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Current Opinion in Cell Biology

Intermediate filaments in the heart: The dynamic duo of desmin and lamins orchestrates mechanical force transmission

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Abstract

The intermediate filament (IF) cytoskeleton supports cellular structural integrity, particularly in response to mechanical stress. The most abundant IF proteins in mature cardiomyocytes are desmin and lamins. The desmin network tethers the contractile apparatus and organelles to the nuclear envelope and the sarcolemma, while lamins, as components of the nuclear lamina, provide structural stability to the nucleus and the genome. Mutations in desmin or A-type lamins typically result in cardiomyopathies and recent studies emphasized the synergistic roles of desmin and lamins in the maintenance of nuclear integrity in cardiac myocytes. Here we explore the emerging roles of the interdependent relationship between desmin and lamins in providing resilience to nuclear structure while transducing extracellular mechanical cues into the nucleus.

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Current Opinion in Cell Biology 2023, **85:**102280

This review comes from a themed issue on **80: Cell Architecture (2023)**

Edited by **John Eriksson** and **Patrick Lusk**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.ceb.2023.102280

Keywords

Intermediate filaments, Heart, Cardiomyopathy, Lamin, Desmin, Mechanotransduction, DNA damage.

All Authors contributed equally.

Introduction

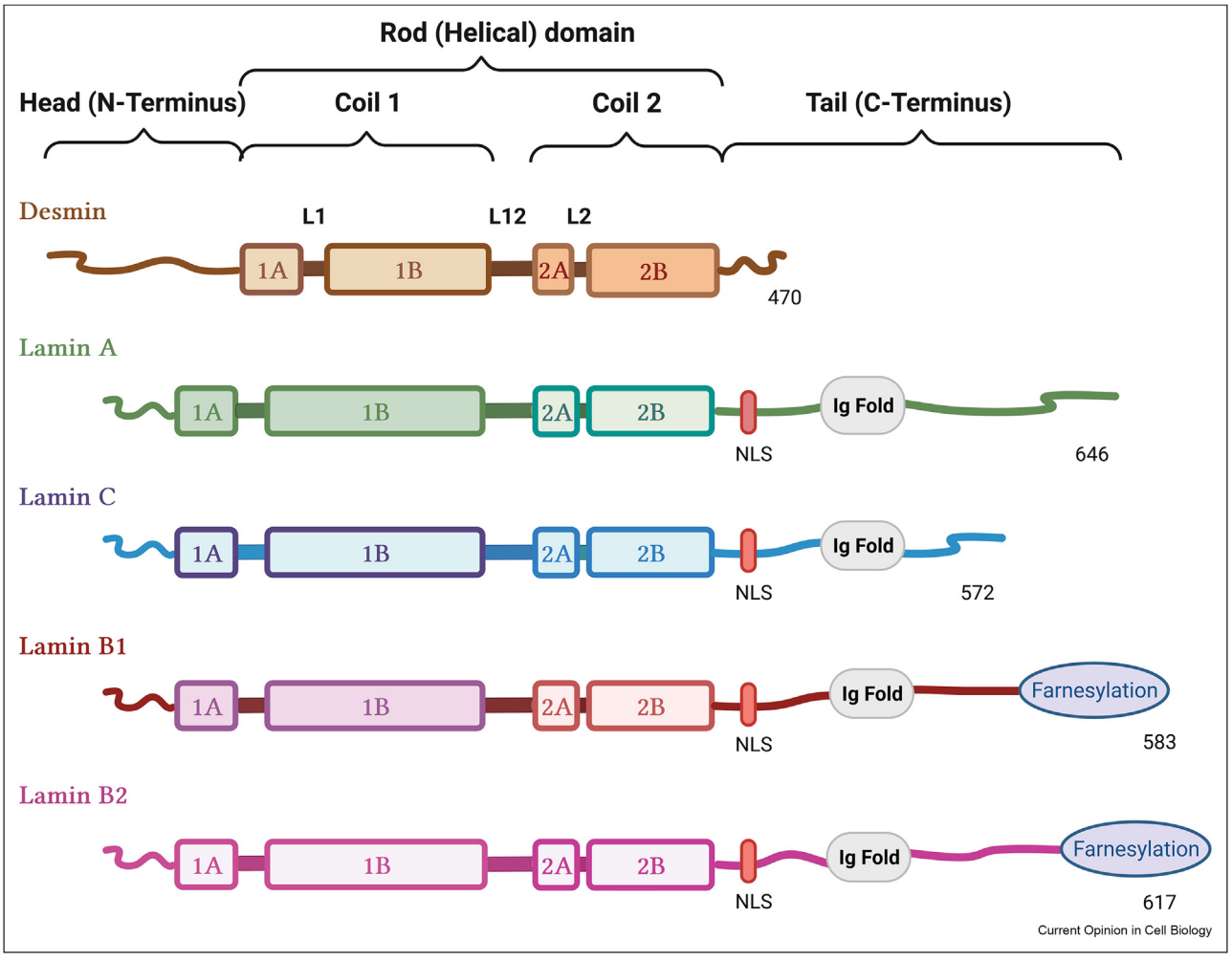
Cardiac tissue undergoes constant mechanical contraction and stretching which require the ability to sense, adapt, and facilitate contractile signaling from the sarcomeres throughout the cell under the prevailing circumstances. The cytoskeleton regulates this adaptive cellular response by fine-tuning the density, turn-over, and interconnectivity of intermediate filaments (IF), actin microfilaments, and tubulin microtubules (MT). Over 70 genes encode for distinct IF proteins that are expressed in a cell-type-specific fashion and are divided into six groups (types I-VI) based on their structural and functional homology [1]. The variability in the sequence and length of structural domains, in particular their N-terminal head and C-terminal tail, is the main source of heterogeneity in the IF family [2] (Figure 1).

Cardiac tissue expresses various IF proteins (Table 1). Desmin is the most abundant cytoplasmic IF protein in adult cardiomyocytes and skeletal muscle cells. Nuclear A-type lamins (A and C) and B-type lamins (B1 and B2) are ubiquitously expressed in all differentiated nucleated cells but the expression levels of A-type lamins are particularly high in skeletal and cardiac muscle. Additionally, less abundant and characterized IF proteins, synemin and syncoilin, are expressed throughout cardiac development [3]. Nestin and vimentin, on the other hand, are primarily found in skeletal myoblasts and non-cardiomyocytes (endothelial cells, smooth muscle cells, and fibroblasts), but not in mature cardiomyocytes [4]. Mutations or loss of desmin or A-type lamins result in myofibrillar myopathies which are characterized by cardiomyopathy in a wide majority of the cases [1]. Similarly, synemin and syncoilin, have been associated with the development of cardiomyopathy [5,6]. In this review we focus on the connection of desmin and lamins in cardiomyocytes, and address their synergistic roles in transducing mechanical signals through the cardiac myocyte, maintaining nuclear morphology, and regulating gene expression.

Cardiac desmin

Desmin is a type III IF and the main constituent of the IF cytoskeleton in striated and, to a lesser extent, in smooth muscle cells [7,8]. In striated muscle cells,

Figure 1



Structural domains in desmin lamins. All IF proteins include an amino-terminal "head" domain, a central, alpha-helical "rod" domain, and a carboxy-terminal "tail". While the head and tail domains are intrinsically disordered and heavily post-translationally modified, the rod domain comprises two highly conserved subdomains (coil 1 and 2), and a non-helical L12 linker. Coil 1 and 2 are further divided into 1A/1B and 2A/2B regions by non-helical linkers L1 and L2, respectively [2]. For both desmin and lamins, mature proteins are shown. The C-terminal tail of lamins contains nuclear localization signal (NLS) and immunoglobulin-like fold (Ig Fold). Mature B-type lamins remain farnesylated and carboxymethylated at the C-terminus while A-type lamins do not. Image created with Biorender.

desmin is mainly localized at the Z- and intercalated discs, and its network spans the width of the cell between the nuclear and the cellular membranes while tethering different organelles [9,10]. The Z-discs define the length of a sarcomere, or contractile unit (Figure 2), and serve as hubs for signaling and localized translation of sarcomeric proteins [11,12]. Desmin marked distribution at the Z-discs suggests its involvement in regulating both these aspects. The distribution of the desmin network, and the early adverse remodeling that characterizes its loss [13,14], also show that this network is important for the maintenance of cellular ultrastructure. For instance, desmin IF safeguards the juxtaposition of mitochondria, the sarcoplasmic reticulum (SR), and the contractile apparatus to sustain optimal excitation-contraction coupling through efficient delivery of ATP and Ca^{2+} from the mitochondria and the SR to the sarcomeres, respectively [15,16]. Pertinent to this review article, a cage-like desmin structure surrounding the nucleus prevents the MT network from impinging the nuclear lamina [17] and it is disrupted in lamin A/C-deficient mice [18].

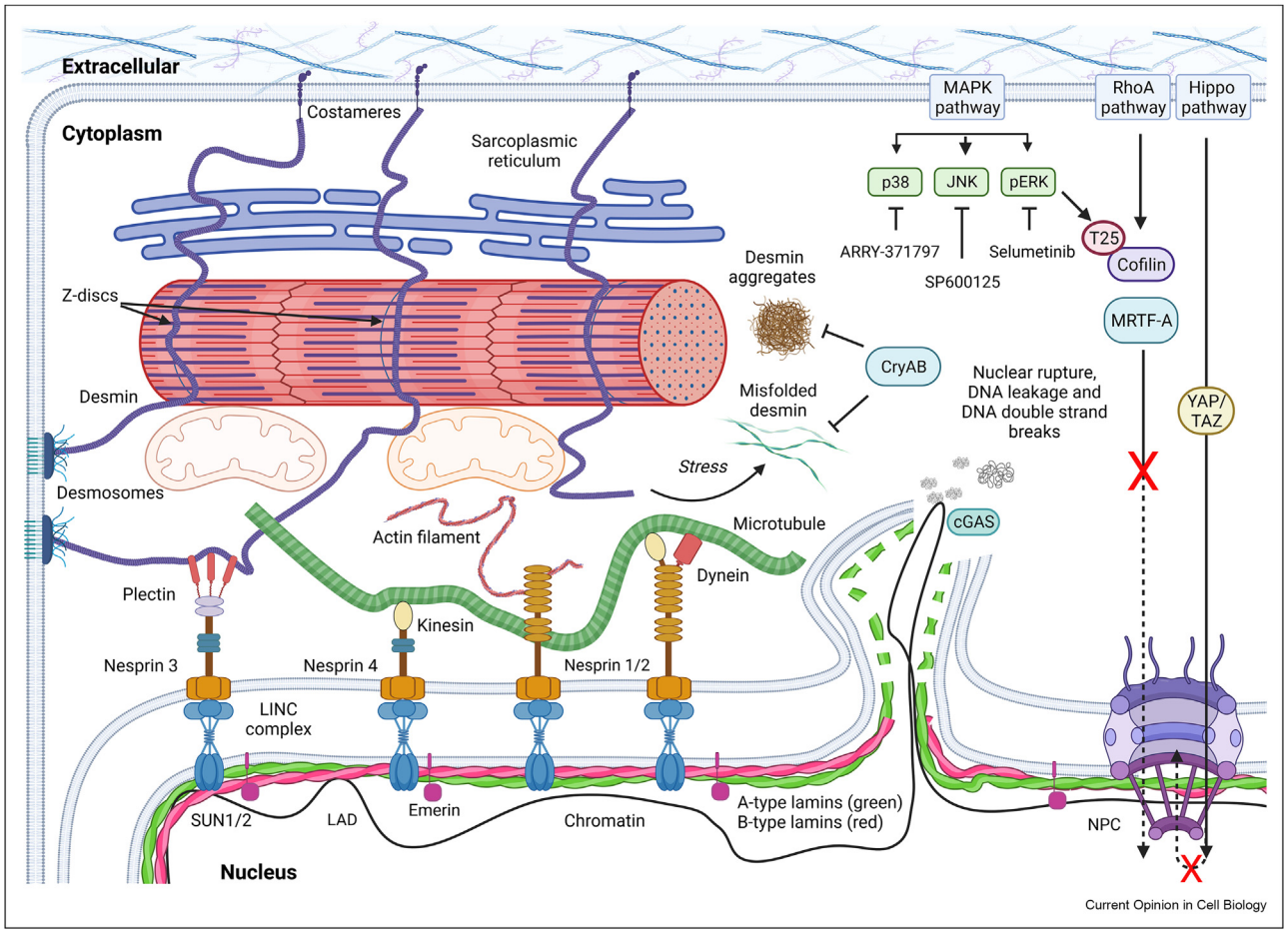
Desmin-related myopathies (DRM) are a group of muscle disorders caused by mutations in the desmin and desmin-related genes and are characterized by distal skeletal muscle weakening, cardiomyopathy, and conduction defects [19,20]. Desmin mutations occurring in regions encoding for N-terminal end of 1A helical domain typically result in worse outcomes [21]. In

Table 1

Expression of different intermediate filaments in the heart.

Classification	IF	Embryogenesis	Adult heart	Disease/Aged heart	Reference
Type I	Keratin 8/18			aberrant	[68]
Type III	Desmin	ubiquitously	cardiomyocytes	loss/aggregates	[69]
	Syncoilin	ubiquitously	muscle cells		[70]
	Vimentin	mesenchyme	non-myocardial cells		[71]
Type IV	Synemin	ubiquitously	muscle cells		[72,73]
	Paranemin	ubiquitously	ubiquitously		[72]
Type V	A-type lamins	differentiated cells	ubiquitously	decreased, altered assembly	[69,74]
	B-type lamins	ubiquitously	ubiquitously, B2 decreased	B2 decreased	[34]
Type VI	Nestin	cardiomyocytes, ventricular fibroblasts	ventricular fibroblasts	expressed in cardiomyocytes	[4,75,76]

Figure 2



Signaling and interconnectivity in the cytoskeleton of cardiac myocytes. Schematic illustration of cardiomyocyte cytoskeleton with emphasis on desmin and lamins, their established binding partners, and signaling pathways involved in the remodeling of the cytoskeleton in cardiac myocytes. Desmin connects to microtubules and transmits contractile forces from the cell surface to the nucleus. Loss of desmin results in increased microtubule detyrosination and cardiac stiffness [32]. The majority of desmin mutations lead to its aggregation, which can be prevented by alpha-B-crystallin. Desmin aggregates also hallmark human heart failure of ischemic and non-ischemic origin [77]. Mutations in A-type lamins activate MAPK signaling, Hippo, and RhoA pathways, leading to actin filament disassembly. Binding of phospho(T25)-cofilin-1 to MRTF-A prevents the stimulation of SRF in the nucleus and leads to decreased α-tubulin acetylation and microtubule destabilization. Lamin mutations further cause nuclear blebbing, fragility, membrane rupture, and DNA damage which activates the cGAS/STING pathway. MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; ERK1/2, extracellular signal-regulated kinase 1/2; RhoA, Ras homolog family member A; MRTF-A, myocardin-related transcription factor A; YAP, Yes-associated protein; TAZ, transcriptional co-activator with PDZ-binding motif; NPC, nuclear pore complex; LAD, lamina-associated domains; cGAS, cyclic GMP–AMP synthase; CryAB, alpha-B-crystallin. Image created by Biorender.

DRM, loss of desmin is often accompanied by the deposition of desmin aggregates. Aggregation of mutant desmin further exacerbates the loss of functional desmin and actively impairs mitochondrial function, as well as excitation-contraction coupling [8,22]. The dysregulation of Ca^{2+} homeostasis [23] and desmosomal instability [24] are likely contributors to conduction defects in DRM patients. The multifaceted roles and complex interactions of desmin with key organelles and protein complexes in striated muscle cells, along with environmental factors, likely underlie the heterogeneous penetrance and manifestations of DRM, spanning dilated, hypertrophic and arrhythmogenic cardiomyopathy, and skeletal muscle weakness [8].

Desmin stabilizes nuclear shape and positioning

The biophysical properties of the surrounding environment and local mechanical forces play a major role in the development, maturation, and function of cardiomyocytes [25]. The highly dynamic nuclear and cytoplasmic IF network (established by lamin and desmin, respectively), along with other interacting proteins, such as the MT, determine the proper positioning and shape of the nucleus [1]. In addition to force-dependent signaling cascades, biophysical cues can be transferred directly to the nucleus via the LINC (linker of nucleoskeleton and cytoskeleton) complex [17,26,27]. The LINC complex, formed by nesprins on the outer nuclear membrane and SUN (Sad1 and UNC84)-domain transmembrane proteins in the inner nuclear membrane, plays a key role in transmitting biophysical cues to the lamina and mediates the force-dependent gene expression [25,28] (Figure 2). Desmin is connected to the nuclear membrane, lamina, and chromatin via the LINC complex and the ubiquitously expressed plectin-1 isoform [25,29,30] (Figure 2). Application of cyclic stretch to maturing cardiomyocytes results in increased expression of LINC-interacting proteins including desmin, plectin, and dynactin, supporting a role for IF and IF-related proteins in force transmission to the nucleus [31]. One mechanism preventing the nucleus from collapsing in the face of external mechanical forces is the counter-interference of two forces produced by desmin IF, mainly running along the short axis of cardiomyocytes, and tubulin MT, which are preferentially distributed in an orthogonal fashion along the long axis of cardiomyocytes [17] (Figure 2). Desmin IF stabilize the Z-discs, and both detyrosinated tubulin and desmin IF are increased in the hypertrophied and failing heart. MT acetylation is also increased with heart disease and while detyrosination and acetylation of tubulin increase MT stability these adaptations are prevented in the absence of desmin [32]. Failure of cardiac cells to properly respond to mechanical cues, such as with mutations in proteins involved in mechanosensing and mechanotransduction, classically results in cardiac abnormalities [25].

Cardiac lamins

Lamins are type V IF proteins that constitute the nuclear lamina, a filamentous meshwork located underneath the inner nuclear membrane. The lamina provides structural support and regulates chromatin organization and gene activity by tethering heterochromatin-rich regions known as lamina-associated domains (LADs). Some lamins are also present in the nucleoplasm, where they associate with both heterochromatin and transcriptionally active euchromatic genomic regions [33]. In the developing heart, lamin B2 levels decrease postnatally as cardiomyocytes transit from a proliferative to a non-proliferative state, while lamin B1 levels remain stable throughout maturation [34]. Interestingly, physiological lamin B2 downregulation reduces nuclear envelope breakdown and M-phase progression, leading to polyploid cardiomyocytes and decreased myocardial regeneration whereas increasing lamin B2 levels improves myocardial regeneration in developing mice [34,35]. Further, lamin B2 downregulation reduces the number of nuclear pore complexes in maturing mouse cardiomyocytes, which reduces the nuclear translocation of signaling proteins and protects from pathological cardiac remodeling [36]. Lamin B2 has also been identified as a key regulator of cardiomyocyte maturation in human induced pluripotent stem cell (iPSC)-derived cardiomyocytes [37].

The expression of A-type lamins typically starts in differentiating cells after their commitment to a given lineage, where lamin depletion promotes cardiac over endothelial cell lineage during cardiogenesis [38]. Mutations in A-type lamin gene (*LMNA*) lead to a heterogenous group of diseases called laminopathies [39]. Dilated cardiomyopathy (DCM), characterized by left ventricular enlargement, reduced systolic function, atrioventricular conduction defects, and malignant arrhythmias is the most frequent clinical outcome in laminopathy patients [40]. In addition, some *LMNA* mutations have been linked to arrhythmogenic right ventricular cardiomyopathy and left ventricle noncompaction cardiomyopathy [38,41]. Although various cell and mouse models of *LMNA*-DCM have been generated, the underlying molecular mechanisms of pathogenesis are still incompletely understood. Defects in multiple signaling pathways, such as mitogen-activated protein kinase (MAPK) (ERK1/2, p38, JNK), AKT-mTOR, WNT/β-catenin, PDGF, TGF-β/Smad and YAP/Hippo have been reported in transgenic mouse models expressing DCM-related mutant forms of lamin A/C [15,42]. Furthermore, nuclear envelope rupture leading to activation of DNA damage response (DDR) in cardiomyocyte-specific (cs)*Lmna*-null mice has been suggested as a potential disease mechanism [43,44]. So far, the research for therapeutics has mainly concentrated on the $Lmna^{H222P/H222P}$ and $Lmna^{N195K/N195K}$ mouse models where inhibition of signaling pathways,

such as MAPK, delays or even prevents the disease phenotype [45]. Unfortunately, no similar beneficial effects were found with a small-molecule inhibitor of p38α (ARRY-371797) in the recent clinical phase III trial on *LMNA*-DCM patients [46].

Nuclear lamins as guardians of the genome

The levels of A-type lamins correlate with the biophysical properties of the environment with up to ~30-fold increase from soft to stiff tissues, while levels of B-type lamins exhibit minimal variation [47]. Elevated levels of A-type lamins contribute to nuclear stiffening, with cortical stiffness being determined by lamin interaction with actin through nesprin-2, a component of LINC complex (Figure 2) [48,49]. Both A- and B-type lamins also regulate cytoplasmic stiffness and cellular contractility through connections to nesprin-3 [50]. A recent study on *D. Melanogaster* showed that age-related or induced premature reduction of A-type lamins correlates with cardiac degeneration while maintaining lamin expression in aged flies prevents age-dependent cardiac decline [51]. Supported by data from mice and monkeys, the authors concluded that age-dependent nuclear remodeling plays a key role in cardiac transcriptional inactivity and dysfunction [51].

Nuclear elasticity is also regulated by lamin phosphorylation status. A-type lamins are increasingly phosphorylated in detached cells and in soft tissues, increasing lamin solubility and susceptibility for degradation [52]. Similarly, cellular stress, such as heat shock, induces reversible phosphorylation of A-type lamins [53]. In summary, the modulation of lamin levels and phosphorylation status both serve as mechanisms to integrate external mechanical and biochemical stimuli for cellular adaption.

Disease-associated mutations in lamin A/C frequently cause defects in lamin assembly and localization [54,55] and at least some of the mutations activate endoplasmic reticulum (ER) stress [54,56]. In addition, lamin mutant cells commonly exhibit nuclear blebbing, fragility, rupture, and DNA damage through an imbalance in contrasting forces, or stress, that converge at the nuclear membrane [44] (Figure 2). After nuclear rupture, nucleoplasmic lamin A/C but not lamin B1 rapidly accumulate at the rupture site [57,58]. Cyclic GMP-AMP synthase (cGAS) and the barrier-to-autointegration factor (BAF) also accumulate at the rupture site to repair nuclear leakage of DNA into the cytoplasm. However, several laminopathy-associated mutant forms of lamins failed to accumulate [58]. In cardiomyocyte-specific (cs)*Lmna*-null mice showing DCM phenotype, DNA double-strand breaks are released into the cytosol and accompanied by activation of the DNA damage response triggering expression of proinflammatory cytokines [44,59]. Interestingly, deletion of cGAS in the (cs)*Lmna-null* mice prolonged survival, improved cardiac function, and decreased apoptosis and fibrosis [43] (Figure 2). In addition, disruption of LINC complex components prevents cardiomyopathy progression which shows that nuclear damage induced by mechanical forces is indisputably involved in the disease mechanism [28,44,60]. The contribution of DNA damage to the pathophysiology of laminopathies could potentially be extended to other genetic and acquired forms of cardiomyopathy that are characterized by nuclear membrane damage due to mechanical stress.

Although the specific molecular mechanisms of altered cellular signaling in lamin mutant cells are mostly unclear, some specific defects have been identified. For example, a recent study revealed that trapping of TEA domain transcription factor 1 (TEAD1) at the nuclear membrane underlies the pathogenesis of p.Q353R-*LMNA*-related DCM, and both transcriptional dysregulation and structural maturation abnormalities of mutant cardiomyocytes were mitigated by inhibition of Hippo pathway [42] (Figure 2).

Overarching disruption of desmin-lamin interplay in cardiomyopathies

Desminopathies and laminopathies demonstrate a functional relationship between the nuclear and cytoplasmic IF networks in cardiomyocytes. This is evident through partially overlapping phenotypes induced by *LMNA* and *DES* mutations, which often manifest with cardiomyopathy. Multiple lines of evidence underscore the intricate interplay between desmin and lamins, emphasizing its pivotal importance in safeguarding nuclear and cellular integrity. Disruptions in either desmin or lamin A/C can lead to altered nuclear morphology, which results in chromatin disorganization and altered gene expression [1,18,29,61]. Moreover, a recent study demonstrated that p.T10I and p.R541C *LMNA* mutations result in disruption of lamina-chromatin interactions at specific regions and upregulation of corresponding non-myocyte genes in hiPSCs and myocardial tissue from *LMNA*-DCM patients [61]. Although this so-called "gene expression" model of pathogenesis is intriguing, the global changes in chromatin organization in correlation to gene expression are limited in lamin knockdown or mutant cardiomyocytes [62]. Desmin mislocalization is evident in the hearts of $Lmna^{p.N195K/N195K}$ mice, a model for DCM [63]. Moreover, *LMNA*-deficient mice exhibit detachment of desmin IFs from the nuclear surface in cardiomyocytes in conjunction with enlargement of the nuclear envelope leading to complete separation of cytoskeleton surrounding the nucleus [18,25]. This irregular desmin pattern extends to heart tissue derived from individuals with an *LMNA* p.E161K mutation [64], and presumably many others. Formation of desmin aggregates has been

observed in laminopathies, including *Lmna*$^{p.H222P/H222P}$ mice, where disruption of the desmin network and the accumulation of desmin aggregates leads to severe abnormalities in intercalated discs and mitochondria, likely facilitating the development of *LMNA*-cardiomyopathy [65].

Alpha-B-crystallin (cryAB) is the most abundant small heat shock protein in the heart and a well-established chaperone of desmin [66]. Interestingly, overexpression of cryAB improved cardiac function and reduced cardiac fibrosis in *Lmna*$^{p.H222P/H222P}$ mice [65] reinforcing the notion that nuclear and cytoplasmic IF networks are interdependent and to a certain extent complementary, thus providing a new potential target of pharmacological intervention in patients with laminopathies. More detailed analysis and understanding of molecular mechanisms behind IF-related cardiomyopathies will open new avenues and potential targets of therapy further. Most recently, it was discovered that the actin-microtubule interplay, mediated by phospho(T25)-cofilin-1 via MRTF-A/SRF signaling and α-tubulin acetylation, is impaired in *Lmna*$^{p.H222P/H222P}$ mice [67]. Increasing α-tubulin acetylation levels with tubastatin A treatment improved cardiac function in these mice showing that defects in lamin-desmin axis may have multiple unexpected and potentially druggable consequences beyond IF cytoskeleton [67].

Conclusions and future perspectives

Over two decades after the identification of *DES* and *LMNA* mutations causing cardiomyopathy, significant progress has been made in unraveling the molecular mechanisms underlying myocardial degeneration in these patients. Despite the different subcellular localization of lamins and desmin, defects in either of these proteins trigger cellular deterioration eventually leading to adverse cardiac remodeling and failure. An emerging consensus exists around cellular adaptations induced by *DES* and *LMNA* mutations: first, instability of both desmin and lamin IF networks may impair mechanotransduction signaling which is an essential feature for cardiac adaptation under stress. Second, perturbation of desmin or lamin A/C networks frequently leads to nuclear fragility, rupture, and DNA damage response. Third, disruption of lamina-chromatin interaction at LADs may cause the aberrant expression of various genes in cardiomyocytes and overall dysregulation in gene expression. At least some of these phenomena are linked to each other and/or mediated by numerous lamin and desmin interaction partners, which is why the causality of pathogenetic steps is unclear. In the coming years, it will be crucial to further test the relative contribution of these mechanisms of toxicity and determine the most beneficial strategies to prevent them in IF-myopathies. Because these mechanisms underlie "garden variety" types of cardiac dysfunction, their interpretation could have a broader impact on our understanding of cardiac disease and failure, at large.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

We are grateful to Prof. Jan Lammerding for his valuable comments on the figures. This work was supported by grants from the Academy of Finland, Sigrid Juselius Foundation, and the Finnish Foundation for Cardiovascular Research (to PT), and by the Leducq Foundation TNE ID#673168, the Zegar Family Foundation, 18TPA34170382 from the American Heart Association, and the Magic that Matters Foundation (to GA).

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