Intermediate filaments in cardiomyopathy

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Abstract

Intermediate filament (IF) proteins are critical regulators in health and disease. The discovery of hundreds of mutations in IF genes and posttranslational modifications has been linked to a plethora of human diseases, including, among others, cardiomyopathies, muscular dystrophies, progeria, blistering diseases of the epidermis, and neurodegenerative diseases. The major IF proteins that have been linked to cardiomyopathies and heart failure are the muscle-specific cytoskeletal IF protein desmin and the nuclear IF protein lamin, as a subgroup of the known desminopathies and laminopathies, respectively. The studies so far, both with healthy and diseased heart, have demonstrated the importance of these IF protein networks in intracellular and intercellular integration of structure and function, mechanotransduction and gene activation, cardiomyocyte differentiation and survival, mitochondrial homeostasis, and regulation of metabolism. The high coordination of all these processes is obviously of great importance for the maintenance of proper, life-lasting, and continuous contraction of this highly organized cardiac striated muscle and consequently a healthy heart. In this review, we will cover most known information on the role of IFs in the above processes and how their deficiency or disruption leads to cardiomyopathy and heart failure.

Keywords Intermediate filaments · Cardiomyopathies · Desmin · Lamin · Mitochondrial defects · Dilated cardiomyopathy · Heart failure · Desminopathies · Laminopathies

Abbreviations

IF	Intermediate filament
ID	Intercalated disc
ER	Endoplasmic reticulum
SR	Sarcoplasmic reticulum
ECM	Extracellular matrix
ESC	Embryonic stem cell
CPC	Cardiac progenitor cell
CM	Cardiomyopathy
DCM	Dilated cardiomyopathy
HCM	Hypertrophic cardiomyopathy
RCM	Restrictive cardiomyopathy
ARVD/C	Arrhythmogenic right ventricular dysplasia/cardiomyopathy

HF	Heart failure
DRM	Desmin-related myopathy
LMNA	Lamin A
αB-crystallin	alpha Beta crystallin
αBCry	alpha Beta crystallin
CryAB	gene: crystallin, alpha Beta
R120GCryAB	mutation R120G in CryAB
OPN	Osteopontin
EMT	Epithelial-to-mesenchymal transition
EndoMT	Endothelial-to-mesenchymal transition
PTM	Posttranslational modification
<i>Des</i> ^{−/−}	Desmin knockout
MAM	Mitochondria-associated ER/SR membranes
OM	Outer mitochondrial membrane
IMS	Inner mitochondrial space
IMM	Inner mitochondrial membrane
ANT	Adenine nucleotide translocator
CK	Creatine kinase
DG	Dystroglycan
PLB	Phospholamban
RyR	Ryanodine receptor
serca	Sarcoplasmic reticulum calcium ATPase

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SG	Sarcoglycan
VDAC	Voltage-dependent anion channel
MICOS	mitochondrial contact site and cristae organizing system
LINC	linker of the nucleoskeleton and the cytoskeleton
CMYA5	Cardiomyopathy-associated protein 5
AKAP	A-kinase anchor protein
shsp	Small heat shock protein
TRIM	Tripartite motif-containing protein
Bcl-2	B-cell lymphoma 2
EC coupling	Excitation-contraction coupling
CCD	Conduction system disease
MAPK	mitogen-activated protein kinase
ERK1/2	extracellular signal-regulated kinase 1/2
JNK	Jun N-terminal kinase
a.a.	Amino acids

Intermediate filaments in heart

The cytoskeleton of higher eukaryotic cells consists of three cytoskeletal networks, actin microfilaments, microtubules, and intermediate filaments (IFs). In contrast to the former two, IFs are composed of a variety of proteins which show cell type-specific expression and have been implicated in numerous human diseases (Eriksson et al. 2009). There are more than 73 different **intermediate filament** proteins identified which are classified into six groups based on similarities between their **amino acid** sequences (Table 1).

In cardiac tissue, the cytoskeletal IF proteins expressed are the type III: desmin, vimentin, paranemin, and syncoilin; type IV: synemin and nestin; and type V: the nuclear lamins. Desmin is the muscle-specific IF and the most abundant IF protein expressed in cardiomyocytes, whereas vimentin is not expressed in cardiomyocytes but rather is found mainly in mesenchyme-derived cells—both resident fibroblasts and pathologic myofibroblasts—and in the vascular tissue of the heart (vascular endothelial and smooth muscle cells). The non-muscle-specific synemin, paranemin, and syncoilin are expressed at a lower degree. Very early in cardiogenesis, there is low expression of nestin, originally identified as a brain stem cell-specific IF protein (Sejersen and Lendahl 1993; Kachinsky et al. 1994), that is eliminated in the adulthood from the heart and remains in skeletal myoblasts (Capetanaki et al. 2007). The nuclear **lamins** (lamin A, B1, B2, C1, and C2), components of the nucleoskeleton and particularly the nuclear lamina, are found in most **eukaryotic cells**.

Despite the diversity in size and **amino acid** sequence, the various IF proteins have common structural organization. All IF proteins have a central, conserved α -helical rod domain flanked by amino- and carboxy-terminal **domains**, which vary

Table 1 General classification of intermediate filament (IF) proteins

IF type	General categorization	IF protein members
Type I	Acidic keratins	28 members
Type II	Basic keratins	26 members
Type III	Muscle and neuron specific or ubiquitous	Desmin, GFAP, Peripherin, vimentin, syncoilin
Type IV	Mainly in neurons and some muscle	Neurofilaments, nestin, synemin a, synemin b, a-internexin
Type V	Nuclear IFs	Lamins (A, B1, B2, C1, C2)
Type VI	Lens-specific beaded IFs	Phakinin (CP49), Filensin

among the different intermediate filament proteins in size, sequence, and **secondary structure**. The variability in the amino-terminal head domain and the carboxy-terminal tail domains is responsible for the diversity, specificity, and regulation of IFs (Guharoy et al. 2013; Kornreich et al. 2015). The central α -helical rod domain is interrupted by linker domains (L1, L12, and L2) thus forming four helical subdomains (coil 1A, coil 1B, coil 2A, and coil 2B) with the characteristic heptad repeats that are required for coiled-coil dimer formation. On the other hand, the ability of IFs to assemble into high order structures is thought to depend on the interaction of alternating clusters of acidic and basic amino acids present throughout the α -helical rod, with the basic amino-terminal head domain (Geisler and Weber 1982; Chernyatina et al. 2012; Koster et al. 2015). The helical subdomains, 1A and 2B, are the most conserved regions among the various types of IFs and mutations within them in most cases lead to IF network disruption. The non-helical domains share little homology among the various types of IF but are similar within a given type. It has been suggested that the amino-terminal domains are essential for IF assembly, whereas the carboxy-terminal domains are involved in the organization of the IF network (Goldman et al. 2012). These non-helical domains have numerous phosphorylation sites which appear to be of crucial importance for their assembly, localization, and function (Eriksson et al. 2004). The IF proteins form homo or hetero dimers, elongate and get compacted in an organized way to finally give mature IFs (Herrmann et al. 2009). This organization probably gives IF the property to be resilient and at the same time very dynamic, a property regulated by phosphorylation, but its functional significance remains elusive. IFs were believed to reinforce cells to be organized into tissues, and for many years, their most important function was thought to provide mechanical support; however, this perception was recently challenged (Capetanaki et al. 1997; Weisleder et al. 2004a; Capetanaki et al. 2007, 2015; Diokmetzidou et al. 2016a). This was due to the fact that knockout or mutations in the genes encoding IF proteins contribute to diseases that are not due to structural defects per se but rather involved in a broader spectrum of functions, such as organelle biogenesis, positioning and function,

mechanochemical signal transduction, transcription and cell differentiation, and regulation of adhesion and migration (Chang and Goldman 2004; Capetanaki et al. 2007; Chang et al. 2009; Windoffer et al. 2011; Dingli et al. 2012; Chung et al. 2013; Schofield and Bernard 2013; Snider and Omary 2014; Capetanaki et al. 2015).

The heart myocardium is a striated muscle that requires a high coordination and tight regulation of adapting, sensing, and properly propagating any mechanochemical signaling from the sarcolemma and contractile apparatus to the nucleus as well as for cross talk between organelles (Capetanaki et al. 2007; Capetanaki et al. 2015). The link between the IF proteins desmin and lamins seems to act as a major integrator point of this intracellular communication either through the spanning LINC (linker of the nucleoskeleton and the cytoskeleton) complexes or through nuclear pores (Georgatos et al. 1987; Capetanaki et al. 2007; Cattin et al. 2013; Ho et al. 2013; Swift et al. 2013; Capetanaki et al. 2015). In addition, this nuclear–cytoskeletal coupling has a crucial role in the maintenance of whole-cell architecture as well as in the cytoskeletal tension transmission (Ho et al. 2013; Swift et al. 2013; Capetanaki et al. 2015; Kim et al. 2017).

In this review, we will focus on these cardiac IF networks and describe how their improper function can lead to cardiomyopathies.

Desmin in muscle development and adult muscle maintenance

Expression pattern of desmin in embryonic myogenesis and cardiogenesis

Desmin is encoded by a single copy gene which is expressed in all muscle tissues, cardiac, skeletal, and smooth, as the major IF protein (Capetanaki et al. 2007). It is one of the earliest known myogenic markers and one of the first muscle-specific proteins to appear during mouse embryonic development at 8.25 days postcoitum (d.p.c.) in the primitive cardiac tube, where it is transiently expressed together with vimentin, nestin, and keratins (Furst et al. 1989; Kuisk et al. 1996). Due to this early expression, it precedes not only all muscle-specific structural genes but also the myogenic HLH transcription regulators MyoD, myogenin, and MRF4 (Capetanaki et al. 2007). It is interesting that desmin can regulate these factors, along with members of the MEF2 family of transcription regulators, while being regulated itself by them in return (Li and Capetanaki 1993; Li and Capetanaki 1994; Kuisk et al. 1996; Capetanaki et al. 2007; Capetanaki et al. 2015). Adding to the importance of the early expression, desmin has been found in the adult skeletal muscle progenitors, the satellite cells (Allen et al. 1991), and in a subpopulation of cardiac progenitor cells, the side population (SP cells) (Pfister et al. 2005). Recent studies have demonstrated that amino-terminal mutations of

desmin interfere with cardiogenesis by impairing important cardiogenic regulators, such as brachyury, goosecoid, *nkx2.5*, and *mef2* (Hollrigel et al. 2002; Hofner et al. 2007; Hollrigel et al. 2007), while its ectopic expression in ES cells promotes upregulation of brachyury and *nkx2.5* and thus cardiogenesis (Hofner et al. 2007). In addition, it has been shown that small amounts of desmin transiently enter the nucleus of ESC-derived (CPCs) (Fuchs et al. 2016), thus suggesting a more direct nuclear role. This data suggests a regulatory role of desmin during myogenic and cardiogenic commitment and differentiation.

Desmin in muscle maintenance of adult heart

Desmin, the major IF protein in heart, together with its multiple binding partners, forms a 3D scaffold that extends across the entire diameter of the cardiomyocyte, surrounds the Z-discs linking the contractile apparatus with the costameres and intercalated discs of the plasma membrane, as well as with most membranous cellular organelles, including mitochondria, sarcoplasmic reticulum, and the nucleus (Fig. 1) (Capetanaki et al. 2007).

Desmin and the sarcolemma: organization and function of costameres and intercalated discs

Costameres, which are structures at the sarcolemma present at the membrane overlying Z-discs, consist of a complex protein network of cytoskeletal proteins and signaling kinases (Samarel 2005). Through costameres, desmin can connect the intracellular contractile apparatus to the extracellular environment and the extracellular matrix (ECM) and link many signaling molecules thus helping to sense mechanical stretch and transduce downstream signals. Desmin filaments are linked to costameres through plectin isoform 1f (Konieczny et al. 2008), spectrin (Langley and Cohen 1986), and through the binding of synemin to dystrophin (Bhosle et al. 2006) and α -dystrobrevin (Mizuno et al. 2001). Studies with desmin-deficient (*Des*^{−/−}) mice, which develop dilated cardiomyopathy (see below), have shown that desmin IFs play an important role in stabilizing the organization of the sarcolemma into costameres (O'Neill et al. 2002; Capetanaki et al. 2007). Additionally, desmin associates with the desmosomes of the intercalated discs through desmoplakin (Capetanaki et al. 2015). Intercalated discs (IDs) are structures of the plasma membranes with various proteins, consisting of three types: adherent junctions, desmosomes, and gap junctions. IDs are extremely important for cell-cell mechanical and electrical connections, crucial for cardiac function. Desmin deficiency or disruption leads to disease development (Capetanaki et al. 2007; Panagopoulou et al. 2008; Papathanasiou et al. 2015; Diokmetzidou et al. 2016a).

**Desmosome
of Intercalated disk**

**Mitochondria/Sarcoplasmic Reticulum
IF connections**

◀ **Fig. 1** Schematic representation of the cardiac intermediate filament network and its associations with different membranous compartments and organelles. In striated cardiac muscle, the IF lattice, composed predominantly of the muscle-specific IF protein desmin (yellow), together with its associated proteins forms an extended scaffold which connects the entire contractile apparatus to different membranous compartments [sarcolemma costameres and desmosomes of the intercalated disks (blow-up of blue box at lower left panel)] and organelles [nucleus, mitochondria, lysosomes, and the sarcoplasmic reticulum (SR)]. Desmin IF-link complex-lamin IF associations could facilitate mechanotransduction from sarcolemma and contractile apparatus to the nucleus. On the other hand, maintenance of organelle proximity by IFs (as is known for ER/SR and mitochondria contact site/MAM formation) could allow efficient biogenesis and functional cross talk (e.g., protein, lipid, and calcium traffic) between them, (MAMs are shown in the red box and, at higher magnification, in the lower right panel; see text and blow-up of red box at lower right panel). Desmin interacts directly with VDAC (MAM protein) and is also associated with the MICOS complex, suggesting its importance in mitochondrial biogenesis and maintenance. Disruption of the desmin IF network results in cardiomyopathy (mainly DCM). Desmin-associated proteins that have been implicated in DCM development are marked with asterisk. ID proteins, associated directly or indirectly with desmin, that are implicated in ARVC are marked with blue and white asterisk. The alternative ectopic keratin [k8/k18] IF network induced in heart failure by TNF- α as a compensatory mechanism (Papathanasiou et al. 2015), normally not expressed in healthy myocardium, is shown in red. The lower abundant non-muscle-specific IFs, synemin paranemin and syncoilin, are not shown. IFs, intermediate filaments; SR, sarcoplasmic reticulum; MAM, mitochondria-associated ER/SR membranes; OM, outer mitochondrial membrane; IMS, inner mitochondrial space; IMM, inner mitochondrial membrane; ANT, adenine nucleotide translocator; CK, creatine kinase; DG, dystroglycan; PLB, phospholamban; RyR, ryanodine receptor; serca, sarcoplasmic reticulum calcium ATPase; SG, sarcoglycan; VDAC, voltage-dependent anion channel; MICOS complex, mitochondrial contact site and cristae organizing system; OPA, dominant optic atrophy; SAM, sorting and assembly machinery; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy. Adapted from Capetanaki et al. (2007)

Desmin and the contractile apparatus-sarcomeres/myofibrils

The original finding that desmin surrounds the Z-discs and potentially links them together has suggested that it might be responsible for the lateral alignment of myofibrils and the integrity of the contractile apparatus (Granger and Lazarides 1979). However, this hypothesis was challenged by studies with desmin-null mice which demonstrated that overexpression of Bcl-2 (Weisleder et al. 2004b), a mitochondrial antiapoptotic protein, can rescue the proper Z-disc alignment in the absence of desmin. Nevertheless, desmin associates with nebulin (Bang et al. 2002; Conover and Gregorio 2011) and nebulin (Hernandez et al. 2016), known to stabilize the actin filaments of the sarcomeres but the precise function of this association remains elusive. It is known, however, that an anomaly of the interaction between desmin and nebulin, caused by a Glu245Asp mutation in desmin, or an anomaly of the interaction between desmin and nebulin, caused by a Q128R mutation of nebulin, underlies a human desminopathy with perturbed striated muscle actin filament architecture (Conover et al. 2009).

Desmin and the mitochondria It has been known that mitochondria are linked with the IFs (and microtubules) (Rappaport et al. 1998); however, the interplay between the desmin IF cytoskeleton and mitochondria came from studies with desmin-deficient mice (*Des*^{-/-}) (Milner et al. 2000; Capetanaki et al. 2007; Capetanaki et al. 2015). Proper muscle maintenance requires a tight link between energy production and demand; thus, mitochondria abnormalities are a common pathological feature among desmin-related cardiomyopathies. Indeed, the earliest and most prominent features of *Des*^{-/-} mice pathology are mitochondrial structural perturbations, arising before any other cardiac dysfunction (Milner et al. 2000). Mitochondrial defects include loss of proper morphology followed by cardiomyocyte death, inflammation, fibrosis, and calcification, all leading to extensive myocardial degeneration, dilated cardiomyopathy, and heart failure (Milner et al. 1996; Kay et al. 1997; Milner et al. 1999; Milner et al. 2000; Fountoulakis et al. 2005; Psarras et al. 2012; Mavroidis et al. 2015; Diokmetzidou et al. 2016a). Desmin's presence is important for cristae structure, respiratory function, mitochondrial permeability transition pore (mPTP) activation, sensitivity to oxidative stress, and proper mitochondrial membrane potential ($\Delta\psi$ m) (Diokmetzidou et al. 2016a, b). Desmin IF network could maintain mitochondria in close proximity to myofibrils and facilitate sensing and transferring of the energy needs, thus coupling mechanochemical signaling to metabolism. Indeed, mitochondrial proteomic studies in *Des*^{-/-} mice have shown differences in most metabolic pathways, particularly ketone body and acetate metabolism, NADH shuttle components, amino acid metabolism, and respiratory enzymes (Fountoulakis et al. 2005). Levels of proteins that have been implicated in apoptosis and calcium homeostasis are also differentially affected (Fountoulakis et al. 2005). It can also support proper protein and lipid targeting to the right compartments and/or stabilize and properly target functional complexes (Fountoulakis et al. 2005). In addition, the desmin IF network can facilitate functional cross talk of mitochondria with organelles such as endoplasmic reticulum/sarcoplasmic reticulum (ER/SR) (Capetanaki et al. 2007; Capetanaki et al. 2015; Diokmetzidou et al. 2016a). Intriguing studies showed that desmin is localized at the contact sites between SR and mitochondria (MAMs, mitochondria-associated membranes), important structures for multiple cellular processes, including Ca^{2+} and metabolite transfer, lipid metabolism, mitochondrial shape regulation, and autophagosome and inflammasome formation (Diokmetzidou et al. 2016a). This association could be mediated through voltage-dependent anion channel (VDAC), present both in mitochondria and SR, which was found to directly interact with desmin (Fig. 1). The importance of desmin in mitochondrial function is reinforced by the finding that desmin associates with different members of the MICOS (mitochondrial contact site and cristae organizing system) complex (Mitofilin/

Mic60, Mic19, and Mic27), the mitochondrial outer membrane (OMM) Sam50, involved in protein transport, OPA1, involved in fusion and ATP synthase β (Diokmetzidou et al. 2016a). It is still unclear if VDAC is the mediator of the desmin association to MICOS complex or there are other/multiple components of the complex also interacting directly with desmin.

Moreover, a recently shown association of RyR2a with the desmin-associated protein myospryn (CMYA5, cardiomyopathy-associated 5), a novel tripartite motif family (TRIM)-like protein, demonstrated in addition to VDAC an indirect way of desmin association to the SR of cardiomyocytes (Benson et al. 2017). The desmin-myospryn interaction is important for perinuclear and lysosomal localization of myospryn (see below) (Kouloumenta et al. 2007). Therefore, it would be important to find if this applies to association of myospryn with MAMs, which would suggest that desmin might play an important role in the proper assembly and maintenance of ryanodine receptor (RyR), and potentially other protein clusters at SR, very essential for physiological EC-coupling.

Myotubularin is another desmin-associated protein and mutations in this gene impair its association with desmin lead to mitochondrial defects and X-linked centronuclear myopathy (Hnia et al. 2011).

Desmin and the lysosome-related organelles Studies in neonatal cardiomyocytes revealed an association of desmin with myospryn. Myospryn was initially identified as an associated partner to the biogenesis of lysosome-related organelles complex 1 (BLOC-1) protein dysbindin, and it appears that its proper positioning to lysosomes is desmin dependent (Kouloumenta et al. 2007). These data implicate desmin IF cytoskeleton and associated proteins in vesicle trafficking and the control of the endo/lysosomal compartments, proper lysosome biogenesis and distribution in cardiomyocytes, and potentially proper autophagosome/autophagophore formation, processes very significant in cardiac pathology (Kouloumenta et al. 2007; Wang and Robbins 2014).

Desmin IF network as a mechanochemical integrator and transducer to the nuclei Throughout development, cells both exert and are subject to a variety of forces and interactions. For each tissue to maintain its multicellular integrity, cells must avoid rupturing due to mechanical strain and remain adherent to one another. Among the three cytoskeletal networks, intermediate filaments appear to be flexible, elastic, and highly extensible (Sanghvi-Shah and Weber 2017). They exhibit strain-induced strengthening, perform as intracellular load bearing springs (Ackbarow et al. 2009; Pawelzyk et al. 2014), and regulate cell stiffness (Ramms et al. 2013; Seltsmann et al. 2013). Striated muscle cells have an intrinsic ability to sense and respond to mechanical load and undergo physiological remodeling, through a process known as mechanotransduction. Desmin's 3D network can

host a number of proteins that have been proposed as key mechanosensors and mechanotransducers. These proteins can directly sense and respond to mechanical load (stress and/or strain) and translate it to structural, signaling, and functional alterations, thus affecting various cellular processes such as regulation of electrophysiology via stretch-sensitive channels, contractile function, calcium regulation, changes to metabolic status, and importantly gene expression, ultimately leading to the remodeling of the myofiber (Potthoff et al. 2007). Indeed, there is a tight coordination of the desmin IF cytoskeleton with the lamin IF nucleoskeleton propagating stimuli coming from the ECM down to the nucleus. These two systems form a continuous network, either directly through the nuclear pores (Georgatos and Blobel 1987; Lockard and Bloom 1993) or indirectly through plectin-nesprin3-LINC (linker of the nucleoskeleton and the cytoskeleton) complex (Frock et al. 2006).

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 (Lockard and Bloom 1993; Shah et al. 2004; Ralston et al. 2006). Complementary to this, lamin A/C null (*Lmna*^{-/-}) cardiomyocytes show disorganization and detachment of desmin filaments from the nuclear surface (Nikolova et al. 2004; Jahn et al. 2012), while ectopic expression of desmin in *Lmna*^{-/-} myoblasts rescues their compromised differentiation potential (Frock et al. 2006), suggesting a role of desmin-lamin network in cardiac differentiation. The suggested mechanochemical coupling is reinforced by the established need of desmin for proper localization of myospryn around the nucleus (Benson et al. 2004; Kouloumenta et al. 2007). Since myospryn is an A-kinase anchoring protein (AKAP) and moreover it has been shown to be a negative regulator of calcineurin modulation, it is possible that through this interaction desmin regulates calcineurin-dependent transcriptional activity and regeneration (Kielbasa et al. 2011; Tsoupri and Capetanaki 2013). In addition, there is an interaction of desmin with the stretch-sensing transcription factor cardiac ankyrin repeat protein (Ankrd1/CARP), known to shuttle in and out the nucleus (Witt et al. 2005). Moreover, recent studies show a direct interaction of desmin with DUX4, a potent transcription factor that causes facioscapulohumeral muscular dystrophy (FSHD) demonstrating an additional connection of desmin in gene regulation and its importance in muscle differentiation and in neuromuscular and cardiac pathologies (Ansseau et al. 2016). Studies of great interest suggest a temporary presence of desmin in the nuclei of differentiating CPCs suggesting a direct association of desmin with the transcriptional machinery of cardiac genes (Fuchs et al. 2016). Based on these findings, it has been

proposed that the desmin IF scaffold could participate in a bidirectional mechanochemical signaling process leading to de novo gene activity and tissue homeostasis.

Desmin interactome

In order to achieve its multi-level functions, desmin forms a rich and complex interactome. Desmin interacts directly with more than 15 proteins, while there are numerous additional proteins with which its network interacts indirectly. In this section, we will add some additional proteins to those previously described, assuming their association with desmin may be important for the proper desmin IF function in the heart.

Interaction with other IF proteins There are six IF proteins that show a spatiotemporal interaction with desmin. Five are cytoplasmic IFs: vimentin, nestin, syncoilin, synemin, and paranemin. Symemin, syncoilin, and paranemin are expressed throughout cardiac development and possibly contribute to the stability of the desmin IF network. In addition, at least nuclear B-type lamins have been suggested to be a direct binding partner of desmin (Georgatos and Blobel 1987; Lockard and Bloom 1993).

Interactions with proteins linking to costameres and intercalated discs There are multiple ways by which desmin interacts with the costameres. These associations include the IF proteins synemin and syncoilin, the cytolinker Plectin 1f, spectrin (Langley and Cohen 1986), and ankyrin (Georgatos and Blobel 1987). Desmin also interacts through myospryn to dysbindin-dystrobrevin-dystrophin complex (Benson et al. 2004). There is also evidence of desmin's binding with the nicotinic acetylcholine receptor (Mitsui et al. 2000) and caveolin 3 (Mermelstein et al. 2007).

At the ID level, desmin interacts directly with desmoplakin (Kartenbeck et al. 1983; Lapouge et al. 2006) and myospryn (Kouloumenta et al. 2007).

Interactions with small heat shock proteins, chaperones, and apoptosis-related proteins There are two small heat shock proteins (shsp) that directly interact with desmin at multiple sites: Hsp25 (Hsp27) and alpha Beta crystallin (α B-crystallin) (Bennardini et al. 1992; Kawano et al. 2012; Wettstein et al. 2012). The interaction of desmin- α B-crystallin appears to be significant for the pathology of cardiomyopathies. Mutations in this shsp cause the same desmin-related dilated cardiomyopathy and heart failure with similar mitochondrial defects (see below). Both proteins co-localize in the mitochondria-SR contact sites (MAMs) and their proper interaction has mito- and cardioprotective effects (Diokmetzidou et al. 2016a). Overexpression of α B-crystallin in desmin-deficient hearts

ameliorates all mitochondrial defects and improves cardiac function significantly (see below) (Diokmetzidou et al. 2016a).

Interactions with other proteins and nucleic acids Calponin, a calmodulin and tropomyosin-binding protein, has been shown to be in direct association with desmin in smooth muscle (Fujii et al. 2000). Surfactant protein A (SP-A), a member of the collectin family that regulate innate immunity, associates with desmin and vimentin and appears to regulate their polymerization (Garcia-Verdugo et al. 2008). Finally, desmin has been demonstrated to bind to single-stranded RNA and DNA molecules in vitro (Vorgias and Traub 1986; Wang et al. 2001a).

Nuclear Lamins

Lamins are proteins of the class V IF family and consist of two different types, A or B, depending upon their structural similarities and isoelectric points. The major A-type lamins, lamin A and C (or lamin A/C), are expressed in most terminally differentiated cells and are identical in their first 566 amino acids (a.a.) but have distinct tail domains. They are encoded by the single lamin A (*LMNA*) gene on human chromosome 1q21.2-21.3 and result from alternative splicing of the *LMNA* mRNA transcript (Lin and Worman 1993; Worman 2012). While lamin C is translated as a mature protein, lamin A is synthesized as a precursor, prelamin A, which has a unique carboxy-terminal amino acid tail that undergoes posttranslational modification processes including farnesylation, cleavages, and methylation to reach the mature lamin A. *LMNA* also encodes a minor protein isoform, lamin A Δ 10, and a germ cell-specific isoform, lamin C2. The B-type lamins are present in all or most somatic cells and they are encoded by two other genes, B1 from the *LMNB1* and B2 from *LMNB2* genes, respectively (Worman 2012; Cattin et al. 2013). The expression of B-type lamins starts at the earliest stages of development, before any A/C lamins can be detected. In contrast, lamin A/C expression starts at about embryonic day 12 in some differentiating mouse tissues, whereas in cardiac muscle at day 5 after birth (Rober et al. 1989).

A-type lamins polymerize and assemble together with B-type lamins in order to form the nuclear lamina, a fibrous and highly organized meshwork beneath the inner nuclear membrane (Aebi et al. 1986). Inside the nucleus, lamin A/C proteins largely interact with several nucleoplasmic or inner nuclear membrane proteins as well as with chromatin. Therefore, apart from the critical role of lamin A/C in providing support and stiffness to the nucleus, they influence also numerous other functions (e.g., DNA replication, RNA transcription, and genome organization), extending their properties to the regulation of gene expression and transmission of signaling cascades (Dechat et al. 2008; Worman 2012; Choi and Worman 2014).

Other intermediate filaments

Vimentin, syncoilin, synemin, and paranemin

Vimentin (Zehner and Paterson 1983) is mainly expressed in undifferentiated and proliferative cells of mesenchymal origin and, upon differentiation, is replaced by the corresponding cell type-specific IF protein (Tapscott et al. 1981; Capetanaki et al. 1984; Olson and Capetanaki 1989). It has been implicated in growth and differentiation of different systems, including muscle (Olson and Capetanaki 1989), lens (Capetanaki et al. 1989; Mou et al. 2010), and osteoblasts (Lian et al. 2009). As an exception to proliferating cells, vimentin has been shown to be expressed in fully differentiated blood and lens cells. In the cardiac tissue, it is expressed early in cardiogenesis and during development its levels are reduced while desmin expression is upregulated (Kim 1996). In agreement with its role in proliferation, vimentin's overexpression inhibits differentiation (Capetanaki et al. 1989). Importantly, it is expressed in almost all cancer cells and its levels have been linked to metastasis and poor prognosis (Cheng and Eriksson 2016).

Syncoilin and paranemin, type III IFs, and synemin, a type IV IF protein, have similar properties and spatial and temporal expression profile. While they have been observed in a variety of cell types, they have been best studied in skeletal and cardiac myocytes where they might modulate the association of desmin to costameres and Z-discs (Bloch et al. 2002).

Intermediate filaments in cardiomyopathy and heart failure

There are more than 45 different diseases of the heart, muscle, skin, liver, brain, adipose tissues, and premature aging that are attributed to disturbance of the IF network and a major one is cardiomyopathy (Capetanaki et al. 2007; Oshima 2007; Capetanaki et al. 2015). Cardiomyopathies (CMs) are classified into four main categories: hypertrophic (HCM), dilated (DCM), restrictive (RCM), and arrhythmogenic right ventricular dysplasia (ARVD/C). DCM is the primary cause of heart failure (HF) among CMs and the most common after ischemic heart disease.

On the other hand, HF is a result of several pathological conditions; at least 17 etiologies have been already estimated and four among them (ischemic, hypertensive and valvular/rheumatic heart disease, and chronic obstructive pulmonary disease) may be responsible for up to 2/3 of cases (Ziaieian and Fonarow 2016). Ischemic conditions underlie almost half of HF, whereas up to 36% of HF cases can be of ischemia-independent etiology, such as DCM, characterized by dilation of the ventricular chambers and systolic dysfunction accompanied by thinning or not of ventricular walls.

Among DCM cases, a considerable component (35–50%) may be inherited. Inherited CMs in general are associated with mutations in over 100 genes encoding mostly structural proteins, ion channels, mitochondrial proteins, and calcium metabolism and transcription factors, either primarily affecting the myocardium or including skeletal muscle and extramuscular manifestations (Watkins et al. 2011; McNally et al. 2015). DCM is the most genetically heterogeneous and the second most abundant form among inherited CM.

Years of clinical research focusing on HF including interventions based on beta-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid antagonists improved only the outcomes in patients but do not cure the disease. One of the hallmarks of CM and HF is pronounced and progressive cardiomyocyte death. Even though basic research has shown that sarcomeric, cytoskeletal, and desmosomal proteins are the primary cause of inherited HCM, DCM, and ARVD/C, respectively, the need for understanding the molecular and cellular mechanisms that lead to common phenotypes is of great importance.

Various studies have shown that mutations in IF proteins especially in desmin and lamins and/or perturbations in their networks are the most common causes of human inherited DCM or cause DCM and HF in animal models (Capetanaki et al. 2015; Captur et al. 2018). On the contrary, there are few studies implicating the rest of the cytoplasmic IF proteins expressed in the heart, vimentin, syncoilin, synemin, and paranemin, in CMs. In the next sections, we will address the basic features and mechanisms of their involvement in cardiac pathology.

Desmin-related cardiomyopathies—desminopathies

Desmin-related myopathy and cardiomyopathy (DRM or desminopathy) is an autosomal inherited skeletal and cardiac myopathy, caused by dysfunctional desmin network mainly due to mutations in the desmin gene (*DES*) or posttranslational modifications in the desmin protein (Dalakas et al. 2000). Desminopathy is considered as a subgroup of a genetically heterogeneous group of neuromuscular disorders termed myofibrillar myopathies (MFM) (Selcen 2011) and except from mutations in the desmin gene are also caused by mutations in α B-crystallin, dystrophin, filamin C, myotilin, ZASP, BAG3, FHL1, VCP, plectin, and nebulin (Vicart et al. 1998; Selcen and Engel 2003; Goldfarb et al. 2008; Goldfarb and Dalakas 2009; Hernandez et al. 2016). They are characterized by desmin network disruption and desmin aggregation with degenerative changes in the myofibrillar network (Schroder and Schoser 2009; Selcen 2011), which seem to be secondary to myocyte death caused in most cases by mitochondrial defects (Capetanaki et al. 2007; Capetanaki et al. 2015; Jackson et al. 2015). We will focus on desmin since

most of the knowledge of the disease pathology comes from studying its deficiency, mutations, or posttranslational modifications (Capetanaki et al. 2015), all of which lead to different forms of cardiomyopathy but most commonly to DCM and HF (Towbin and Bowles 2006; Capetanaki et al. 2015).

Desmin mutations

DRM appears to have a plethora of phenotypic manifestations possibly due to the fact that different mutations can affect differentially the long and complex IF network (Goldfarb et al. 2004). The desmin gene consists of nine exons and is highly conserved among vertebrate species. Desmin is organized, as mentioned above, into three domains—a highly conserved α -helical rod domain flanked by globular N- and C-terminal structures (the “head” and “tail” domains, respectively) (Weber and Geisler 1985), a structure typical for cytoskeletal IFs. More than 70 human *DES* mutations associated with desminopathies have been reported so far (Goldfarb and Dalakas 2009; van Spaendonck-Zwarts et al. 2011; Clemen et al. 2013) (Fig. 2). The majority of *DES* mutations are missense mutations within the central rod domain causing cytoplasmic desmin aggregates (Baer et al. 2005; Brodehl et al. 2012), whereas nonsense, insertions, deletions (Munoz-Marmol et al. 1998; Schirmer et al. 2018), or combined insertion and deletion (indel) mutations (Cao et al. 2013) are rare. A phenotype–genotype correlation meta-analysis showed that patients with predominant mutations in the rod 2B domain of desmin demonstrated skeletal and cardiac muscle defects (90%), whereas most of the patients with isolated cardiological signs had a mutation in the head or the tail domain (65%) (van Spaendonck-Zwarts et al. 2011).

The vast majority of genetically proven DRMs follow an autosomal dominant trait of inheritance. However, rare autosomal recessive cases with an earlier and more severe disease manifestation have been described (Clemen et al. 2015). Moreover, gene dosage effects caused by heterozygous, homozygous, double heterozygous, and compound heterozygous mutations in the desmin gene are also at play (Azzimato et al. 2016). It is also clear that modifier genes together with epigenetic mechanisms interfere with the presence of *DES* mutations and could account for the incomplete, age-dependent, gender-specific penetrance, and phenotypic variability observed even within the same family (Bergman et al. 2007; van Spaendonck-Zwarts et al. 2011; Brodehl et al. 2013) (Otten et al. 2010).

Clinical manifestations The incidence and prevalence of DRMs are currently unclear. Interpretation of the published data so far allows the assumption that DRMs fulfill the

definition of a rare disease. In a study on the prevalence of desmin mutations in dilated cardiomyopathy, desmin mutations accounted for up to 2% of disease manifestations (Taylor et al. 2007). A meta-analysis of 159 patients with 40 different *DES* mutations reported in the literature (van Spaendonck-Zwarts et al. 2011) indicated that up to 50% of carriers had cardiomyopathy, mostly DCM (17%), RCM (12%), and HCM (6%) and to lesser extend ARVC (1%). About 60% of the patients had cardiac conduction disease or arrhythmias, with atrioventricular block as an important hallmark. A recent report of the largest family of a single *DES* mutation (*DES*-p.Glu401Asp) causing predominantly inherited right ventricular arrhythmogenic cardiomyopathy suggested that the prevalence of desmin mutations in ARVC may be higher (Bermudez-Jimenez et al. 2018).

Desmin-positive protein aggregates as well as granulofilamentous and electron-dense amorphous materials are the morphological hallmarks of desmin-related cardiomyopathies. Further reported pathological findings were myocyte hypertrophy, disarray of the myocytes, mis-shaped myonuclei, cytoplasmic vacuolar degeneration, focally lysed myofibrils, intercalated discs abnormalities, mitochondrial abnormalities, and various degrees of diffuse interstitial fibrosis (Goldfarb and Dalakas 2009).

Desmin caspase cleavage in heart failure: the most common mutation-free desminopathy

Upregulation of tumor necrosis factor- α (TNF- α), one of the major stress-induced proinflammatory cytokines, is often seen in heart tissue after injury, and it has been shown to contribute to the development of HF (Mann 2003). It has been shown, both in a mouse TNF- α model of heart failure (Panagopoulou et al. 2008) as well as in human failing heart (Papathanasiou et al. 2015), that desmin is cleaved by TNF- α -induced caspase-6 and this leads to desmin IF network disruption, desmin aggregate formation, mitochondrial and ID defects, cardiomyocyte death, DCM, and HF (Papathanasiou et al. 2015). This proteolytic cleavage seems to be responsible for the disease development since a caspase cleavage resistant form of desmin rescues this phenomenon (Panagopoulou et al. 2008). Given that the desmin aggregate formation resembles that of a desminopathy, heart failure with elevated levels of TNF- α can be considered the most common desminopathy independent of desmin mutations. Another study showed that N-terminal head domain cleavage occurs in a canine cardiomyopathy model and human heart failure (Agnetti et al. 2014). Interestingly, a missense mutation at the C-terminus of desmin promotes its *in vivo* proteolytic cleavage at the N-terminus leading to impairment of desmin’s localization at the Z-discs (Mavroidis et al. 2008).

Fig. 2 Cardiomyopathy and myopathy-related desmin mutations. Schematic representation of the human desmin and distribution of the mutations that cause cardiac disease. Desmin protein exhibits a tripartite structure consisting of an amphipathic central α -helical rod domain (interrupted by three short non-helical linkers, L1, L12, L2, which generate four helices, 1A, 1B, 2A, and 2B, flanked by the flexible non- α -helical “head” and “tail” domains. Numbers indicate the amino acid position of the domain borders. The majority of the 73 pathogenic desmin mutations identified so far reside within the 2B helical domain and the tail. Most of the mutations are missense (Brodehl et al. 2012); however, there are some non-sense, insertions, deletions (Munoz-Marmol et al.

1998; Schirmer et al. 2018), or even a combination of insertion-deletion (M349_R355delinsG) (Cao et al. 2013). Solid red (P) represents mutations that affect known phosphorylation sites, while dotted red (P) represents mutations on potential phosphorylation sites. The two known substrates of ADP-Ribosylation (Arg58 and Arg73) at the head domain are indicated with green triangle -R. Mutations with cardiac manifestation are indicated with different colored dots. DCM causing mutations are shown with blue, HCM with green, RCM with red, and ARVC with purple. TNF- α -induced caspase 6 cleavage of desmin at Met263 within the L12 linker domain is shown

Desmin and posttranslational modifications

Proteomic studies highlight the enormous complexity and regulatory potential of IF protein posttranslational modifications (PTMs). PTMs can affect IF assembly, disassembly (Sihag et al. 2007; Hyder et al. 2008; Snider and Omary 2014) and cell migration (Tang and Gerlach 2017), preserve the structural and functional integrity of IFs by regulating their solubility (Zhang and Sarge 2008), facilitate important interactions between IFs and other cellular components and structures, and can generate or eliminate defective IF proteins that are a direct cause of, or contribute to, the pathogenesis of diseases (Omary 2009).

Desmin extensive network can serve as a scaffold for many signaling molecules such as kinases and phosphatases affecting their regulation and be regulated by them in return. Desmin's PTMs include phosphorylation, ADP-ribosylation, ubiquitination, glycation, oxidation, and nitration (Winter et al. 2014). Most of PTMs cause disassembly of desmin network, with the exception of ubiquitination which leads to its degradation. Among other enzymes (PKA, PKC, PAK, CaMKII) (Winter et al. 2014), desmin is phosphorylated by Rho kinase (Inada et al. 1998), Aurora-B (Kawajiri et al. 2003), and by Cdk1 (Makihara et al. 2016), all PTMs required

for efficient separation of desmin-IFs in mitosis (Inada et al. 1999; Kawajiri et al. 2003).

Recently, another kinase, GSK-3 β , has been shown to bi-phosphorylate desmin, as a requirement for its incorporation into the Z-discs (Agnetti et al. 2014; Rainer et al. 2018). Interestingly, some cases of heart failure exhibit decreased levels or inhibition of this enzyme (Agnetti et al. 2014; Rainer et al. 2018), and as a consequence, desmin is monophosphorylated and this leads to its decreased incorporation to the Z-disc, as well as to increased desmin-positive protein aggregates with toxic effects (Rainer et al. 2018).

In conclusion, in DRMs and upon HF, desmin could be (a) hyper/or/abnormally phosphorylated (Caron and Chapon 1999; Panagopoulou et al. 2008; Diguët et al. 2011; Agnetti et al. 2014; Rainer et al. 2018) leading to its cleavage and/or aggregate formation which can have toxic effects, (b) oxidized and nitrated forming pathological protein aggregates (Janue et al. 2007), and (c) a preferential target of advanced glycation end products (AGE) leading to the disorganization of its filament network (Diguët et al. 2011). These modifications and aggregate formations lead, in addition to loss of desmin's function, to cytotoxic effects, including impairment of desmin's degradation via the ubiquitin-proteasome system.

Desmin life cycle and turn over

Impairment of desmin turnover could be a crucial mechanism in DRMs. Indeed, its accumulation has been reported in human patients with dilated cardiomyopathy (Heling et al. 2000). This could be due to its deregulated turnover, since DRMs show a proteasome impairment (Liu et al. 2006a). E3 ubiquitin ligases shown to regulate desmin turnover are TRIM32 (Cohen et al. 2012) and Atrogin-1 (Lokireddy et al. 2012), both involved in myopathies (Kudryashova et al. 2009; Bodine and Baehr 2014). Moreover, the deubiquitinating enzyme YOD1 was found to stabilize desmin protein levels and its downregulation is involved in cardiac failure induced by Coxsackievirus B3 infection (Ye et al. 2014).

Desminopathies—mechanism of disease development

There have been several animal models recapitulating desmin mutations that help us unravel the underlying mechanism of desmin's function under normal and disease development. These can include models where desmin is completely absent, *Des*^{−/−}, and transgenic mice that express different desmin mutations found in human patients. The obvious question that emerges is which mechanism is responsible for the disease development?

Toxic aggregate formation or loss of desmin function

Examination of the myocardium in the majority of the transgenic models and in some cases in human patients revealed an accumulation of chimeric intracellular aggregates containing desmin and other proteins, which may associate directly or indirectly with the desmin network. The formed aggregates disrupt the continuity and overall organization of desmin network throughout the cell (Wang et al. 2001b). Biochemical analysis showed that, along with desmin, these aggregates contain α B-crystallin, hsp27, synemin, syncoilin, nestin, plectin, filamin C, hsp72/73, myotilin, dystrophin, utrophin, a and b-dystroglycan, a, b, g, and d-sarcoglycans, caveolin, dysferlin, actin, actinin, N-CAM, NOS, collagen VI, laminin, b-spectrin, and ubiquitin (Goldfarb and Dalakas 2009). Proteomic analysis of skeletal muscle biopsies of DRM patients identified 22 proteins significantly overrepresented in the aggregates, with desmin and filamin C in the highest levels, followed by Xirp2, α B-crystallin, N-RAP, Xin, and Hsp27 (Maerkens et al. 2013). Studies have shown that these aggregates contain oligomers with amylogenic potential which are toxic (Sanbe et al. 2004), similar to the ones seen in many neurodegenerative diseases. Actually, it appears that an early intermediate step is responsible for toxicity, forming the toxic preamyloid oligomers (PAO) which mature to amyloid fibrils and later form aggregates (Glabe 2008). Cardiomyocyte-specific expression of an exogenous peptide

capable of assuming a PAO conformation was sufficient to cause heart failure resulting to mortality in a transgenic mouse model (Pattison et al. 2008). Many PTMs, as discussed above, are responsible for initiating the nucleation process that leads to the toxic formation of PAOs (Agnetti et al. 2014; Del Monte and Agnetti 2014; Rainer et al. 2018), thus reinforcing their crucial role in cardiomyopathies. In addition, desmin mutants that are responsible for either forming short, segmented filaments or causing enhanced adhesiveness or rapid disintegration, all lead to filament aggregation attesting to the importance of proper filament assembly.

However, even though formation of PAOs is emerging as a common hallmark of experimental and human acquired heart failure (Sanbe et al. 2004; Gianni et al. 2010; Agnetti et al. 2014; Subramanian et al. 2015; Rainer et al. 2018), studies with the *Des*^{−/−} mice which do not contain any type of aggregates prove that the pathological aggregates may not be the main reason for the disease development. Indeed, *Des*^{−/−} mice may be viable and fertile, but after birth, they develop dilated cardiomyopathy (Li et al. 1996; Capetanaki et al. 2007; Psarras et al. 2012; Diokmetzidou et al. 2016a). The *Des*^{−/−} model suggests that the underlying mechanism of the observed pathology is due mostly to the loss of function of desmin IF network and the consequences that this has on its interacting molecules and organelles, rather than gain of aggregate toxic function.

Consequences of desmin loss on its interacting proteins

As discussed, above desmin IF network can affect directly or indirectly multiple protein partners, placing them on the proper location, bringing them in close proximity to each other or even helping their trafficking, targeting to the right place and assembly into complexes. Many of these interacting proteins are actually found in the aggregates formed in DRMs. What is of interest is the fact that mutations on these proteins can also cause DRMs independently of genetic mutations in desmin's sequence. Among those, worth mentioning example is α B-crystallin (α BCry), desmin's main chaperone whose mutations, including the best studied R120GCryAB, can cause the exact same DRM pathology as desmin deficiency (Vicart et al. 1998; Wang et al. 2001b). As a chaperone, α B-crystallin may assist to the proper normal desmin folding. This appears to be one of the many consequences of desmin- α B-crystallin interaction, as discussed below. (Diokmetzidou et al. 2016a). Mutations in CryAB that inhibit proper folding and degradation can cause DRM. Additionally, in DRMs, the aggregate phenotype is exasperated by the fact that the ubiquitin-proteasome pathway is impaired. Studies overexpressing mutant desmin in cultured cardiac myocytes (Liu et al. 2006a) and transgenic mice (Liu et al. 2006b) showed inhibition of the ubiquitin-proteasome system eliminating the possibility of the removal of toxic aggregates.

In addition to the proteins found in the toxic aggregates, there are additional ones not found in PAOs (such as myotubularin (Hnia et al. 2011), nebulin (Conover et al. 2009), the nuclear lamin A/C (Captur et al. 2018), emerin and LAP2a) that show similar DCM phenotypes, suggesting that regardless of the mutated protein, desmin is often the responsible player. Loss of interaction between desmin and its interacting proteins does not always lead to protein aggregation as studies have shown with lamin B in limb-girdle muscular dystrophy (Cetin et al. 2013) and nebulin which leads to destabilization of actin filament network (Conover and Gregorio 2011).

Concluding, what these studies reveal is that the disruption of desmin organization, regardless of the genetic cause, will affect the proper function of the entire network leading to multiple defects which can be enhanced by the presence of toxic aggregates leading to different myopathies and cardiomyopathies.

Loss of proper mitochondrial function as an early prominent defect

Mitochondrial defects appear before any other abnormalities and they do constitute the common pathological feature among DRMs (Capetanaki et al. 2007; Clemen et al. 2013; Capetanaki et al. 2015). In *Des*^{-/-} myocytes, mitochondria are swollen with ruined morphology and cristae structure, impaired respiratory function, increased ROS levels, abnormal mPTP activation, and impaired mitochondrial membrane potential (Milner et al. 1996; Milner et al. 2000; Capetanaki et al. 2007; Capetanaki et al. 2015; Diokmetzidou et al. 2016a). Even in the disease cases where the toxic PAO aggregates are manifested, mitochondrial defects are prominent (Goldfarb and Dalakas 2009). Indeed, most of the mouse model studies suggest that the *mitochondrial deficiency is the main underlying reason for the disease pathology*. Overexpression of the mitochondrial protein Bcl-2, in both the *Des*^{-/-} and R120GCryAB DRM mouse models, significantly ameliorates the pathology (Weisleder et al. 2004b; Maloyan et al. 2010). Moreover, moderate MnSOD and/or catalase overexpression in *Des*^{-/-} hearts resulted in a decreased intracellular reactive oxygen species (ROS), ameliorating mitochondrial and other ultrastructural defects (Rapti et al. 2017). The best protection so far has been achieved by α B-crystallin overexpression in *Des*^{-/-} heart, where structural and functional defects are rescued to almost wild type levels (Diokmetzidou et al. 2016a) (Fig. 3). These studies have suggested that desmin deficiency or disruption compromises the interplay between desmin and α B-crystallin required for proper targeting of proteins to mitochondria and SR, as well as the proper assembly and/or stabilization of mitochondrial and ER complexes thus affecting cross talk between these organelles and proper mitochondrial biogenesis and function. α B-

crystallin overexpression in desmin-deficient cardiomyocytes rescues the decreased levels of mitochondrial proteins and the MICOS super complex, provides stabilization and proper cristae formation, inhibits oxidative stress, abnormal mPTP activation, and maintains a proper mitochondrial membrane potential ($\Delta\psi_m$) (Diokmetzidou et al. 2016a). This extensive rescue could be facilitated by formation and stabilization of MAMs and consequently all crucial functions mediated by them.

Loss of proper costameres/ID formation

Desmin IF network extends to costameres and IDs; thus, its deficiency impairs their proper organization and consequently their function both in cell adhesion, cell-cell communication, and electrical conductivity. As mentioned above, proteolytic cleavage of desmin by TNF- α -induced caspase 6 results in loss of proper localization of desmin, desmoplakin and connexin at the IDs, problems with mitochondria, and aggregate formation eventually leading to cell death and HF (Panagopoulou et al. 2008; Papathanasiou et al. 2015). Reinforcing the importance of desmin presence for ID regulation comes also from the studies that show Cocksackievirus B3-induced heart failure is due to deregulation of desmin degradation that leads to ID disorganization (Ye et al. 2014).

Effects on cardiac differentiation

Even though most of the pathological issues arising in DRMs are based on desmin's role in the adult myocardium, we cannot eliminate the possibility that its absence can compromise developmental processes whose defects accumulate and are presented later in adulthood. Indeed, as discussed earlier, desmin's early expression and its direct association with transcription factors suggest a role in early cardiomyogenesis (see section "[Desmin in muscle development and adult muscle maintenance](#)"). Moreover, as a mechanotransducer, desmin may also impact cardiac differentiation. Cardiomyogenesis in vivo is governed, in addition to chemical signals, by mechanical cues that act on the developing embryo throughout cardiac development. Passive or active forces can regulate cardiac specification thus the stiffness of the microenvironment can affect cardiac commitment as do the forces generated by the blood flow (Vermot et al. 2009; Happe and Engler 2016). This notion is reinforced by studies performed in *Lmna*^{-/-} cardiomyocytes whose compromised differentiation potential is restored by ectopic expression of desmin (Frock et al. 2006). In addition, the connection between mitochondrial fusion, cardiomyocyte differentiation, calcineurin and myospryn (Kasahara et al. 2013; Tsoupri and Capetanaki 2013) suggests that the role of desmin in differentiation could also be linked to desmin's role in mitochondrial dynamics and calcineurin signaling. Last but not least, the presence of

Fig. 3 α B-crystallin overexpression considerably improves desmin-deficient cardiomyocyte ultrastructural defects. Mitochondria ultrastructure from myocardial tissue of 3-month-old mice by using transmission electron microscopy. Desmin deficiency affects mitochondria size, shape, and the ultrastructure of the inner

mitochondrial membrane (IMM), leading to fewer, less dense, and occasionally disorganized and degenerating cristae. The mitochondria from *Des*^{-/-} α BCry transgenic myocardium appear completely normal. Scale bars = 0.2 μ m. α BCry, alpha Beta crystallin; c, cristae. Adapted from Diokmetzidou et al. (2016)

desmin in adult stem cells (Allen et al. 1991; Pfister et al. 2005) is possibly implying an involvement in cardiac regeneration, an important aspect in cardiac pathology where there is massive cardiomyocyte loss and the need for regeneration is urgent.

Contribution to cardiac fibrosis and inflammation

Cardiac fibrosis is a final common pathway of a wide spectrum of heart diseases characterized by uncontrolled and excessive accumulation of collagens and other ECM components, which increase the ventricular stiffness, deteriorate the diastolic function, and may eventually lead to HF. Activation of cardiac fibroblasts is the critical event, as myofibroblasts and other specialized activated fibroblasts emerging out of this heterogenous population mediate collagen and ECM deposition (Moore-Morris et al. 2014; Fu et al. 2018).

HF is also characterized by adverse cardiac remodeling; the heart is an organ showing a marginal regenerative capacity upon stress or injury (Cahill et al. 2017) which is partially compensated by its high plasticity accompanied by shifts in expression (Hill and Olson 2008); in that sense, the hypertrophic response forms part of an adaptive mechanism attempting to redistribute increased myocardial wall stress generated during conditions of pressure or volume overload and cardiac injury (Opie et al. 2006). Upon increased or chronic exposure to stress supported by neurohormonal activation (e.g., activation of the renin-angiotensin-aldosterone system), a decompensated cardiac remodeling—wall thinning and chamber dilatation in combination to fibrosis—leads to HF, which in that sense is just another fibroproliferative disease (Wynn 2007). Indeed, the extent of myocardial fibrosis is positively correlated with cardiac dysfunction (mainly diastolic), reduced ventricular compliance, and arrhythmias (Gourdie

et al. 2016), whereas the greater the size of scar formed after a myocardial infarction the higher the probability to eventually develop HF. On the other hand, systemic and local inflammation are characterizing HF and cytokines such as TNF- α or IL1 β have been recognized as HF causing agents particularly in animal models (Fildes et al. 2009).

In the desmin-null mouse, the spontaneous inflammatory response starts at the beginning of the second week of the lifespan, along with cardiomyocyte mitochondrial defects and death, and is characterized by infiltrates enriched in monocytes/macrophages and activation of inflammation and remodeling programs regulated by mediators such as osteopontin (Psarras et al. 2012) and members of the complement pathway (Mavroidis et al. 2015). Accordingly, it has been assumed that danger signals released or activated by mitochondrial defects and cardiomyocyte death may initiate and sustain inflammation and adverse remodeling (Psarras et al. 2012; Mavroidis et al. 2015). This worsens the pathophysiology of the desmin-deficient mouse, recapitulating central features of cardiac injury and repair (Psarras et al. 2012) in multiple CMs, including transient hypertrophic response, followed by DCM (Milner et al. 1999), and eventually HF with compromised systolic and diastolic function and fibrosis (Psarras et al. 2012). It also shares important features with ARVD/C (Mavroidis et al. 2015).

Furthermore, the overexpressed osteopontin (Mavroidis and Capetanaki 2002), an integrin-binding multifunctional cytokine and matricellular protein, seems to promote fibrosis and cardiac dysfunction in this model (Psarras et al. 2012). Importantly, it also promotes the cardiac expression of additional remodeling modulators such as MMP12 and Galectin-3 (Psarras et al. 2012), the latter being recently emerged as a HF biomarker with remarkable performance in predicting cardiovascular events and deaths (Imran et al. 2017; Zivlas et al. 2017). This carbohydrate-binding

protein is readily secreted by activated macrophages in an osteopontin (OPN)-dependent manner (Psarras et al. 2012) and may be involved in fibrosis of several organs, including the heart (Meijers et al. 2016). On the other hand, massive complement activation was observed in the desmin-deficient myocardium in areas of necrotic cell debris and inflammatory infiltrate. Mice with absent or inhibited signaling of the C5a complement component showed improved cardiac function, histopathology, and arrhythmias probably by containment of the inflammatory reaction (Mavroidis et al. 2015). So far, suppression of the inflammatory response by targeting the complement pathway (Mavroidis et al. 2015) or by its modulation by targeting osteopontin, which also led to indirect restriction of the macrophage-mediated release of galectin-3 (Psarras et al. 2012), resulted in considerable reduction of fibrosis and cardiac dysfunction. These results indicate that at least parts of the inflammatory and fibrotic events initiated by the absence of desmin are modifiable and that therapeutic interventions targeting appropriate mediators are feasible. On the other hand, approaches protecting against the desmin deficiency-associated mitochondrial defects and resulting cardiomyocyte death by cardiomyocyte-specific Bcl-2 and α B-crystallin overexpression have proven more efficient than the immunomodulatory approaches described above in suppressing inflammation, fibrosis, adverse remodeling, and cardiac dysfunction (Weisleder et al. 2004b; Diokmetzidou et al. 2016a). Also, cardiomyocyte-specific reintroduction of desmin is sufficient to correct the cardiac phenotype despite the defective smooth muscle vascular component and microvascular function (Loufrani et al. 2004; Weisleder et al. 2004a). Moreover, overexpression of TNF- α paradoxically ameliorates the desmin-null inflammatory and remodeling phenotype by inducing cyto- and mitoprotective keratin network formation in cardiomyocytes to replace the absent desmin (Papathanasiou et al. 2015).

In summary, the desmin-deficient mouse not only pointed out dramatically the significance of desmin in maintaining cardiomyocyte and heart homeostasis, but it also forms a *passerpartout* tool for studies elucidating mechanisms underlying IF disorder-associated CM, as well as inflammatory and fibrosis pathways in HF.

Lamin-related cardiomyopathies—laminopathies

Lamin mutations

Mutations on the *LMNA* gene are associated with more than 10 clinical disorders, commonly known as “laminopathies.” These pathologies involve either specific tissues (e.g., heart and/or skeletal muscle, adipose tissue, peripheral nerves) or can have multisystem effects (e.g., premature aging syndromes) with some overlapping phenotypes between affected

organs and tissues (Worman and Bonne 2007; Worman 2012; Cattin et al. 2013). Striated muscle laminopathies (SMLs) are the most frequent type of laminopathies with common feature the cardiac involvement which can occur isolated or be associated with disorders of the skeletal muscles (Worman 2012; Cattin et al. 2013; Captur et al. 2018). SMLs comprise Emery-Dreifuss muscular dystrophy (EDMD) (Bonne et al. 1999), limb-girdle muscular dystrophy type 1B (LGMD1B) (Muchir et al. 2000), *LMNA*-related congenital muscular dystrophy (L-CMD) (Quijano-Roy et al. 2008), and DCM associated with cardiac conduction system disease (CCD) (Fatkin et al. 1999). The *LMNA* mutations that cause SMLs are predominantly missense and generally lead to amino acid substitutions throughout lamin A/C proteins. However, non-sense or frameshift sequence-level alterations resulting in loss of function of lamin A/C and haploinsufficiency have also been reported as well as genetic variances that result in mRNA splicing defects (Worman 2012; Captur et al. 2018).

The mutations of the *LMNA* gene represent one of the most prevalent genetic causes of DCM as they account for approximately 6–9% of DCM cases in patients (Parks et al. 2008; Millat et al. 2011) and even up to 33% in those with conduction defects (Arbustini et al. 2002). An updated list with the most common human genetic variations associated with *LMNA*-dilated cardiomyopathy phenotype as well as their distribution within the functionally important lamin A/C protein domains are described in Fig. 4. For detailed information about each mutation, refer to www.UMD.be/LMNA/ online database or at the recent review of Captur et al. (2018).

Clinical manifestations Patients who suffer from *LMNA*-dilated cardiomyopathy exhibit a high rate of malignant cardiac events with life-threatening arrhythmias often leading to sudden cardiac death (van Berlo et al. 2005). More specifically, common disease manifestations include supraventricular and ventricular arrhythmias, extreme bradycardia due to high degree atrioventricular block, atrial standstill, end-stage HF, as well as arterial and venous thromboembolic events (Cattin et al. 2013; Captur et al. 2018). The clinical course of the disease is characterized by worse prognosis and poorer cumulative survival compared with the DCM patients, non-carriers of *LMNA* gene mutations (Taylor et al. 2003). Interestingly, conduction system defects associated with *LMNA* mutations can precede the onset of DCM symptoms meaning that fatal arrhythmias may occur before any noticeable changes in left ventricular function or dilatation of the heart (Brodt et al. 2013) underlying the complex pathophysiology of the disease. Implantation of a defibrillator may prevent sudden cardiac death (van Berlo et al. 2005) improving lifespan of the patients; however, the progressive HF can eventually develop resistance to the treatment (Cattin et al. 2013).

Fig. 4 Schematic representation of the human lamin A/C and distribution of the mutations that cause cardiac disease within the functionally important protein domains. Lamin A/C proteins consist of a short amino-terminal head domain, a central α -helical rod domain, and the carboxy-terminal tail domain containing the nuclear localization signal (NLS, blue) which is essential for their active nuclear transport after synthesis as well as an immunoglobulin-like domain (Ig-like, yellow) important for protein-protein interactions. Lamin A (646 a.a.) is first translated as prelamin A (664 a.a.), a precursor protein that undergoes posttranslational modification processes (including farnesylation, cleavages, and methylation) to yield the mature lamin A. Lamin C is synthesized as a mature protein and is identical to lamin A through the first 566 amino acids after which it has six unique carboxy-terminal amino acids. The depicted mutations are associated with DCM with or without CCD and arrhythmias, as well as sudden cardiac death and/or end-stage HF. The majority of *LMNA* genetic variants are missense mutations (depicted with black color) and fewer are non-sense

(indicated with red color). The cartoon also describes the insertion/deletion/duplication events marked with green or purple color for frameshift or in-frame mutations respectively. There have been also identified at least 12 different nucleotide substitutions (not shown) within sequences of *LMNA* gene introns, mainly causing abnormal mRNA splicing events. Note that the H222P mutation marked with asterisk (*) causes in human a type of autosomal dominant EDMD with cardiac involvement including arrhythmias but limited or unavailable echo data for sufficient diagnosis of DCM in the affected patients (Bonne et al. 2000). However, the *Lmna*^{H222P/H222P} mouse model, which carries the same disease-causing *Lmna* gene mutation, is a faithful animal model of cardiomyopathy as it develops muscular dystrophy and DCM with CCD similar to the clinical features of human laminopathies (Arimura et al. 2005). DCM, dilated cardiomyopathy; CCD, cardiac conduction system disease; HF, heart failure; L1, linker 1; L2, linker 2; a.a., amino acid

Laminopathies—mechanism of disease development

When evaluating the cellular mechanisms that could be involved in the pathophysiology of *LMNA* cardiomyopathy, there are three main hypotheses to be distinguished. They consist of the *mechanical hypothesis*, the *gene expression hypothesis*, and the hypothesis based on *cellular toxicity* (Schreiber and Kennedy 2013; Brayson and Shanahan 2017; Captur et al. 2018). These potential pathological mechanisms arise directly from the different functions of lamin A/C, which are the maintenance of the nuclear stiffness and integrity as

well as the genome organization (Dechat et al. 2008; Worman 2012; Choi and Worman 2014).

The *mechanical hypothesis* suggests that lamin A/C mutations can lead to impaired cell stress resilience resulting in aberrant force transmission and progressive cellular dysfunction. Lamin A/C together with B-type lamins assembles the nuclear lamina network under the inner nuclear membrane with extension into the nucleoplasm. Meanwhile, lamin A/C interactions with transmembrane proteins such as SUN1/2 and nesprins provide (via LINC complexes) physical link with the three cytoplasmic structural components of the cytoskeleton,

actin microfilaments, desmin intermediate filaments, and microtubules. These complex nucleo-cytoskeletal networks provide external support to the nucleus and connect the nuclear lamina to the extracellular matrix affecting the whole-cell mechanics and structural resistance. The pathological mechanism proposes that defective lamin A/C could cause nuclear uncoupling and disruption of the anchorage with the cytoskeletal components affecting the structural integrity as well as the mechanical sensing of the cell (Brayson and Shanahan 2017; Captur et al. 2018). In addition to that, lamin A/C mutations might increase nuclear fragility by weakening the nuclear envelope resulting in cell damage and eventually death (Hutchison 2002). The *gene expression* hypothesis proposes that defective lamin A/C proteins not only change the viscoelastic behavior of the nucleus impairing the nuclear–cytoskeletal coupling, but they can also lead to aberrant gene expression due to disturbed chromatin dynamics and genomic instability. Nuclear lamina forms a docking platform for regulatory proteins influencing numerous signaling pathways (Gonzalez et al. 2008) as well as chromatin and tissue-specific transcription factors (Dechat et al. 2008; Choi and Worman 2014). More specifically, inside the nucleus, lamin A/C interact with lamin-associated polypeptides (LAPs) such as emerin, MAN1, LAP2 α , or LAP2 β and several transcription factors (c-fos, Rb, etc.). Through these interactions, lamin A/C regulate several important signaling cascades such as mitogen-activated protein kinase (MAPK) pathways, β -catenin and TGF β implicated in cardiac remodeling processes, as well as differentiation pathways through E2F/Rb and Rb/MyoD interactions. Thus, laminopathy-causing mutations might alter these interactions and may inhibit binding to tissue-specific factors leading to abnormal gene activation/silencing (Hutchison 2002; Brayson and Shanahan 2017; Captur et al. 2018). Moreover, studies on animal models of *LMNA* cardiomyopathy and specifically, data from the knock-in *Lmna*^{H222P/H222P} mouse model of EDMD with DCM phenotype (Arimura et al. 2005), emphasized that abnormalities in signal transduction pathways appear to underlie the pathophysiology of *LMNA* cardiomyopathy (Muchir et al. 2007; Choi et al. 2012; Muchir et al. 2012b). Such abnormalities include increased activation of a number of kinases, such as MAPKs, ERK1/2 (extracellular signaling regulated kinase 1/2), JNK (Jun-N-terminal kinase), (Muchir et al. 2007), and p38 α (Muchir et al. 2012b), even prior to the onset of cardiac disease. Interestingly, in *Lmna*^{H222P/H222P} mice, pharmacological administration of inhibitors of MEK1/2 (the MAPK kinase that phosphorylates ERK1/2), or JNK pathways, either before (Muchir et al. 2009; Wu et al. 2010) or after the DCM development (Wu et al. 2011) prevented or delayed the left ventricular dilatation, the decreased ejection fraction, and the development of myocardial fibrosis compared with placebo-treated mice. Similar results were obtained with the administration of a p38 α inhibitor in these mice, since

this pharmacological approach was capable to prevent the heart dilatation and the deterioration of fractional shortening, but it did not improve cardiac fibrosis (Muchir et al. 2012b).

It seems that dysfunctional autophagy could also contribute to the pathophysiology of cardiomyopathy caused by *LMNA* mutations, thus suggesting the hypothesis based on *cellular toxicity* (Captur et al. 2018). Specifically, hearts of a knock-in mouse model of autosomal EDMD (Arimura et al. 2005) have abnormally increased activation of AKT/mTOR signaling pathway leading to impaired cardiomyocyte autophagy and a potential toxic accumulation of many different proteins within the cell including misfolded or farnesylated lamins (Choi et al. 2012).

After studying the potential mechanisms explaining the occurrence of laminopathies, one can conclude that these hypotheses are not mutually exclusive. It is likely that the disease pathology can arise from the combination of different defects in lamin function (Schreiber and Kennedy 2013; Brayson and Shanahan 2017; Captur et al. 2018).

Cardiomyopathies linked to other intermediate filaments

Vimentin

Contrary to desmin, vimentin is not expressed in mature cardiac myocytes and mutations in its gene have not been directly associated with CM. However, its proposed function in the heart, where it is expressed by non-cardiomyocytes, including fibroblasts, smooth muscle, and endothelial cells, as well as pathogenic myofibroblasts, indicated a potential role in the progression of cardiac disease. This could be supported by the fact that vimentin seems to be a key molecule in the epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition (EndoMT), a subset of EMT. EMT is a fundamental process during development, including cardiogenesis. Endocardial cells of the forming atrioventricular canal undergo EndoMT to generate mesenchymal cells that give rise to the semilunar valves (Markwald et al. 1977). Epicardial cells also undergo EMT to give rise to epicardium-derived cells (Kisanuki et al. 2001). EMT is also required for myocardial growth and coronary vessel formation, and it generates cardiac fibroblasts, vascular smooth muscle cells, a subset of coronary endothelial cells, and possibly a subset of cardiomyocytes (von Gise and Pu 2012).

Moreover, EMT events in vimentin expressing cells in the cardiovascular system may contribute to the cardiac pathophysiology (Chen et al. 2012; Maddaluno et al. 2013; Chen et al. 2014; Qiao et al. 2014; Ranchoux et al. 2015; Zeisberg et al. 2007; Aisagbonhi et al. 2011; Yao et al. 2013; Martinez-Gonzalez et al. 2001; Brokopp et al. 2011).

From all the above, it is expected that vimentin should play a crucial role in cardiac homeostasis and pathology. Despite these notions, initial studies with the vimentin-null mice did not show reproductive, developmental, growth, or functional defects in the heart or other organs (Colucci-Guyon et al. 1994). However, more careful examination revealed several defects, including compromised motility and directional migration of vimentin-deficient fibroblasts affecting wound healing (Eckes et al. 2000) and mechanotransduction of shear stress (Henrion et al. 1997). Furthermore, vimentin, like desmin, is linked to mitochondrial behavior and function (Chernoivanenko et al. 2015). These characteristics could have implications for the remodeling and fibrotic events following cardiac injury. In addition, lymphocyte adhesion and transendothelial migration are compromised in the absence of vimentin (Niemenen et al. 2006). This, together with the recent demonstration that vimentin interacts with components of the NLRP3 inflammasome and regulates its activation in the lung (dos Santos et al. 2015), suggests a possible role of vimentin in interleukin-1-mediated inflammation. The latter is known to be involved in cardiovascular disease, including myocardial infarction and HF (Long 2001). In support of the above, vimentin is expressed and secreted by activated macrophages and may be involved in their maturation and function (Morvaknin et al. 2003; Benes et al. 2006) which is important given the recently emerged role of these cells in cardiac injury and function, including diastolic dysfunction (Hulsmans et al. 2018). Finally, in human cardiac transplantation, development of autoantibodies to vimentin is a predictor and cause of accelerated rejection of the cardiac allografts (Mahesh et al. 2007; Sharma et al. 2018).

Additionally, vimentin is highly expressed in mesenchymal stem cells (MSCs). Multiple studies have shown that administration of these cells improves cardiac function and reduces scar size (Bagno et al. 2018). MSCs have the potential to differentiate into several cell types, including cardiomyocytes (Wang et al. 2004; Ohnishi et al. 2007), and may have beneficial paracrine action in cardiovascular disease (Rehman et al. 2004; Mirotsoy et al. 2007; Markel et al. 2008; Lai et al. 2010). However, whether the expression of vimentin per se provides the plasticity to the MSCs has not been studied.

In summary, despite the potential implications, direct proof that vimentin is indeed playing crucial roles in cardiac development and disease is still lacking.

Syncoilin, synemin, and paranemin

Very little is known regarding the implication of syncoilin, synemin, and paranemin in cardiomyopathies. However, through their interaction with desmin, they could be associated with cardiac disease. Particularly, paranemin appears to be contributing to the formation of a proper desmin filament

network, while syncoilin is not properly localized in the absence of desmin (Howman et al. 2003). Syncoilin has been shown to bind to α -dystrobrevin, a component of the dystrophin-associated protein complex (DAPC) (Blake and Martin-Rendon 2002) (Poon et al. 2002) linking desmin to the sarcolemma. Mutations in this complex lead to major skeletal and cardiac diseases. Synemin, initially purified as a desmin-associated molecule (Granger and Lazarides 1980), is found in costameres via its interaction with the vinculin/ α 7 β -integrin complex (Sun et al. 2008). Interestingly, while desmin interacts with an AKAP (Kouloumenta et al. 2007; Reynolds et al. 2007), synemin has been shown to be an AKAP with higher expression in failing human hearts suggesting a role in temporal and spatial targeting of PKA in cardiac myocytes (Russell et al. 2006). Additionally, recent data show synemin null mice develop, mostly at an older age, left ventricular systolic dysfunction, left ventricular hypertrophy, and dilation while isolated cardiomyocytes showed alterations in calcium transients (Garcia-Pelagio et al. 2018).

Therapeutic strategies

So far, the attempts to protect against cardiomyopathy development due to IF abnormalities, and more specifically due to desmin and lamin A/C deficiency or IF network disruption and aggregation in animal models, have been mainly focused in inhibition of mitochondrial defects and cardiomyocyte death (Weisleder et al. 2004b; Diokmetzidou et al. 2016a, b; Rapti et al. 2017). Overexpression of the anti-death mitochondrial protein Bcl-2 (Weisleder et al. 2004b), anti-oxidant enzyme catalase (Rapti et al. 2017), and the chaperon small heat shock protein α B-crystallin (Diokmetzidou et al. 2016a) has ameliorated most structural and functional defects of the desmin-deficient HF model. Importantly, the degree of rescue obtained by α B-crystallin was not just the best among the three but unexpectedly good, reaching wild-type levels. As discussed above, mitochondrial defects and cardiomyocyte death trigger innate immunity activation, inflammation, and fibrosis which contribute to the progress of the disease (Psarras et al. 2012; Mavroidis et al. 2015). Among others, OPN (Psarras et al. 2012) and the complement system (Mavroidis et al. 2015) seem to be good therapeutic targets and possibly a combination targeting both intrinsic and extrinsic factors might be the best choice.

As it was recently demonstrated, TNF- α can confer cardioprotection by an unexpected mechanism, that is by ectopic expression of keratins K8 and K18 (Papathanasiou et al. 2015), two epithelial-specific IF proteins normally not expressed in healthy myocardium. This alternative IF network seems to compensate for the loss of desmin function caused by the TNF- α induced caspase cleavage of desmin in HF, as described above (Panagopoulou et al. 2008). These findings explained the negative results of the anti TNF- α clinical trial

for heart failure (Feldmann and Maini 2003) and suggested an alternative therapeutic strategy, given that the desmin cleavage is expected to occur in most cases of heart failure where TNF- α is elevated. Inhibition of this cleavage might be indeed a very efficient therapeutic strategy for this fatal disease.

In the case of *LMNA* cardiomyopathy, therapeutic strategies have focused in correcting abnormalities in signal transduction pathways and more specifically the increased activation status of a number of kinases such as MAPK, branches ERK1/2, JNK, and p38 α (Muchir et al. 2007; Choi et al. 2012; Muchir et al. 2012b). Importantly, selumetinib, one potent and selective inhibitor of ERK1/2 signaling which is safely given to human patients in clinical trials for cancer, has been administered to *Lmna*^{H222P/H222P} mice after the onset of cardiac deterioration with beneficial effects in cardiac pathology and promising results for a potential use of this compound to treat *LMNA* cardiomyopathy in humans (Muchir et al. 2012a). Another very encouraging therapeutic strategy comprises the modulation of the abnormally increased AKT/mTOR signaling pathway by the rapalogue temsirolimus which in turn affects the defective autophagy in *Lmna*^{H222P/H222P} mice hearts. Specifically, the in vivo blockade of AKT/mTOR signaling by administration of temsirolimus in *Lmna*^{H222P/H222P} mice restored cellular autophagy and prevented cardiac defects improving the heart function (Choi et al. 2012). Future studies are awaited to definitively assess the therapeutic benefit of these compounds as some of these promising therapies may have adverse side effects when administered or applied to humans.

Conclusions and perspectives

The desmin-lamin IF network abnormalities seem to play a major role in cardiomyopathy development. This is obviously due to the fact that the IF cytoskeletal network plays a central role in the maintenance of an efficient integration of structure and function, absolutely required by the intra- and intercellular communication and coordination of cardiac muscle. The studies so far have demonstrated that this continuous cytoskeletal network can achieve the above by forming, together with the plethora of its associated proteins, a dynamic scaffold responsible for the regulation of transport and signaling processes. Such regulation would guarantee the assembly and stabilization of critical protein complexes at their proper position, thus allowing proximity and cross talk between organelles, as well as sensing and transmission of mechanochemical signals from the contractile apparatus to the nucleus and mitochondria. This way, proper regulation of energy production based on energy demands will lead to a fine regulation of the balance between membranous structures and organelle biogenesis and turnover. Further understanding of how all the above are fine tuned will allow the identification of the best and most

efficient therapeutic targets. If we assume that the already identified interplay between desmin and a chaperon protein can facilitate most of the above processes, then any disruption of this network, known to lead to desminopathy/laminopathy-based cardiomyopathy, is expected to compromise one or more of these processes as well. Given that the endogenous cytoprotective chaperon system will be also compromised, both due to its inefficient targeting to the right place the right time and its sequestration and inactivation within the formed aggregates, busting its function by an overexpression is expected to both considerably decrease the desmin aggregates and also protect against the consequences of some of the above disturbances. Since mitochondria are the most vulnerable and highly affected organelles upon the IF network disruption in the heart, and chaperon overexpression has been shown to entirely protect them in animal models of cardiomyopathy and heart failure, the prediction is that there is a high possibility of great success of this double hit strategy in human patients.

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Compliance with ethical standards

Conflict of interest Mary Tsikitis declares that she has no conflicts of interest. Zoi Galata declares that she has no conflicts of interest. Manolis Mavroidis declares that he has no conflicts of interest. Stelios Psarras declares that he has no conflicts of interest. Yassemi Capetanaki declares that she has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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