J Mol Cell Cardiol, 33(9): 1659-71. DOI: 10.1006/jmcc.2001.1418.

[342] White, MY, Hambly, BD, Jeremy, RW and Cordwell, SJ (2006). *Ischemia-specific phosphorylation and myofilament translocation of heat shock protein 27 precedes alpha B-crystallin and occurs independently of reactive oxygen species in rabbit myocardium.* J Mol Cell Cardiol, 40(6): 761-74. DOI: 10.1016/j.yjmcc.2006.02.007.

[343] Dimauro, I, Grasso, L, Fittipaldi, S, Fantini, C, Mercatelli, N, Racca, S, Geuna, S, Di Gianfrancesco, A, Caporossi, D, Pigozzi, F and Borrione, P (2014). *Platelet-rich plasma and skeletal muscle healing: a molecular analysis of the early phases of the regeneration process in an experimental animal model.* PLoS One, 9(7): e102993. DOI: 10.1371/journal.pone.0102993.

[344] Jacko, D, Bersiner, K, Schulz, O, Przyklenk, A, Spahiu, F, Hohfeld, J, Bloch, W and Gehlert, S (2020). *Coordinated alpha-crystallin B phosphorylation and desmin expression indicate adaptation and deadaptation to resistance exercise-induced loading in human skeletal muscle.* Am J Physiol Cell Physiol, 319(2): C300-C312. DOI: 10.1152/ajpcell.00087.2020.

[345] Golenhofen, N, Htun, P, Ness, W, Koob, R, Schaper, W and Drenckhahn, D (1999). *Binding of the stress protein alpha B-crystallin to cardiac myofibrils correlates with the degree of myocardial damage during ischemia/reperfusion in vivo.* J Mol Cell Cardiol, 31(3): 569-80. DOI: 10.1006/jmcc.1998.0892.

[346] Koteiche, HA and McHaourab, HS (2003). *Mechanism of chaperone function in small heat-shock proteins. Phosphorylation-induced activation of two-mode binding in alphaB-crystallin.* J Biol Chem, 278(12): 10361-7. DOI: 10.1074/jbc.M211851200.

[347] Ciano, M, Allocca, S, Ciardulli, MC, Della, VL, Bonatti, S and D'Agostino, M (2016). *Differential phosphorylation-based regulation of alphaB-crystallin chaperone activity for multipass transmembrane proteins.* Biochem. Biophys. Res. Commun, 479(2): 325-330. DOI: 10.1016/j.bbrc.2016.09.071.

[348] Jin, JK, Whittaker, R, Glassy, MS, Barlow, SB, Gottlieb, RA and Glembotski, CC (2008). *Localization of phosphorylated alphaB-crystallin to heart mitochondria during ischemia-reperfusion.* Am J Physiol Heart Circ Physiol, 294(1): H337-44. DOI: 10.1152/ajpheart.00881.2007.

[349] Whittaker, R, Glassy, MS, Gude, N, Sussman, MA, Gottlieb, RA and Glembotski, CC (2009). *Kinetics of the translocation and phosphorylation of alphaB-crystallin in mouse heart mitochondria during ex vivo ischemia.* Am J Physiol Heart Circ Physiol, 296(5): H1633-42. DOI: 10.1152/ajpheart.01227.2008.

[350] Roquemore, EP, Dell, A, Morris, HR, Panico, M, Reason, AJ, Savoy, LA, Wistow, GJ, Zigler, JS, Jr., Earles, BJ and Hart, GW (1992). *Vertebrate lens alpha-crystallins are modified by O-linked N-acetylglucosamine.* J Biol Chem, 267(1): 555-63.

[351] Roquemore, EP, Chevrier, MR, Cotter, RJ and Hart, GW (1996). *Dynamic O-GlcNAcylation of the small heat shock protein alpha B-crystallin.* Biochemistry, 35(11): 3578-3586. DOI: 10.1021/bi951918j.

[352] Cieniewski-Bernard, C, Bastide, B, Lefebvre, T, Lemoine, J, Mounier, Y and Michalski, JC (2004). *Identification of O-linked N-acetylglucosamine proteins in rat skeletal muscle using two-dimensional gel electrophoresis and mass spectrometry.* Mol. Cell Proteomics, 3(6): 577-585. DOI: 10.1074/mcp.M400024-MCP200.

[353] Tarbet, HJ, Toleman, CA and Boyce, M (2018). *A Sweet Embrace: Control of Protein-Protein Interactions by O-Linked beta-N-Acetylglucosamine.* Biochemistry, 57(1): 13-21. DOI: 10.1021/acs.biochem.7b00871.

[354] Yu, SH, Boyce, M, Wands, AM, Bond, MR, Bertozzi, CR and Kohler, JJ (2012). *Metabolic labeling enables selective photocrosslinking of O-GlcNAc-modified proteins to their binding partners.* Proc Natl Acad Sci U S A, 109(13): 4834-9. DOI: 10.1073/pnas.1114356109.

[355] Krishnamoorthy, V, Donofrio, AJ and Martin, JL (2013). *O-GlcNAcylation of alphaB-crystallin regulates its stress-induced translocation and cytoprotection.* Mol Cell Biochem, 379(1-2): 59-68. DOI: 10.1007/s11010-013-1627-5.

[356] Balana, AT, Levine, PM, Craven, TW, Mukherjee, S, Pedowitz, NJ, Moon, SP, Takahashi, TT, Becker, CFW, Baker, D and Pratt, MR (2021). *O-GlcNAc modification of small heat shock proteins enhances their anti-amyloid chaperone activity.* Nat Chem. DOI: 10.1038/s41557-021-00648-8.

[357] Reddy, VS, Madala, SK, Trinath, J and Reddy, GB (2018). *Extracellular small heat shock proteins: exosomal biogenesis and function.* Cell Stress Chaperones, 23(3): 441-454. DOI: 10.1007/s12192-017-0856-z.

[358] Malik, ZA, Kott, KS, Poe, AJ, Kuo, T, Chen, L, Ferrara, KW and Knowlton, AA (2013). *Cardiac myocyte exosomes: stability, HSP60, and proteomics.* Am J Physiol Heart Circ Physiol, 304(7): H954-65. DOI: 10.1152/ajpheart.00835.2012.

[359] Kore, RA and Abraham, EC (2016). *Phosphorylation negatively regulates exosome mediated secretion of cryAB in glioma cells.* Biochim Biophys Acta, 1863(2): 368-77. DOI: 10.1016/j.bbamcr.2015.11.027.

[360] Gupta, R and Srivastava, OP (2004). *Effect of deamidation of asparagine 146 on functional and structural properties of human lens alphaB-crystallin.* Invest Ophthalmol Vis Sci, 45(1): 206-14. DOI: 10.1167/iovs.03-0720.

[361] Wilmarth, PA, Tanner, S, Dasari, S, Nagalla, SR, Riviere, MA, Bafna, V, Pevzner, PA and David, LL (2006). *Age-related changes in human crystallins determined from comparative analysis of post-translational modifications in young and aged lens: does deamidation contribute to crystallin insolubility?* J Proteome Res, 5(10): 2554-66. DOI: 10.1021/pr050473a.

[362] White, MY, Tchen, AS, McCarron, HC, Hambly, BD, Jeremy, RW and Cordwell, SJ (2006). *Proteomics of ischemia and reperfusion injuries in rabbit myocardium with and without intervention by an oxygen-free radical scavenger.* Proteomics, 6(23): 6221-33. DOI: 10.1002/pmic.200600219.

[363] Nandi, SK, Rakete, S, Nahomi, RB, Michel, C, Dunbar, A, Fritz, KS and Nagaraj, RH (2019). *Succinylation Is a Gain-of-Function Modification in Human Lens alphaB-Crystallin.* Biochemistry, 58(9): 1260-1274. DOI: 10.1021/acs.biochem.8b01053.

[364] Nahomi, RB, Huang, R, Nandi, SK, Wang, B, Padmanabha, S, Santhoshkumar, P, Filipek, S, Biswas, A and Nagaraj, RH (2013). *Acetylation of lysine 92 improves the chaperone and anti-apoptotic activities of human alphaB-crystallin.* Biochemistry, 52(45): 8126-38. DOI: 10.1021/bi400638s.

[365] Nahomi, RB, Oya-Ito, T and Nagaraj, RH (2013). *The combined effect of acetylation and glycation on the chaperone and anti-apoptotic functions of human alpha-crystallin.* Biochim Biophys Acta, 1832(1): 195-203. DOI: 10.1016/j.bbadis.2012.08.015.

[366] Bhattacharyya, J, Shipova, EV, Santhoshkumar, P, Sharma, KK and Ortwerth, BJ (2007). *Effect of a single AGE modification on the structure and chaperone activity of human alphaB-crystallin.* Biochemistry, 46(50): 14682-92. DOI: 10.1021/bi701326b.

[367] Lapko, VN, Smith, DL and Smith, JB (2001). *In vivo carbamylation and acetylation of water-soluble human lens alphaB-crystallin lysine 92.* Protein Sci, 10(6): 1130-6. DOI: 10.1110/ps.40901.

[368] Thornell, E and Aquilina, A (2015). *Regulation of alphaA- and alphaB-crystallins via phosphorylation in cellular homeostasis.* Cell Mol Life Sci, 72(21): 4127-4137. DOI: 10.1007/s00018-015-1996-x.

[369] Bunkenborg, J, Falkenby, LG, Harder, LM and Molina, H (2016). *Covalent perturbation as a tool for validation of identifications and PTM mapping applied to bovine alpha-crystallin.* Proteomics, 16(4): 545-553. DOI: 10.1002/pmic.201500068.

[370] Muranova, LK, Sudnitsyna, MV and Gusev, NB (2018). *alphaB-Crystallin Phosphorylation: Advances and Problems.* Biochemistry (Mosc), 83(10): 1196-1206. DOI: 10.1134/S000629791810005X.

[371] Anbarasu, K and Sivakumar, J (2016). *Multidimensional significance of crystallin protein-protein interactions and their implications in various human diseases.* Biochim. Biophys. Acta, 1860(1 Pt B): 222-233. DOI: 10.1016/j.bbagen.2015.09.005.

[372] Garrido, C, Paul, C, Seigneuric, R and Kampinga, HH (2012). *The small heat shock proteins family: the long forgotten chaperones.* Int. J. Biochem. Cell Biol, 44(10): 1588-1592. DOI: 10.1016/j.biocel.2012.02.022.

[373] Ecroyd, H and Carver, JA (2009). *Crystallin proteins and amyloid fibrils.* Cell Mol Life Sci, 66(1): 62-81. DOI: 10.1007/s00018-008-8327-4.

[374] Boncoraglio, A, Minoia, M and Carra, S (2012). *The family of mammalian small heat shock proteins (HSPBs): implications in protein deposit diseases and motor neuropathies.* Int J Biochem Cell Biol, 44(10): 1657-69. DOI: 10.1016/j.biocel.2012.03.011.

[375] Fischer, C, Kleinschnitz, K, Wrede, A, Muth, I, Kruse, N, Nishino, I and Schmidt, J (2013). *Cell stress molecules in the skeletal muscle of GNE myopathy*. BMC Neurol, 13: 24. DOI: 10.1186/1471-2377-13-24.

[376] Fischer, D, Matten, J, Reimann, J, Bonnemann, C and Schroder, R (2002). *Expression, localization and functional divergence of alphaB-crystallin and heat shock protein 27 in core myopathies and neurogenic atrophy.* Acta Neuropathol, 104(3): 297-304. DOI: 10.1007/s00401-002-0559-z.

[377] Brinkmeier, H and Ohlendieck, K (2014). *Chaperoning heat shock proteins: proteomic analysis and relevance for normal and dystrophin-deficient muscle.* Proteomics Clin Appl, 8(11-12): 875-95. DOI: 10.1002/prca.201400015.

[378] Unger, A, Beckendorf, L, Bohme, P, Kley, R, von Frieling-Salewsky, M, Lochmuller, H, Schroder, R, Furst, DO, Vorgerd, M and Linke, WA (2017). *Translocation of molecular chaperones to the titin springs is common in skeletal myopathy patients and affects sarcomere function.* Acta Neuropathol Commun, 5(1): 72. DOI: 10.1186/s40478-017-0474-0.

[379] Pilotto, A, Marziliano, N, Pasotti, M, Grasso, M, Costante, AM and Arbustini, E (2006). *alphaB-crystallin mutation in dilated cardiomyopathies: low prevalence in a consecutive series of 200 unrelated probands.* Biochem Biophys Res Commun, 346(4): 1115-7. DOI: 10.1016/j.bbrc.2006.05.203.

[380] Reilich, P, Schoser, B, Schramm, N, Krause, S, Schessl, J, Kress, W, Muller-Hocker, J, Walter, MC and Lochmuller, H (2010). *The p.G154S mutation of the alpha-B crystallin gene (CRYAB) causes late-onset distal myopathy.* Neuromuscul Disord, 20(4): 255-9. DOI: 10.1016/j.nmd.2010.01.012.

[381] Mitzelfelt, KA, Limphong, P, Choi, MJ, Kondrat, FD, Lai, S, Kolander, KD, Kwok, WM, Dai, Q, Grzybowski, MN, Zhang, H, Taylor, GM, Lui, Q, Thao, MT, Hudson, JA, Barresi, R, Bushby, K, Jungbluth, H, Wraige, E, Geurts, AM, Benesch, JL, Riedel, M, Christians, ES, Minella, AC and Benjamin, IJ (2016). *The Human 343delT HSPB5 Chaperone Associated with Early-onset Skeletal Myopathy Causes Defects in Protein Solubility.* J Biol Chem, 291(29): 14939-53. DOI: 10.1074/jbc.M116.730481.

[382] Forrest, KM, Al-Sarraj, S, Sewry, C, Buk, S, Tan, SV, Pitt, M, Durward, A, McDougall, M, Irving, M, Hanna, MG, Matthews, E, Sarkozy, A, Hudson, J, Barresi, R, Bushby, K, Jungbluth, H and Wraige, E (2011). *Infantile onset myofibrillar myopathy due to recessive CRYAB mutations.* Neuromuscul Disord, 21(1): 37-40. DOI: 10.1016/j.nmd.2010.11.003.

[383] Sacconi, S, Feasson, L, Antoine, JC, Pecheux, C, Bernard, R, Cobo, AM, Casarin, A, Salviati, L, Desnuelle, C and Urtizberea, A (2012). *A novel CRYAB mutation resulting in multisystemic disease.* Neuromuscul Disord, 22(1): 66-72. DOI: 10.1016/j.nmd.2011.07.004.

[384] Fichna, JP, Potulska-Chromik, A, Miszta, P, Redowicz, MJ, Kaminska, AM, Zekanowski, C and Filipek, S (2017). *A novel dominant D109A CRYAB mutation in a family with myofibrillar myopathy affects alphaB-crystallin structure.* BBA Clin, 7: 1-7. DOI: 10.1016/j.bbacli.2016.11.004.

[385] Brodehl, A, Gaertner-Rommel, A, Klauke, B, Grewe, SA, Schirmer, I, Peterschroder, A, Faber, L, Vorgerd, M, Gummert, J, Anselmetti, D, Schulz, U, Paluszkiewicz, L and Milting, H (2017). *The novel alphaB-crystallin (CRYAB) mutation p.D109G causes restrictive cardiomyopathy.* Hum Mutat, 38(8): 947-952. DOI: 10.1002/humu.23248.

[386] van der Smagt, JJ, Vink, A, Kirkels, JH, Nelen, M, ter Heide, H, Molenschot, MM, Weger, RA, Schellekens, PA, Hoogendijk, J and Dooijes, D (2014). *Congenital posterior pole cataract and adult onset dilating cardiomyopathy: expanding the phenotype of alphaB-crystallinopathies.* Clin Genet, 85(4): 381-5. DOI: 10.1111/cge.12169.

[387] Ma, K, Luo, D, Tian, T, Li, N, He, X, Rao, C, Zhong, B and Lu, X (2019). *A novel homozygous initiation codon variant associated with infantile alpha-Bcrystallinopathy in a Chinese family.* Mol Genet Genomic Med, 7(8): e825. DOI: 10.1002/mgg3.825.

[388] Del Bigio, MR, Chudley, AE, Sarnat, HB, Campbell, C, Goobie, S, Chodirker, BN and Selcen, D (2011). *Infantile muscular dystrophy in Canadian aboriginals is an alphaB-crystallinopathy.* Ann Neurol, 69(5): 866-71. DOI: 10.1002/ana.22331.

[389] Tedesco, B, Cristofani, R, Ferrari, V, Cozzi, M, Rusmini, P, Casarotto, E, Chierichetti, M, Mina, F, Galbiati, M, Piccolella, M, Crippa, V and Poletti, A (2022). *Insights on Human Small Heat Shock Proteins and Their Alterations in Diseases.* Front Mol Biosci, 9: 842149. DOI: 10.3389/fmolb.2022.842149.

[390] Datskevich, PN, Nefedova, VV, Sudnitsyna, MV and Gusev, NB (2012). *Mutations of small heat shock proteins and human congenital diseases.* Biochemistry (Mosc), 77(13): 1500-14. DOI: 10.1134/S0006297912130081.

[391] Schroder, R and Schoser, B (2009). *Myofibrillar myopathies: a clinical and myopathological guide.* Brain Pathol, 19(3): 483-492. DOI: 10.1111/j.1750-3639.2009.00289.x.

[392] Claeys, KG and Fardeau, M (2013). *Myofibrillar myopathies.* Handb Clin Neurol, 113: 1337-42. DOI: 10.1016/B978-0-444-59565-2.00005-8.

[393] Claeys, KG, van der Ven, PF, Behin, A, Stojkovic, T, Eymard, B, Dubourg, O, Laforet, P, Faulkner, G, Richard, P, Vicart, P, Romero, NB, Stoltenburg, G, Udd, B, Fardeau, M, Voit, T and Furst, DO (2009). *Differential involvement of sarcomeric proteins in myofibrillar myopathies: a morphological and immunohistochemical study.* Acta Neuropathol, 117(3): 293-307. DOI: 10.1007/s00401-008-0479-7.

[394] Sarparanta, J, Jonson, PH, Kawan, S and Udd, B (2020). *Neuromuscular Diseases Due to Chaperone Mutations: A Review and Some New Results.* Int J Mol Sci, 21(4). DOI: 10.3390/ijms21041409.

[395] Sanbe, A (2011). *Molecular mechanisms of alpha-crystallinopathy and its therapeutic strategy.* Biol Pharm Bull, 34(11): 1653-8. DOI: 10.1248/bpb.34.1653.

[396] Batonnet-Pichon, S, Behin, A, Cabet, E, Delort, F, Vicart, P and Lilienbaum, A (2017). *Myofibrillar Myopathies: New Perspectives from Animal Models to Potential Therapeutic Approaches.* J Neuromuscul Dis, 4(1): 1-15. DOI: 10.3233/JND-160203.

[397] Benndorf, R, Martin, JL, Kosakovsky Pond, SL and Wertheim, JO (2014). *Neuropathy- and myopathy-associated mutations in human small heat shock proteins: Characteristics and evolutionary history of the mutation sites.* Mutat Res Rev Mutat Res, 761: 15-30. DOI: 10.1016/j.mrrev.2014.02.004.

[398] Clemen, CS, Fischer, D, Roth, U, Simon, S, Vicart, P, Kato, K, Kaminska, AM, Vorgerd, M, Goldfarb, LG, Eymard, B, Romero, NB, Goudeau, B, Eggermann, T, Zerres, K, Noegel, AA and Schroder, R (2005). *Hsp27-2D-gel electrophoresis is a diagnostic tool to differentiate primary desminopathies from myofibrillar myopathies.* FEBS Lett, 579(17): 3777-82. DOI: 10.1016/j.febslet.2005.05.051.

[399] Simon, S, Michiel, M, Skouri-Panet, F, Lechaire, JP, Vicart, P and Tardieu, A (2007). *Residue R120 is essential for the quaternary structure and functional integrity of human alphaB-crystallin.* Biochemistry, 46(33): 9605-14. DOI: 10.1021/bi7003125.

[400] Goldfarb, LG, Olive, M, Vicart, P and Goebel, HH (2008). *Intermediate filament diseases: desminopathy.* Adv Exp Med Biol, 642: 131-64. DOI: 10.1007/978-0-387-84847-1_11.

[401] Kamradt, MC, Chen, F, Sam, S and Cryns, VL (2002). *The small heat shock protein alpha B-crystallin negatively regulates apoptosis during myogenic differentiation by inhibiting caspase-3 activation.* J Biol Chem, 277(41): 38731-6. DOI: 10.1074/jbc.M201770200.

[402] Maloyan, A, Sanbe, A, Osinska, H, Westfall, M, Robinson, D, Imahashi, K, Murphy, E and Robbins, J (2005). *Mitochondrial dysfunction and apoptosis underlie the pathogenic process in alpha-B-crystallin desmin-related cardiomyopathy.* Circulation, 112(22): 3451-61. DOI: 10.1161/CIRCULATIONAHA.105.572552.

[403] Chen, Q, Liu, JB, Horak, KM, Zheng, H, Kumarapeli, AR, Li, J, Li, F, Gerdes, AM, Wawrousek, EF and Wang, X (2005). *Intrasarcoplasmic amyloidosis impairs proteolytic function of proteasomes in cardiomyocytes by compromising substrate uptake.* Circ Res, 97(10): 1018-26. DOI: 10.1161/01.RES.0000189262.92896.0b.

[404] Chavez Zobel, AT, Loranger, A, Marceau, N, Theriault, JR, Lambert, H and Landry, J (2003). *Distinct chaperone mechanisms can delay the formation of aggresomes by the myopathy-causing R120G alphaB-crystallin mutant.* Hum. Mol Genet, 12(13): 1609-1620.

[405] den Engelsman, J, Gerrits, D, de Jong, WW, Robbins, J, Kato, K and Boelens, WC (2005). *Nuclear import of {alpha}B-crystallin is phosphorylation-dependent and hampered by hyperphosphorylation of the myopathy-related mutant R120G.* J Biol Chem, 280(44): 37139-48. DOI: 10.1074/jbc.M504106200.

[406] Simon, S, Dimitrova, V, Gibert, B, Virot, S, Mounier, N, Nivon, M, Kretz-Remy, C, Corset, V, Mehlen, P and Arrigo, AP (2013). *Analysis of the dominant effects mediated by wild type or R120G mutant of alphaB-crystallin (HspB5) towards Hsp27 (HspB1).* PLoS. One, 8(8): e70545. DOI: 10.1371/journal.pone.0070545.

[407] Arrigo, AP, Simon, S, Gibert, B, Kretz-Remy, C, Nivon, M, Czekalla, A, Guillet, D, Moulin, M, Diaz-Latoud, C and Vicart, P (2007). *Hsp27 (HspB1) and alphaB-crystallin (HspB5) as therapeutic targets.* FEBS Lett, 581(19): 3665-3674. DOI: 10.1016/j.febslet.2007.04.033.

[408] Maksimiuk, M, Sobiborowicz, A, Tuzimek, A, Deptala, A, Czerw, A and Badowska-Kozakiewicz, AM (2020). *alphaB-crystallin as a promising target in pathological conditions - A review.* Ann Agric Environ Med, 27(3): 326-334. DOI: 10.26444/aaem/111759.

[409] Martin, JL, Mestril, R, Hilal-Dandan, R, Brunton, LL and Dillmann, WH (1997). *Small heat shock proteins and protection against ischemic injury in cardiac myocytes.* Circulation, 96(12): 4343-8. DOI: 10.1161/01.cir.96.12.4343.

[410] Kumarapeli, AR, Su, H, Huang, W, Tang, M, Zheng, H, Horak, KM, Li, M and Wang, X (2008). *Alpha B-crystallin suppresses pressure overload cardiac hypertrophy.* Circ Res, 103(12): 1473-82. DOI: 10.1161/CIRCRESAHA.108.180117.

[411] Pereira, MB, Santos, AM, Goncalves, DC, Cardoso, AC, Consonni, SR, Gozzo, FC, Oliveira, PS, Pereira, AH, Figueiredo, AR, Tiroli-Cepeda, AO, Ramos, CH, de Thomaz, AA, Cesar, CL and Franchini, KG (2014). *alphaB-crystallin interacts with and prevents stress-activated proteolysis of focal adhesion kinase by calpain in cardiomyocytes.* Nat Commun, 5: 5159. DOI: 10.1038/ncomms6159.

[412] Yin, B, Tang, S, Xu, J, Sun, J, Zhang, X, Li, Y and Bao, E (2019). *CRYAB protects cardiomyocytes against heat stress by preventing caspase-mediated apoptosis and reducing F-actin aggregation.* Cell Stress Chaperones, 24(1): 59-68. DOI: 10.1007/s12192-018-0941-y.

[413] Takagi, H, Hsu, CP, Kajimoto, K, Shao, D, Yang, Y, Maejima, Y, Zhai, P, Yehia, G, Yamada, C, Zablocki, D and Sadoshima, J (2010). *Activation of PKN mediates survival of cardiac myocytes in the heart during ischemia/reperfusion.* Circ Res, 107(5): 642-9. DOI: 10.1161/CIRCRESAHA.110.217554.

[414] Mitra, A, Basak, T, Datta, K, Naskar, S, Sengupta, S and Sarkar, S (2013). *Role of alpha-crystallin B as a regulatory switch in modulating cardiomyocyte apoptosis by mitochondria or endoplasmic reticulum during cardiac hypertrophy and myocardial infarction.* Cell Death Dis, 4: e582. DOI: 10.1038/cddis.2013.114.

[415] Chis, R, Sharma, P, Bousette, N, Miyake, T, Wilson, A, Backx, PH and Gramolini, AO (2012). *alpha-Crystallin B prevents apoptosis after H2O2 exposure in mouse neonatal cardiomyocytes.* Am J Physiol Heart Circ Physiol, 303(8): H967-78. DOI: 10.1152/ajpheart.00040.2012.

[416] Fittipaldi, S, Mercatelli, N, Dimauro, I, Jackson, MJ, Paronetto, MP and Caporossi, D (2015). *Alpha B-crystallin induction in skeletal muscle cells under redox imbalance is mediated by a JNK-dependent regulatory mechanism.* Free Radic Biol Med, 86: 331-42. DOI: 10.1016/j.freeradbiomed.2015.05.035.

[417] Mercatelli, N, Dimauro, I, Ciafre, SA, Farace, MG and Caporossi, D (2010). *AlphaB-crystallin is involved in oxidative stress protection determined by VEGF in skeletal myoblasts.* Free Radic Biol Med, 49(3): 374-82. DOI: 10.1016/j.freeradbiomed.2010.04.027.

[418] Hussein, RM, Benjamin, IJ and Kampinga, HH (2015). *Rescue of alphaB Crystallin (HSPB5) Mutants Associated Protein Aggregation by Co-Expression of HSPB5 Partners.* PLoS One, 10(5): e0126761. DOI: 10.1371/journal.pone.0126761.

[419] Thakur, SS, Swiderski, K, Ryall, JG and Lynch, GS (2018). *Therapeutic potential of heat shock protein induction for muscular dystrophy and other muscle wasting conditions.* Philos Trans R Soc Lond B Biol Sci, 373(1738). DOI: 10.1098/rstb.2016.0528.

[420] Himori, K, Ashida, Y, Tatebayashi, D, Abe, M, Saito, Y, Chikenji, T, Westerblad, H, Andersson, DC and Yamada, T (2021). *Eccentric Resistance Training Ameliorates Muscle Weakness in a*

Mouse Model of Idiopathic Inflammatory Myopathies. Arthritis Rheumatol, 73(5): 848-857. DOI: 10.1002/art.41594.

[421] Himori, K, Tatebayashi, D, Ashida, Y and Yamada, T (2019). *Eccentric training enhances the alphaB-crystallin binding to the myofibrils and prevents skeletal muscle weakness in adjuvant-induced arthritis rat.* J Appl Physiol (1985), 127(1): 71-80. DOI: 10.1152/japplphysiol.00102.2019.

[422] Gwag, T, Lee, K, Ju, H, Shin, H, Lee, JW and Choi, I (2009). *Stress and signaling responses of rat skeletal muscle to brief endurance exercise during hindlimb unloading: a catch-up process for atrophied muscle.* Cell Physiol Biochem, 24(5-6): 537-46. DOI: 10.1159/000257510.

[423] Maloyan, A, Gulick, J, Glabe, CG, Kayed, R and Robbins, J (2007). *Exercise reverses preamyloid oligomer and prolongs survival in alphaB-crystallin-based desmin-related cardiomyopathy.* Proc Natl Acad Sci U S A, 104(14): 5995-6000. DOI: 10.1073/pnas.0609202104.

[424] Dimauro, I and Caporossi, D (2022). *Alpha B-Crystallin in Muscle Disease Prevention: The Role of Physical Activity.* Molecules, 27(3). DOI: 10.3390/molecules27031147.

[425] Nagaraj, RH, Nahomi, RB, Mueller, NH, Raghavan, CT, Ammar, DA and Petrash, JM (2016). *Therapeutic potential of alpha-crystallin.* Biochim. Biophys. Acta, 1860(1 Pt B): 252-257. DOI: 10.1016/j.bbagen.2015.03.012.

[426] Webster, JM, Darling, AL, Uversky, VN and Blair, LJ (2019). *Small Heat Shock Proteins, Big Impact on Protein Aggregation in Neurodegenerative Disease.* Front Pharmacol, 10: 1047. DOI: 10.3389/fphar.2019.01047.

[427] Ghosh, JG, Houck, SA and Clark, JI (2008). *Interactive sequences in the molecular chaperone, human alphaB crystallin modulate the fibrillation of amyloidogenic proteins.* Int J Biochem Cell Biol, 40(5): 954-67. DOI: 10.1016/j.biocel.2007.10.035.

[428] Zhu, Y, Shan, X, Yuzwa, SA and Vocadlo, DJ (2014). *The emerging link between O-GlcNAc and Alzheimer disease.* J. Biol. Chem, 289(50): 34472-34481. DOI: 10.1074/jbc.R114.601351.

[429] Ma, Z and Vosseller, K (2014). *Cancer metabolism and elevated O-GlcNAc in oncogenic signaling.* J. Biol. Chem, 289(50): 34457-34465. DOI: 10.1074/jbc.R114.577718.

[430] Dassanayaka, S and Jones, SP (2014). *O-GlcNAc and the cardiovascular system.* Pharmacol. Ther, 142(1): 62-71. DOI: 10.1016/j.pharmthera.2013.11.005.

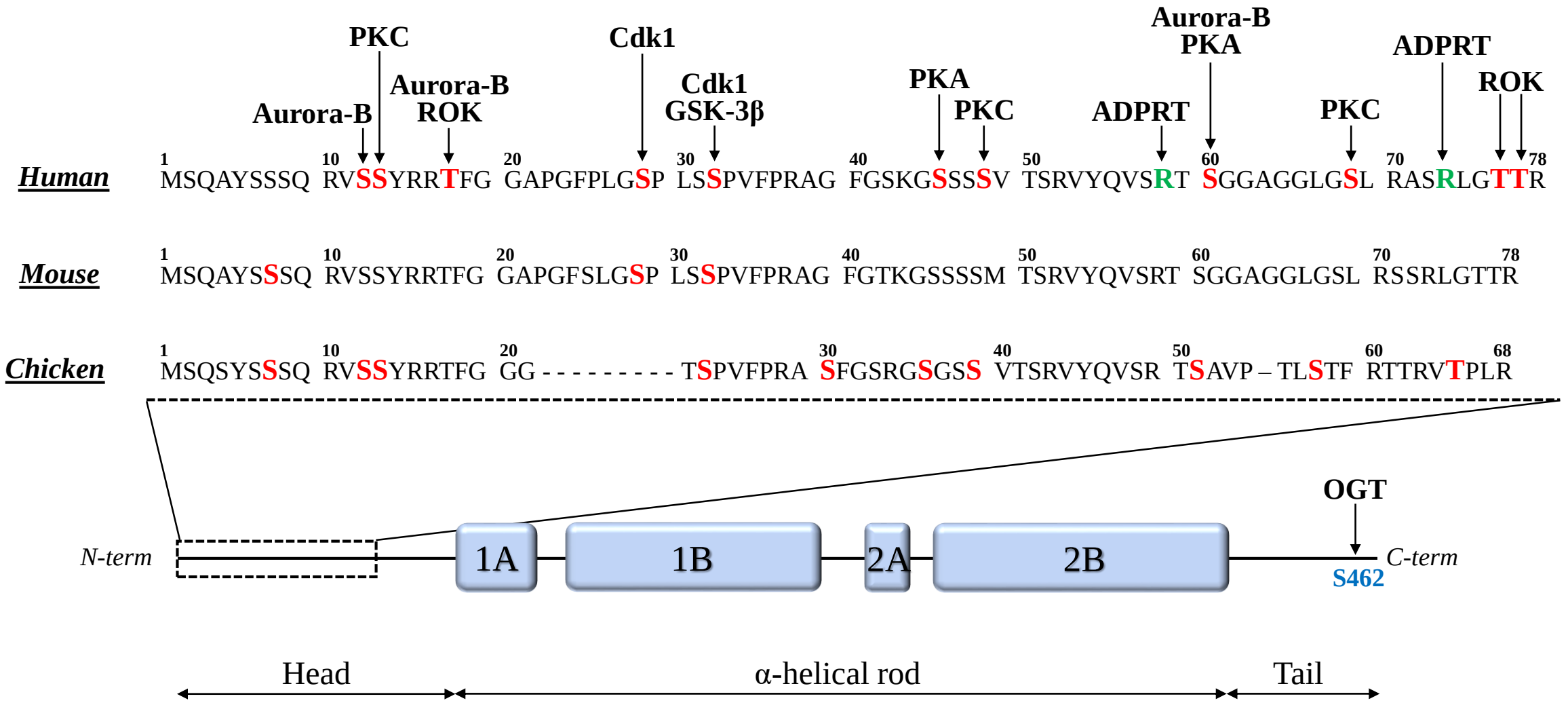
[431] Ma, J and Hart, GW (2013). *Protein O-GlcNAcylation in diabetes and diabetic complications.* Expert. Rev. Proteomics, 10(4): 365-380. DOI: 10.1586/14789450.2013.820536.

[432] Chou, SM and Wang, HS (1997). *Aberrant glycosylation/phosphorylation in chromatolytic motoneurons of Werdnig-Hoffmann disease.* J. Neurol. Sci, 152(2): 198-209.

[433] Nakamura, S, Nakano, S, Nishii, M, Kaneko, S and Kusaka, H (2012). *Localization of O-GlcNAc-modified proteins in neuromuscular diseases.* Med. Mol. Morphol, 45(2): 86-90. DOI: 10.1007/s00795-011-0542-7.

[434] Cieniewski-Bernard, C, Mounier, Y, Michalski, JC and Bastide, B (2006). *O-GlcNAc level variations are associated with the development of skeletal muscle atrophy.* J. Appl. Physiol, 100(5): 1499-1505. DOI: 10.1152/japplphysiol.00865.2005.

[435] Huang, P, Ho, SR, Wang, K, Roessler, BC, Zhang, F, Hu, Y, Bowe, DB, Kudlow, JE and Paterson, AJ (2011). *Muscle-specific overexpression of NCOATGK, splice variant of O-GlcNAcase, induces skeletal muscle atrophy.* Am. J. Physiol Cell Physiol, 300(3): C456-C465. DOI: 10.1152/ajpcell.00124.2010.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Cdk1
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PKC
ADPRT
ROK
Human
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Mouse
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Chicken
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OGT
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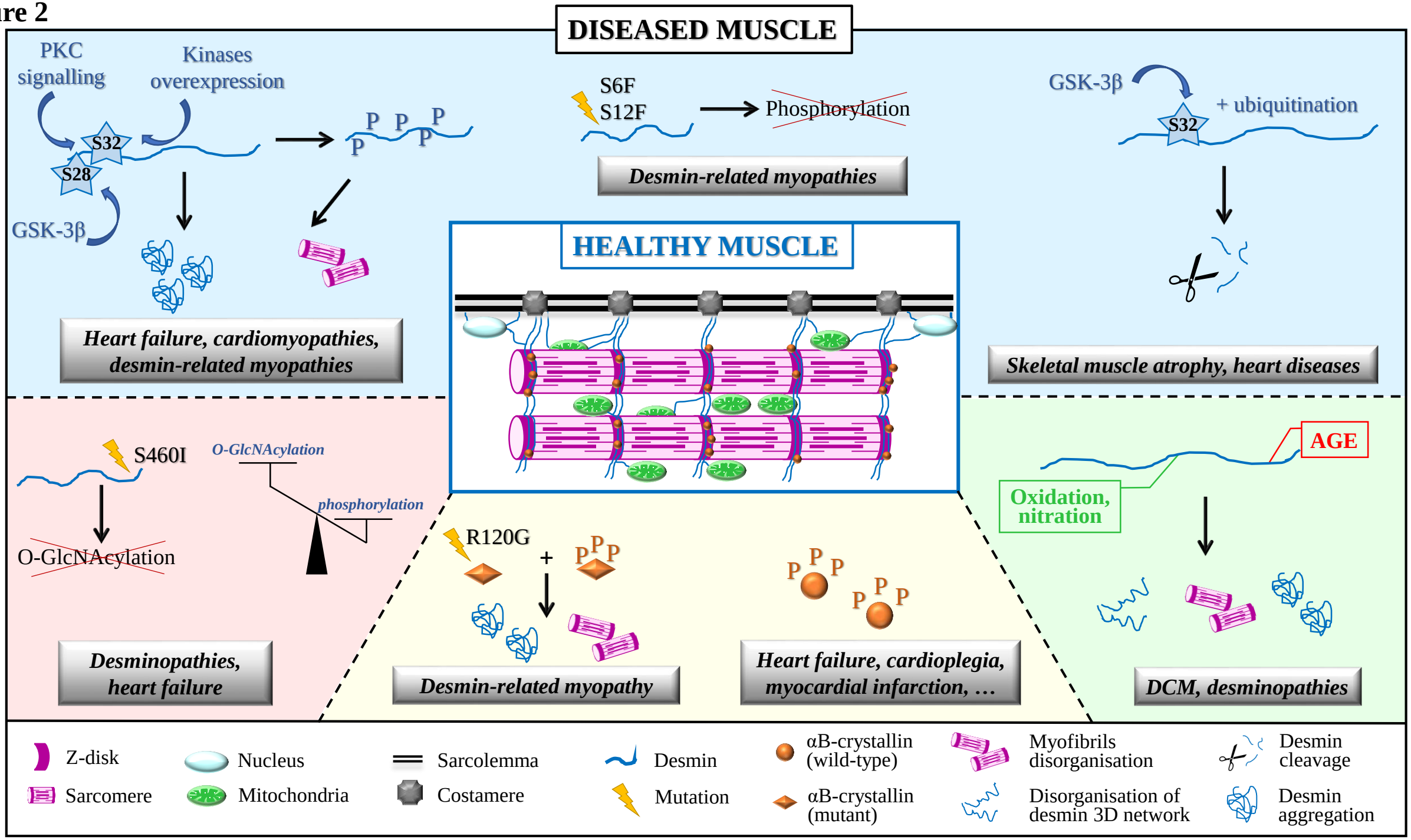
1A
1B
2A
2B
C-term
S462
Head
α-helical rod
Tail

Figure 1

Figure 2


DISEASED MUSCLE
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S28
GSK-3β
P P P P P
S6F
S12F
Phosphorylation
Desmin-related myopathies
GSK-3β
+ ubiquitination
S32
Heart failure, cardiomyopathies, desmin-related myopathies
HEALTHY MUSCLE
Skeletal muscle atrophy, heart diseases
S460I
O-GlcNAcylation
O-GlcNAcylation
phosphorylation
AGE
Oxidation, nitration
R120G
+
P P P
P P P
P P P
Desminopathies, heart failure
Desmin-related myopathy
Heart failure, cardioplegia, myocardial infarction, …
DCM, desminopathies
Z-disk
Sarcomere
Nucleus
Mitochondria
Sarcolemma
Costamere
Desmin
Mutation
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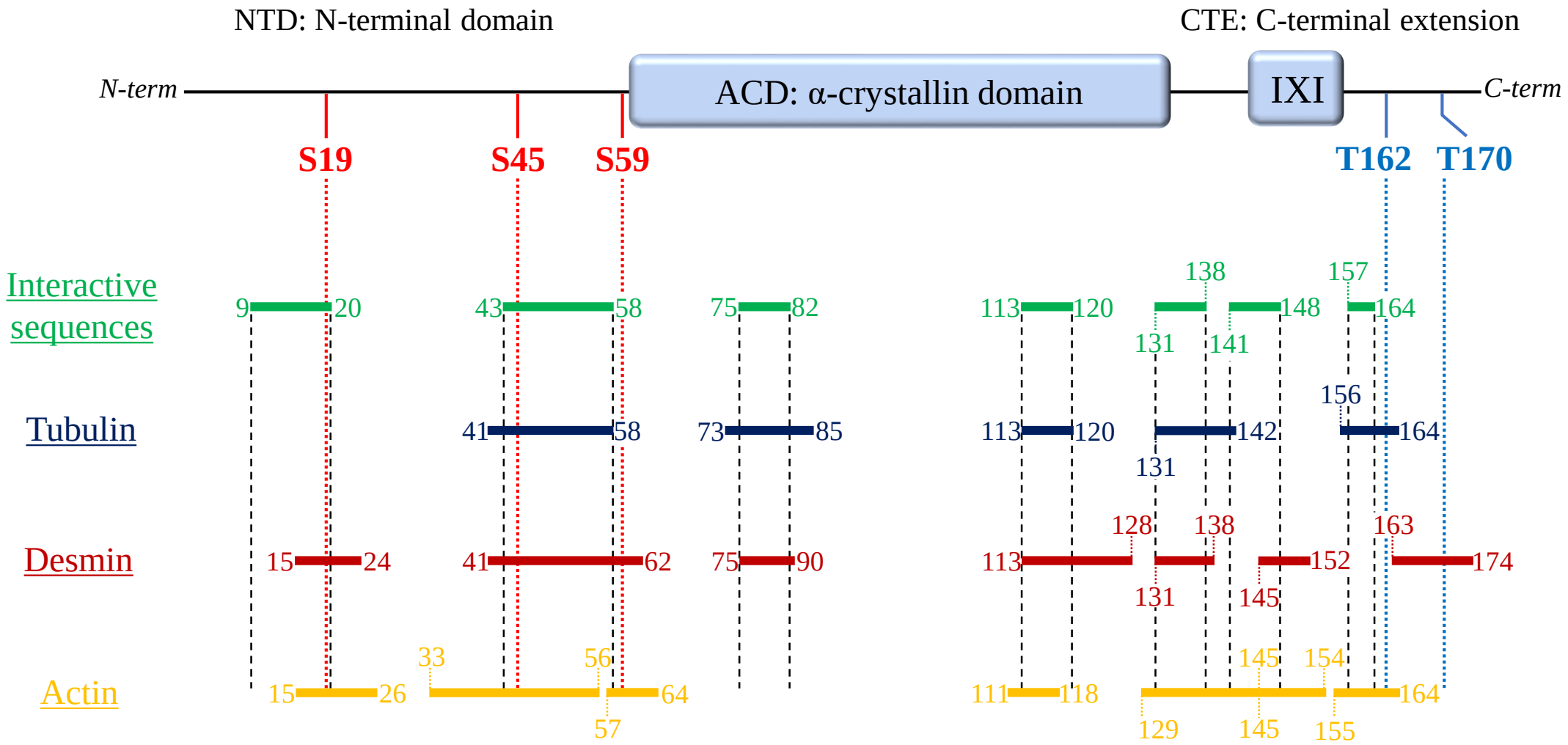
αB-crystallin (mutant)
Myofibrils disorganisation
Disorganisation of desmin 3D network
Desmin cleavage
Desmin aggregation


NTD: N-terminal domain
CTE: C-terminal extension
N-term
ACD: α-crystallin domain
IXI
C-term
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S45
S59
T162
T170
Interactive sequences
Tubulin
Desmin
Actin
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43 58
75 82
113 120
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148
157
164
131
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41 58
73 85
113 120
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15 24
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75 90
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Figure 3