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Desmin Related Disease: A Matter of Cell Survival Failure

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Abstract

Maintenance of the highly organized striated muscle tissue requires a cell-wide dynamic network that through interactions with all vital cell structures, provides an effective mechanochemical integrator of morphology and function, absolutely necessary for intra- and intercellular coordination of all muscle functions. A good candidate for such a system is the desmin intermediate filament cytoskeletal network. Human desmin mutations and post-translational modifications cause disturbance of this network, thus leading to loss of function of both desmin and its binding partners, as well as potential toxic effects of the formed aggregates. Both loss of normal function and gain of toxic function are linked to mitochondrial defects, cardiomyocyte death, muscle degeneration and development of skeletal myopathy and cardiomyopathy.

Introduction

The recent renaissance of research in intermediate filament (IF) biology has strongly suggested that mechanochemical signaling, embodied by cytoskeletal tension and cell and nuclear shape, is fundamental for the regulation of tissue development and maintenance. Specifically in muscle, proper propagation and sensing of the mechanical forces require the coordination of multiple cytoplasmic and nuclear components. A major integrator of this intracellular communication seems to be the desmin-lamin IF network [1–3] (Fig. 1A).

Desmin, the muscle-specific IF protein, together with its multiple binding partners, forms a three-dimensional scaffold that links the contractile apparatus, through Z-discs, to the nucleus, intercalated disks (IDs), and costameres of the plasma membrane, mitochondria and other membranous organelles [3, 4] (Fig. 1A). As a major structure-function integrator of all these components, desmin has the capacity to facilitate mechanochemical signaling and transport processes between the extracellular and nuclear matrix, as well as the crosstalk between different cellular organelles. Dereglulation of this communication leads to chronic skeletal muscle and heart disease and mutations in the genes coding for desmin and lamins seem to be so far major genetic causes of the disease.

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In this review we describe the potential mechanisms by which deficiency, mutations, cleavage and other post translational modifications of the desmin protein cause defects in membranes and membranous organelles (Fig. 1B) thus leading to skeletal and cardiac myopathies in mice and humans.

Desmin Related Disease

Dysfunctional desmin network due to mutations in the desmin gene (*DES*) or posttranslational modifications causes skeletal and cardiac myopathies, collectively called desmin related myopathies (DRMs) or desminopathies. DRMs belong to a genetically heterogeneous group of myopathies called myofibrillar myopathies (MFMs) that are caused by mutations in desmin, α B-crystallin, filamin C, myotilin, ZASP, BAG3, FHL1, VCP and plectin, characterized by desmin positive sarcoplasmic protein aggregates [5]. DRMs show a very wide range of clinical and pathological manifestations overlapping with other myopathies and most types of cardiomyopathies [6–8]. Nearly 70 human *DES* mutations associated with desminopathy have been reported so far [5, 8, 9] (Fig. 2A). A phenotype-genotype correlation meta-analysis showed that mutations in the rod 2B domain of desmin are predominant in patients with both skeletal and cardiac muscle phenotype, whereas head and tail domain mutations are mainly found in patients with an isolated cardiac phenotype [8, 9]. More than 70% of desmin mutations exhibit cardiac manifestation. The cardiac phenotype can involve conduction system defects and all forms of cardiomyopathy (CM), with dilated cardiomyopathy (DCM) being the most frequent, followed by restrictive (RCM), hypertrophic (HCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) and their combinations [6–8, 10]. The most common desmin-related heart disease was recently suggested to be the TNF- α -induced heart failure (HF) in mice [11••] and end-stage HF in humans (Papathanasiou and Capetanaki, unpublished data). Activation of caspases by TNF- α leads to desmin cleavage and aggregate formation, intercalated disk destabilization, mitochondrial defects, cell death and heart failure.

Several studies focus on the factors contributing to disturbances of the desmin based cytoskeletal network and how they lead to cell death and development of skeletal and cardiomyopathy. Below we discuss the progress in the field towards this goal.

Mechanisms of Desmin Network Deregulation

Desmin mutations

As shown in figure 2, most human desmin mutations are localized within coil 2B, the most important domain for IF assembly. Transfection studies in different cell types have indicated that the majority of desmin mutants cannot form a de novo desmin IF network, instead they form non-IF structures and protein aggregates. Furthermore, most mutations cause collapse of a pre-existing IF network [12••]. However, the progressive nature of the human DRM pathology suggests that mutant desmin aggregate formation cannot be the only contributing factor for the disease development.

Post-translational modifications of desmin

Desmin is a substrate of a wide spectrum of post translational modifications (PTMs), such as phosphorylation, ADP-ribosylation, ubiquitination, glycation, oxidation and nitration (Fig. 2A) [13]. Most PTMs cause disassembly of desmin network, except ubiquitination that leads to its degradation. PTMs could also affect the association of desmin with its binding partners. In DRMs, desmin may be hyper-phosphorylated [14] and a target of oxidation and nitration [15]. In cardiac disease, desmin was shown to be abnormally phosphorylated [11•, 16, 17] and also to be a target of advanced glycation end products [16]. Furthermore, a link between desmin phosphorylation and its subsequent ubiquitination and degradation during muscle atrophy [18], proposes a novel pathophysiologic mechanism. Thus, desmin mutations that affect PTM sites (Fig. 2A) could cause deregulation of desmin dynamics and lead to disease development.

Desmin proteolytic cleavage

Novel mechanistic insights on desmin involvement in heart disease were provided by studying its proteolytic cleavage. As mentioned above, desmin has been shown to be a major target in heart failure, by a novel pathophysiologic mechanism involving TNF- α -induced caspase-6 proteolytic cleavage at its L1–L2 linker domain [11•] (Fig. 2A). Desmin cleavage at its N-terminal head domain was recently reported, in both a canine model and human heart failure [17]. On the other hand, a DRM-linked missense mutation at the C-terminus of desmin has been shown *in vivo* to promote its proteolytic cleavage at the N-terminus (Fig. 2A) [19•]. Mutations or PTMs on desmin sites which may lead to caspase cleavage have not yet been identified, however, if they occur, they are expected to cause a severe form of DRM.

Desmin life cycle

Impairment of desmin turnover could be a pathophysiological mechanism in DRMs (Fig. 2B). Indeed, accumulation of desmin has been reported in human patients with dilated cardiomyopathy [20]. This could be the result of a compensatory mechanism, as supported by studies with desmin overexpression in transgenic mice [21], or due to deregulated turnover, as indicated from reports of proteasome impairment in DRMs [22]. Desmin protein turnover was recently suggested to be regulated by TRIM32 ubiquitin ligase [18•], shown to be involved in the development of myopathies [23]. Furthermore, YOD1, a deubiquitinating enzyme, was found to stabilize desmin protein levels and its down regulation is involved in the pathologic mechanism of cardiac failure induced by Coxsackievirus B3 infection [24].

Mechanisms of Desmin Related Disease Development

Loss of function or gain of aggregate toxic function?

A high degree of our understanding of the mechanisms of desmin function in both health and disease comes from studies with desmin deficient and desmin mutant mouse models. The fact that desmin null mice, obviously free of desmin aggregates, develop cardiomyopathy and skeletal myopathy [25–27], strongly suggest that the underlying mechanism of the observed pathology is mostly loss of function of desmin and its

interacting molecules and organelles, like mitochondria, rather than-or in addition to - gain of aggregate toxic function.

Effects on desmin associated proteins

Knowledge on desmin protein interactome promises to advance our understanding of the role of desmin in health and disease (Fig. 1A). Several desmin mutations affect the localization and function of a plethora of desmin-associated proteins and *vice versa*. Indeed, within the abnormal DRM linked protein inclusions, desmin co-aggregates consistently with numerous proteins, associated directly or indirectly with the desmin network, including α B-crystallin, hsp27, synemin, syncoilin, nestin, plectin, filamin C, hsp72/73, myotilin, dystrophin, utrophin, α & β -dystroglycan, α , β , γ & δ -sarcoglycans, caveolin, dysferlin, actin, actinin, N-CAM, NOS, collagen VI, laminin, β -spectrin, and ubiquitin (reviewed in [7]). Some of these data were recently confirmed by a proteomic analysis of skeletal muscle biopsies of DRM patients which identified 22 proteins significantly over-represented in the aggregates, with desmin and filamin C having the highest spectral index, followed by Xirp2, α B-crystallin, N-RAP, Xin and Hsp27 [28]. On the other hand, besides desmin, human mutations in most of the above proteins and some additional ones (such as myotubularin [29] and the nuclear lamins A/C, emerin and LAP2a), lead to myopathy and cardiomyopathy, strongly suggesting that desmin might be a common denominator in most of these cases, regardless of the mutated protein. The effect of desmin mutations on associated proteins does not always require aggregate formation. A recently identified desmin mutation in limb girdle muscular dystrophy, causes no desmin aggregation, but instead leads to loss of desmin interaction with lamin B [30]. Furthermore, a desmin mutation in coil 1B impairs nebulin Z-disc assembly and destabilizes actin thin filaments [31]. All the above data strongly suggest that the disruption of desmin organization regardless of the genetic cause will affect the proper function of the entire network and will lead to different myopathies and cardiomyopathies.

Effects on mitochondrial regulation and metabolism

Mitochondrial abnormalities, first detected in desmin deficient mice [3, 4, 25, 32•], comprise a common pathological feature among DRMs (Fig. 1) (reviewed in [3, 9]). They are the first structural defects detected after birth in $des^{-/-}$ myocytes and include loss of proper morphology, cristae structure and respiratory function [3, 4, 32•]. Furthermore, cardiac specific overexpression of the mitochondrial protein Bcl-2, in both the $des^{-/-}$ and R120GCryAB DRM mouse model, significantly ameliorates the pathology [33•, 34].

Maintenance of proper muscle function requires a tight link between energy production and demand. Desmin, by maintaining mitochondria in close proximity to myofibrils, could facilitate sensing and transferring of the energy needs, thus coupling mechanochemical signaling to metabolism. Indeed, proteomic analysis of mitochondria from $des^{-/-}$ hearts has revealed several changes in proteins involved in key metabolic pathways [35].

The interaction of desmin with mitochondria could be direct or through desmin associated proteins, such as plectin 1b [36]. A direct association of desmin to myotubularin was recently shown to regulate mitochondrial dynamics, morphology and function [29]. Potential

sites of direct desmin-mitochondrial interaction are the contact sites, where important proteins for mitochondrial biogenesis, morphology and function, such as the VDAC channels, ANT and the MICOS complex, are located and cross-talk with sarcoplasmic reticulum (SR) is facilitated [37]. A potential interaction of desmin with any of these proteins could affect mitochondrial permeability transition pore (mPTP) behaviour and respiratory function, thus explaining the observed pathology in the hearts of des^{-/-} mice, DRM models and patients [21, 38].

Effects on ID & costameres

Caspase cleavage of desmin in the TNF- α -induced heart failure model leads to loss of its intercalated disc (ID) localization (Fig. 3) as well as to mistargeting of its associated protein desmoplakin, along with other ID components [11••]. This finding provides a link of ID modification and desmin mislocalization with heart failure, since TNF- α overexpression is a common cardiac pathologic response [39]. Furthermore, another novel desmin-centered mechanism of cardiac pathophysiology involving ID regulation was recently described in Cocksackievirus B3-induced heart failure [24]. Finally, in skeletal muscle desmin has also been linked to proper organization of the costameres [40].

Is there a link to compromised differentiation and development?

Though the role of desmin in disease has mainly been studied in adult muscle, we have not excluded the possibility that the pathology observed is also attributed to compromised processes during development. Desmin is one of the earliest myogenic markers to appear in embryonic development [3] preceding even the early myogenic HLH transcription regulators MyoD, myogenin, and MRF4 [41]. In addition, it is expressed in adult skeletal and cardiac muscle progenitor cells [42, 43]. Inhibition of desmin expression hinders myoblast differentiation [44••, 45], while its amino-terminal mutations interfere with cardiogenesis [46]. Desmin can enhance the expression of myogenic and cardiogenic regulators [44••–48] while its own expression is controlled by them in return [49, 50]. The underlying mechanism by which a cytoskeletal protein, like desmin, could confer regulation of transcription factor steady state levels can only be speculated at this point. By linking the contractile apparatus to the nucleus (Fig. 1), desmin could serve as a potential mechanosensor and transducer of mechanical forces from ECM and Z-disc to the nucleus [3, 51, 52]. Indeed, myofiber nuclei from mice lacking desmin lose their localization and their ability to deform upon increasing strain, thus being unable to translate, through lamins, the mechanical signal to chromatin rearrangements [53, 54]. Complementary, lamin A/C null cardiomyocytes show disorganization and detachment of desmin filaments from the nuclear surface, while restoration of normal desmin levels in Lmna^{-/-} myoblasts rescues their compromised differentiation potential [55]. Further support to desmin's potential contribution to mechanotransduction is provided by its established interaction with myospryn [56•], a negative modulator of calcineurin [57•] as well as its suggested interaction to the stretch sensing transcription factor CARP [58•] (Tsikitis and Capetanaki, unpublished data). On the other hand, the recent connection between mitochondrial fusion, cardiomyocyte differentiation and calcineurin [59••], suggests that the role of desmin in differentiation could be linked to both mitochondrial dynamics and calcineurin signalling modulation.

Contribution of inflammation and fibrosis

In addition to the intrinsic mechanisms discussed above, the consequences of mitochondrial defects and myocyte death in activation of inflammation and fibrosis has been demonstrated in desmin deficient hearts [60•]. Among several remodeling modulators found to be induced, osteopontin seems to be a major regulator of the manifested des—/— adverse myocardial remodeling and it seems to potentiate its function by increasing galectin-3 expression and secretion [60•].

Conclusion and perspectives

The desmin IF network plays a major role in striated muscle development and maintenance by integrating and coordinating most cellular components necessary for proper mechanochemical signaling, organelle cross-talk, energy production and trafficking processes required for proper tissue homeostasis. Direct or indirect deregulation of this network will lead to different myopathies and cardiomyopathies. Mitochondrial abnormalities comprise a hallmark defect in most cases, followed by cell death, inflammation and fibrosis, muscle and myocardial degeneration and death. Future studies must focus on the unraveling of the mechanisms responsible for the development of these defects, starting with mitochondria, the determinants of life and death.

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Figure 1. Schematic representation of the desmin intermediate filament scaffold with its direct and indirect interactome in cardiac muscle (A) and the consequences due to its deficiency or disruption in desmin related disease (B)

A. Desmin, the muscle-specific IF (in yellow) together with its associated non-muscle specific IFs (synemin, syncoilin, paranemin in blue) form a continuous network linking the contractile apparatus at the Z-disc level with different membranous compartments (intercalated discs and costameres) and organelles (nucleus, mitochondria; interaction with other organelles, e.g. sarcoplasmic reticulum (SR) and lysosomes are not shown). Most of the proteins mediating the direct association of desmin with the above compartments

respectively (desmoplakin, myospryn, ankyrin, plectin) are shown. Desmin associates with the chaperon α B-crystallin in multiple compartments. Several other desmin-associated proteins (e.g. hsp27, nebulin etc.) are not shown. **B.** The catastrophic effects of desmin deficiency or disruption of desmin network due to its mutations, PTMs and TNF- α induced cleavage [11••] are depicted. Desmin aggregates, the hallmark of DRMs, often containing high amounts of many other proteins (see text) (here only α B-crystallin and filamin C) are shown. Fragmented and degenerating mitochondria is the first and most prominent defect; disruption of the association of desmin IFs with the nucleus (nuclear deformation), defects of the ID and mislocalization of its components to lateral sarcolemma regions are shown. Myospryn loses completely its perinuclear localization in the absence of desmin [56•]. Increased ECM and fibrosis due to inflammation (not shown) triggered by cardiomyocyte death is evident between cells.

Figure 2. A. Structural organization of the human desmin and the localization of identified disease causing mutations throughout its molecule

The desmin molecule, like all IFs, has a long highly conserved central α -helical rod domain, interrupted by 3 short nonhelical linkers (L1, L12, L2), thus generating 4 helices (1A, 1B, 2A, 2B), responsible for coiled-coil dimer formation. The central rod is flanked by nonhelical head (amino-terminal) and tail (carboxy-terminal) domains that are sites of post-translational modifications. Numbers indicate the amino-acid position of the domain borders. 68 pathogenic desmin mutations have been reported so far. The majority resides within the 2B helical domain and the tail. Most of them (53 out of total 68) are missense mutations, leading to single aminoacid substitutions but some are small in-frame deletions (e.g. Glu359_Ser361del) and frame-shift mutations (e.g. Lys241GlufsX4). Mutations with cardiac manifestation are indicated with different colored dots. DCM causing mutations are shown with blue, HCM with green, RCM with orange and ARVD/C with purple. Mutations that affect known phosphorylation sites (Ser7Phe and Ser13Phe) are indicated with solid red (P), while mutations on potential phosphorylation sites with dotted red (P). Two known substrates of ADP-Ribosylation (Arg58 and Arg73) at the head domain are indicated with green (R). TNF α -induced caspase 6 cleavage of desmin at Met263 within the L12 linker domain [11••] is shown; the Ile451Met mutation at the tail domain that promotes the proteolytic cleavage of desmin at the N-terminus [19] is indicated with asterisk (*). **B.**

Diagram summarizing the mechanisms causing desmin network deregulation and the cellular defects due the loss of function of desmin and desmin-associated proteins, eventually causing desmin related pathology.

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Figure 3. TNF- α -induced heart failure is the most common DRM

TNF- α -induced caspase cleavage of desmin leads to aggregate formation (asterisk) and loss of its intercalated disc (ID) localization, as shown by immunofluorescence analysis of desmin (green) on representative TNF- α (right panel) and WT (left panel) myocardial sections. Arrow: Z-lines, arrowhead: IDs. Nuclei are stained with DAPI (blue). Adopted from [11]. Scalebar: 20 μ m.