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Cardiomyopathies Associated with Myofibrillar Myopathies

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1. Introduction

The aim of this chapter is to describe cardiomyopathies associated with myofibrillar myopathies (MFM, OMIM 601419). Myofibrillar myopathies are a group of heterogeneous neuromuscular disorders usually characterized by a severe myopathy, and generally associated with cardiomyopathy in 15% to 30% of the affected individuals. These familial or sporadic muscle disorders are characterized morphologically by focal disintegration of the myofibrils and abnormal ectopic accumulation of multiple proteins due to their degradation. The six genes that are held responsible so far for this clinically heterogenous, genetically heterogenous and morphologically homogeneous disorders are desmin, αB-crystallin, myotilin, LDB3 (ZASP), FLNC and BAG3. In the first part of the chapter the normal function in skeletal and cardiac muscles of the six genes will be discussed as well as physiopathological consequences of their mutations. The second part will describe how proteins encoded by these genes, together with main contractile proteins such as actin, tropomyosin, myosin, troponin, integrate into functional sarcomeric structures, which in turn determine the main cardiac functions : force generation, force transmission, nervous influx conduction, energy metabolism. Special emphasis will be put on a dynamic point of view, including protein turnover, protein quality control, with the involvement of ubiquitin-proteasome and autophagic systems. The third part gives a view of the latest insight of the clinical and therapeutic perspectives.

2. Clinical manifestations of myofibrillar myopathies

Myofibrillar myopathies represent a group of muscular dystrophies, generally associated with cardiomyopathy. They present specific but not always identical morphologic features. Because aggregates present desmin with other proteins, it has been called desmin-related myopathy.

2.1 Clinical and histopathological features of DRMs

Diagnosis is based on clinical observations of patients and histologic studies using histochemistry and electron microscopy. Common symptoms of the disease are weakness and atrophy of the distal muscles of the lower limbs which progress to the hands and arms, then the trunk, neck and face. Wasting, muscle stiffness, cramps can also be found. The myopathy may progress to facial, cervical, velopharyngeal, truncal and respiratory muscles. The vast majority of MFM patients have an adult onset of their progressive muscle symptoms (Goldfarb et al., 2004). Cardiomyopathy is associated in 15 to 30 % of the affected individuals. However, in some patients, the cardiomyopathy may precede the muscle weakness. Therefore, distal muscle involvement, cardiomyopathy and peripheral neuropathy are important clinical clues, although they are not present in all patients (Bar et al., 2004; Finsterer & Stollberger, 2008; Schroder et al., 2007).

2.1.1 Skeletal

The abnormal size of muscular fibers, with few atrophic fibers, are the characteristics of the disorder. These fibers present amorphous, granular or hyaline deposits that vary in shape and size. As abnormal fibers can be focally distributed, the symptomatic changes may be missed in small samples. Many abnormal fibers show alteration in oxidative enzymes activity, which are diminished or absent. Reduced oxidative activity is often associated with the presence of hyaline structures, and conversely, enhanced activity around the larger inclusions. Some muscular fibers harbor small to large vacuoles containing membranous materials. Many hyaline structures are stained blue or blue-red with Trichome or intensively stained with Congo red, which is an important diagnostic feature of MFM biopsies (Schroder & Schoser, 2009).

Immunohistochemical studies reveal accumulations of desmin, myotilin, dystrophin, sarcoglycans, actin, plectin, gelsolin, filamin C, syncoilin, Bag3, synemin, αB-crystallin, Hsp27 and DNAJB2. Additional pathologic markers may be observed, including phosphorylated tau proteins, β amyloids, ubiquitin, glycoxidation and lipoxidation can be found, more specifically in desmin- and myotilin-opathies (Selcen, 2011).

Electron microscopy shows a marked disorganization of the myofibrils ultrastructure, beginning at the Z-disc. Accumulation of dense materials is found in the close proximity of the Z-disc. In patients with desmin, αB-crystallin or Bag3 mutations, small pleiomorphic dense structures or granulofilamentous materials are found between the myofibrils. At later stages, Z-disc are disintegrated and sarcomeres disorganized, a prelude to myofibrils dislocation (Goldfarb & Dalakas, 2009). Electromyogram (EMO) studies of affected muscles reveal myopathic motor units potentials and abnormal electrical irritability, often with myotonic discharges (Schroder & Schoser, 2009).

2.1.2 Cardiac

All the genes cited in paragraph 2.3 cause cardiomyopathy. In 15 to 30 % of patients, the disorder presents with cardiomyopathy. There are also cases with only cardiomyopathic signs without skeletal muscle involvement. In advanced stages of the disease, cardiomyopathies develop in up to 60 % of the patients. MFM-associated atrioventricular conduction blocks can be associated with dilated (17 %), restricted (12 %), or hypertrophic (6 %) cardiomyopathy (van Spaendonck-Zwarts et al., 2010). When the cardiac muscle is involved, impaired conduction, arrhythmia, cardiac hypertrophy or dilation, secondary

valvular insufficiency, intracardial formation of thrombi and heart failure can be observed. The least severe cases are caused by myotilin mutations. Atrioventricular conduction abnormalities may occur, and require urgent implantation of permanent pacemaker. This feature of MFMs can be attributed to the fact that the conduction system is rich in desmin (Finsterer & Stollberger, 2008; Goldfarb & Dalakas, 2009).

2.1.3 Respiratory

As the diaphragm is the main muscle involved in the respiratory cycle, progressive respiratory muscle impairment can occur, sometimes at early stages. Respiratory insufficiency can therefore be a major cause of disability and death with hypoventilation and ultimately respiratory failure, caused for example by mutations A357P, L370P in the desmin gene, or P209L in the BAG3 gene. Respiratory muscle weakness leads to a restrictive ventilatory failure when there is a mutation on the genes causing any of the myopathies except on ZASPopathy in which respiratory muscle involvement has not yet been described (Goldfarb & Dalakas, 2009).

2.2 Inheritance

The majority of cases follow an autosomal dominant mode of inheritance, and very few an autosomal recessive pattern. However, a significant number of MFMs shows sporadic disease manifestation.

2.2.1 Autosomal dominant mode

80 % of families with MFMs present an autosomal dominant pattern of inheritance, mostly with full penetrance (Goldfarb & Dalakas, 2009). Depending on the mutation, however, these facts can be modulated: for example, in families with the I451M mutation in the desmin gene, incomplete penetrance was demonstrated for the first time (Li et al., 1999). It is not possible, however, to link a specific mutation of the affected genes to clinical signs, although certain mutations are more frequently associated with specific signs. For example, the desmin A350P mutation predisposes male patients to higher risks of sudden cardiac death (Walter et al., 2007), as it is also the case for men and women in mutations p.E114del and N116S of the segment 1A of the desmin gene (Klauke et al., 2010; Vernengo et al., 2010).

2.2.2 Autosomal recessive mode

In a restricted number of families (6%), mutations are autosomal recessive (Goldfarb & Dalakas, 2009). The disease generally develops in childhood with severe clinical symptoms (Goldfarb et al., 2004). This is the case, for example, of the deletion A173_G179del of 21 nucleotides in the 1B helical segment of desmin (Muñoz-Marmol et al., 1998). Another intriguing report indicate two mutations A360P and N393I in the desmin protein, which are not pathogenic in heterozygous state, but give rise to a highly aggressive cardioskeletal myopathy when combined in the same child (Goldfarb et al., 1998). There is also a case reported for αB-crystallin (mutation S21AfsX24) (Selcen, 2011).

2.2.3 Modifying genes

Lamin A/C mutations have been involved in muscular dystrophies but can also lead to completely different pathologies, depending on the mutations involved. A patient with a

combination of Lamin A/C A644C and desmin V469M mutations developed severe muscle weakness and complete heart block, requiring heart transplantation (Muntoni et al., 2006). Lamin A/C and desmin networks are supposed to be indirectly connected (Costa et al., 2004), and therefore may interact in the development of the disease. As individuals from the same family are diversely affected by the disease, one can suspect their individual history (practice of sport) or differential genetic background. The question of the identity of modifying genes remains, however, largely unresolved.

2.3 Molecular genetics

So far, six genes have been formally identified and are held responsible for MFMs associated with cardiomyopathy, but for around 80 % of the patients, the disease still awaits a molecular diagnosis (Selcen, 2011). Schröder et al. include FHL1 and plectin in MFM-causing genes (Schröder, 2009). The knowledge of the structure and function of the already identified genes is, therefore, a prerequisite for the understanding of human MFMs.

2.3.1 Desmin

The human *DES* gene (NM_001927.3), on chromosome 2q35, comprises nine exons within an 8.4 kb region that encodes a 470 amino acids (53 kDa) muscle-specific protein (Li et al., 1989). Desmin belongs to the family of type III intermediate filaments (IF) proteins, which polymerize into 10 nm filaments, a size intermediate between thick (15 nm) and thin (5-6 nm) filaments. Desmin is synthetized only in cardiac, skeletal and smooth muscles (Lazarides & Hubbard, 1976 ; Paulin & Li, 2004). It is organized into three domains, a highly conserved α helical core of 303 amino acids residues flanked by globular N- and C- terminal structures. The helical structure, called the rod domain, is interrupted by three short polypeptide linkers (L1, L12, L2), which determine four consecutive helical segments (1A, 1B, 2A, 2B). Desmin is more abundant in heart muscle (2% of total proteins) of mammals than in their skeletal muscle (0.35%) (Paulin et al., 2004). It forms a three-dimensional scaffold around the myofibrillar Z-disc, and interconnects the entire contractile apparatus with the subsarcolemmal cytoskeleton and the nuclei (Lazarides & Hubbard, 1976). Desmin also forms longitudinal connections between the peripheries of successive Z-discs and along the plasma membrane. In addition, desmin IFs bind and participate to the location of mitochondria. In the heart, desmin is particularly abundant in Purkinje conduction fibers, and at intercalated discs, where it forms a double-banded structure (Thornell & Eriksson, 1981). Since the first description of desminopathy by Goldfarb et al. (Goldfarb et al., 1998) and Muñoz-Marmol et al. (Muñoz-Marmol et al., 1998), more than 50 mutations (45 missenses, 4 in frame deletions, 1 exon skipping, 2 single nucleotide insertion with premature termination) have been described (Klauke et al., 2011; Selcen, 2011; van Spaendonck-Zwarts et al., 2010).

Studies of DES-knockout mice have shown that defects develop in skeletal, smooth and cardiac muscle after birth, principally characterized by a loss of lateral alignment and anchorage of myofibrils, swollen mitochondria and loss of nuclear shape. The hearts develop a myopathy with impaired force generation, increased diastolic pressure with thicker ventricle walls (Li et al., 1996; Milner et al., 1996). Few transgenic mice have been described. With the Arg173_Glu179del desmin mutant transgene, aggregates containing desmin and other cytoskeletal proteins have been found in the heart (Wang et al., 2001a). A clear explanation of the molecular pathogenesis remains to be found.

Misfolded desmin molecules escape regular degradation mechanisms and accumulate with other proteins as aggregates. Cellular transfection studies have demonstrated that aggregates inhibit the proteasome system (Liu et al., 2006). In general, aggregates may accumulate through an active transport mechanism into perinuclear bodies called aggresomes (Johnston et al., 1998). Aggregates and proteasome impairement trigger autophagy (macroautophagy) as a mechanism of cellular cleaning (Tannous et al., 2008a), but recent studies have shown that this process is stalled at least with the desmin S13F mutant used in these studies (Wong et al., 2008).

2.3.2 αB-crystallin

AlphaB-crystallin is a small heat shock protein (sHSP) of 20 kDa that assembles into 500 – 800 kDa homo and heterodimers with other sHSPs. It is encoded by the CRYAB gene (NM_001885.1), a three-exon gene on chromosome 11 (11q21-23) in human beings. αB-crystallin proteins contain a conserved α crystallin domain (residues 67 to 149), surrounded by a N-terminal domain and a C-terminal extension (residues 149 – 175) (Ganea, 2001; MacRae, 2000). αB-crystallin is abundantly expressed, together with αA-crystallin and other similar sHSPs in the lens where it prevents cataract formation (Horwitz, 2003). It is also found in other tissues, with the highest level in cardiac and skeletal muscles (Iwaki et al., 1990; Sax & Piatigorsky, 1994). In these tissues, αB-crystallin is localized to the Z-disc, and its expression is induced after stress (Golenhofen et al., 2004; Lutsch et al., 1997). αB-crystallin is known to act as a molecular chaperone of desmin, actin, tubulin and several other soluble molecules (Goldfarb & Dalakas, 2009). αB-crystallin expression reduces aggregate formation, both *in vitro* and *in vivo*, and is supposed to help neosynthetized desmin proteins by avoiding their aggregation (Bennardini et al., 1992).

The first identification of a MFM case due to a heterozygous missense mutation in the αB-crystallin gene (R120G) was reported in 1998 (Vicart et al., 1998). Since then 9 other mutations have been discovered. Some patients develop also a familial cataract. The only knock-out model is deleted for both αB-crystallin and HspB2 (MKBP) genes because of their close proximity on the chromosome (Brady et al., 2001). CRYAB/HspB2 null mouse heart display poorer functional recovery, high cell death rate, increased stiffness and poor relaxation of myocardium following ischemia / reperfusion. In these mice, mitochondrial permeability transition and calcium uptake were increased in cardiomyocytes (Morrison et al., 2004). In contrast, overexpression of WT αB-crystallin delays or suppresses cardiac hypertrophic response to pressure overload (Kumarapeli et al., 2008). In addition, transgenic mice with cardiac-specific expression of R120G mutant αB-crystallin develop cardiomyopathy in three months and die of heart failure in six – seven months. Just as it is the case of the desmin mutations causing MFMs, αB-crystallinopathies present cytoplasmic aggregates that include desmin, αB-crystallin and several other proteins (Wang et al., 2001b).

2.3.3 Myotilin

Myotilin is a 57 kDa protein that is predominantly expressed in skeletal muscle and more weakly in the heart (Salmikangas et al., 1999). The human gene (NM_001135940) is located at the locus 5q31. The N-terminal region contains serine-rich and hydrophobic stretches, and the C-terminal half two immunoglobulin-(Ig)-like domains. The Ig-like domains are

required for the formation of antiparallel myotilin dimers. Myotilin is located at the Z-disc where it binds to α-actinin, the main component of the Z-disc, and to filamin C at the periphery. Myotilin also cross-links actin filaments and plays a role in the alignment of myofibrils (Salmikangas et al., 2003). The involvement of myotilin was detected in the year 2000 as a missense mutation (T57I) and was identified as limb-girdle muscular dystrophy 1A (LGMD1A) (Hauser et al., 2000). Since then, six new myotilin mutations were identified in eight unrelated patients of the Mayo Clinic MFM cohort. The LGDM1A pathology is therefore a MFM (Selcen & Engel, 2004). Cardiac involvement was found in a subset of patients. While myotilin deletion in mice does not lead to obvious abnormalities, transgenic mice expressing the T57I mutant reproduce morphological and functional features of human myotilinopathies (Garvey et al., 2006). As for desmin, abnormal accumulation of many proteins occur in myotilinopathies.

2.3.4 ZASP

ZASP (Z band Alternatively Spliced PDZ motif-containing protein), also called Oracle or Cypher, is expressed predominantly in cardiac and skeletal muscles (Faulkner et al., 1999). The ZASP gene, called LDB3 (NM_001080114), situated on chromosome 10 (10q22.3-q23.2), encompasses 16 exons, and splice variants exist in cardiac and skeletal muscles, each expressing 3 distincts variants. All ZASP isoforms have a N- terminal PDZ (PSD-95/SAP90, ZO-1 proteins) domain important for interaction with other proteins, and a ZASP-like motif (ZM) needed for the interaction with α-actinin. The largest isoforms have three C-terminal LIM (LIN-11, Isl1m, MEC-3 proteins) domains that interact with Protein kinases C (PKCs) (Zhou et al., 1999). ZASP proteins were shown to localize at the Z disc (Klaavuniemi & Ylanne, 2006). The first case of ZASPopathy causing MFM was described in 2005 in 11 MFM patients carrying heterozygous missense mutations (Selcen & Engel, 2005). There was a cardiac involvement in 3 of these 11 patients. Mutations in ZASP was also shown to be responsible for dilated cardiac myopathy, and left-ventricle non compaction (Vatta et al., 2003). Knockout mice for ZASP develop skeletal and cardiac myopathy with fragmented Z-discs (Zheng et al., 2009).

2.3.5 Filamin C

Filamin C (γ-filamin or Filamin 2) belongs to a family of high molecular weight cytoskeletal proteins, expressed in skeletal and cardiac muscle, in contrast to an ubiquitous expression of filamin A and B. Filamin C (NM_001127487) is a 48-exon gene (280 aminoacids) on chromosome 7 (7q32) which belongs to the filamin family of actin-binding proteins that are involved in the reshaping of the actin cytoskeleton and it is associated to myotilin. The amino terminal domain contains an actin-binding domain, followed by a semiflexible rod comprising 24 Ig-like folds, serving as interface for interaction with numerous filamin-binding proteins (van der Flier & Sonnenberg, 2001). Homodimers of Filamin C are involved in the organization of actin filaments and serve as a scaffold for signaling proteins. They link the Z-disc to the sarcolemma by interacting with Z-disc proteins and sarcoglycans in costameres (Thompson et al., 2000). The Ig-like domain 20 also binds to myotilin, and may represent a Z disc targeting motif (van der Ven et al., 2000). The nonsense mutation W2710X was identified in 2005 in patients presenting MFM signs, associated with cardiomyopathy, respiratory insufficiency and peripheral

neuropathy (Vorgerd et al., 2005). Life expectancy is shortened in patients who have mutations in the filamin C gene because of cardiomyopathy and the involvement of the respiratory muscles. Cataract and peripheral neuropathy can also occur thus demonstrating that there is a multisystem involvement. Filamin C is expressed before formation of myotubules and is required for a proper muscle development (van der Ven et al., 2000).

2.3.6 BAG3

BAG3 (Bcl-2 associated athanogen 3), which gene (NM_004281) is situated on chromosome 10 (10q25.2-q26.2), encodes a 535 aminoacid protein. It is a complex cochaperone which principally mediates interaction with Hsp70, Hsc70 and Bcl-2, an antiapoptotic protein, through its C-terminal BAG domain. The proline-rich domain interacts with the WW-domain (~35–40 amino acid residues including two highly conserved tryptophan (W) residues separated by 20–23 amino acids) that interacts with proteins implicated in signal transduction (Takayama & Reed, 2001). BAG3 forms a stable complex with HspB8 (Hsp22) and therefore participates to the degradation, via autophagy, of misfolded and aggregated proteins (Carra et al., 2008a). The first case of BAG3 mutation causing MFM was described in 2009 (P209L) in exon 3 (Selcen et al., 2009). All patients presented a childhood onset with severe progressive muscle weakness and atrophy, associated with large left atrium, pulmonary and mitral regurgitation with a restrictive cardiomyopathy pattern. There is also bilateral diaphragm paralysis, reduced forced vital capacity and respiratory insufficiency. Patients have a rigid spine and scapular winging. The progression of illness was found rapid when compared to other MFM mutations, and was linked to a significant level of apoptosis (8 % of nuclei). The function of BAG3 is to stabilize myofibril structure through F-actin. When it is mutated there is myofibril disruption and destabilization of the Z-disk structure under mechanical stress. Knockout mice for BAG3 results in a rapidly-developing myopathy with early lethality and apoptotic features, suggesting a role for BAG3 in supporting cytoskeletal connections between the Z-disc and myofibrils under mechanical stress (Homma et al., 2006).

2.4 Conclusion

MFMS are muscular dystrophies with specific, but not always identical morphologic features. All six genes causing MFMs with cardiac involvement identified so far encode proteins (Figure 1) that are related to the Z-disc. It is therefore important to study the Z-disc, which appears increasingly more complex. In fact, it is subjected to an exquisitely fine-tuned process of proteins quality control and protein turnover, and is involved in a mechanism of mechanosensing and signaling. These two important functions will be detailed in the following part.

3. Integrative biology of myofibrillar myopathies-involved genes

To understand how MFMs develop, it is necessary to describe how muscles are depending on the optimal functioning of the products of the genes described above. For that purpose, this part will develop how the different partners of the muscular structure interact with each others, in a static as well as in a dynamic point of view.
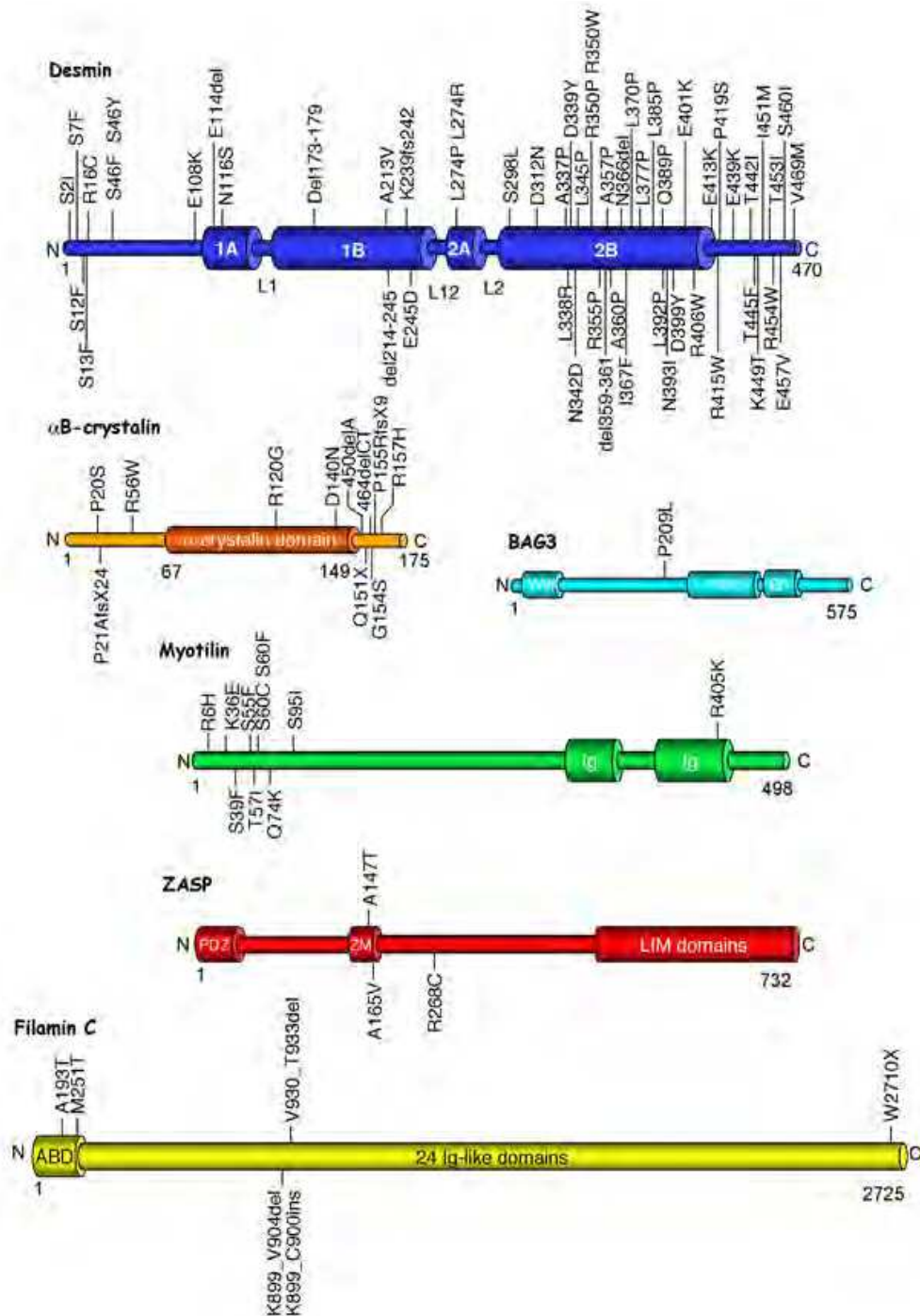
Fig. 1. Schematic representation and localization of mutations in the six proteins involved in myofibrilar myopathies.

N, C: respectively aminoterminal and carboxyterminal extremities. Numbers indicate the aminoacid position in the molecule. 1A, 1B, 2A, 2B are the helical domains of desmin. L1, L12, L2 are the non-helical linkers. WW: tryptophan-conserved domain interacting with proline-rich regions. PRR: Proline-rich region, interacting with WW domains. BD: BAG-domain. Ig: immunoglobulin-like domain. PDZ: PSD-95 / SAP90 / ZO-1 proteins common domain. ZM: ZASP-like motif. LIM domains: LIN-11 / Isl1m / MEC-3 proteins common domain. ABD: Actin-binding domain. Ig-like domains: immunoglobulin-like domain.

3.1 The smallest contractile unit: The sarcomere

The myocardium is composed of an assembly of a number of interconnecting, branching fibers, or short cells, separated at their end by the intercalated disk. The fibers contain numerous fibrils, composed of a regular repeating structure termed the "sarcomere" (Figure 2A) (Sonnenblick, 1968). The sarcomere is the basic and fundamental unit of striated muscles. Understanding the structure-function relationship linking the structure of the sarcomere to the physiology of normal or pathologic heart is therefore essential to understand myofibrillar myopathies development. Sarcomeres are distinguished by the striated distribution of their proteins, visible in light microscopy as three major bands, called A, I and Z (Figure 2B). A bands contain thick filaments of myosin and proteins that bind to myosin. The I band comprise thin actin filaments and proteins that bind actin. In the middle of the A is the "M band" also called "M line". The middle part of the I band is the "Z band", also called the "Z line" or "Z disk". The basic contractile system is the well known actin-myosin tandem. Two heavy myosin chains are associated to two light chains and form a globular part. Actin filaments, the thin structure, are composed of a double helix of G-actin (a globular molecule of 46 kDa) polymerized into a chain (Lehninger et al., 2005). αB-crystallin as chaperone molecule, myotilin and filamin C as scaffolding molecules, are known to interact with actin.

3.2 Force transmission

The first important role of Z-discs is passive transmission of tension through the Z-disc structural assembly. When a mutation occurs, like in MFM, the mechanism that maintains fixed Z-disc may go awry. In addition, Z-disc proteins allow to transmit force and ensure mechanical coupling between sarcomeres and the sarcolemma via the costameres. Three of four filaments systems of the sarcomere, filamentous F-actin, titin and nebulin/nebulette, interact with the Z-disc structure. Two proteins participate to the cardiac sacomeric cytoskeleton: titin and nebulette (Figure 2B).

Titin is a giant 3 MDa elastic protein that spans half sarcomeres from Z-disc to M-band, thus forming a continuous structure from one end of the sarcomere to the other, with consecutive titins. Titin can be considered as a giant bidirectional spring responsible for the generation of passive retraction force in mechanically stretched cardiac myocytes (Granzier & Labeit, 2004). Stiffness of titin can be adjusted during development and diseases through a shift in the expression ratio of the two main titin isoforms in cardiac sarcomeres (Lahmers et al., 2004; Opitz et al., 2004; Warren et al., 2004). Titin binds to more than 20 structural, contractile or signaling molecules, and therefore plays a role as major integrating component in the mechanosensory complexes associated to the sarcomeres.

Nebulette is a 107 kDa nebulin homologue present in the cardiac muscle Z-disc. It is composed of only 22 nebulin motifs (compared to up to 185 in nebulin), and contains a nebulin-like C terminus, mediating Z-disc localization (Moncman & Wang, 1995). At present, however, its molecular function in cardiac myocytes is still unclear.

The backbone of the Z-disc consists of layers of α-actinin aligned in an antiparallel fashion. In muscle, it cross-links actin filaments of opposite polarity originating from adjacent sarcomeres (Stromer & Goll, 1972) and provides anchors for the binding of actin thin filaments, as well as titin and nebulin/nebulette (Otey & Carpen, 2004). Myotilin and ZASP interact with α-actinin, and myotilin is linked to filamin C, thus creating a network of proteins at the Z-disc.
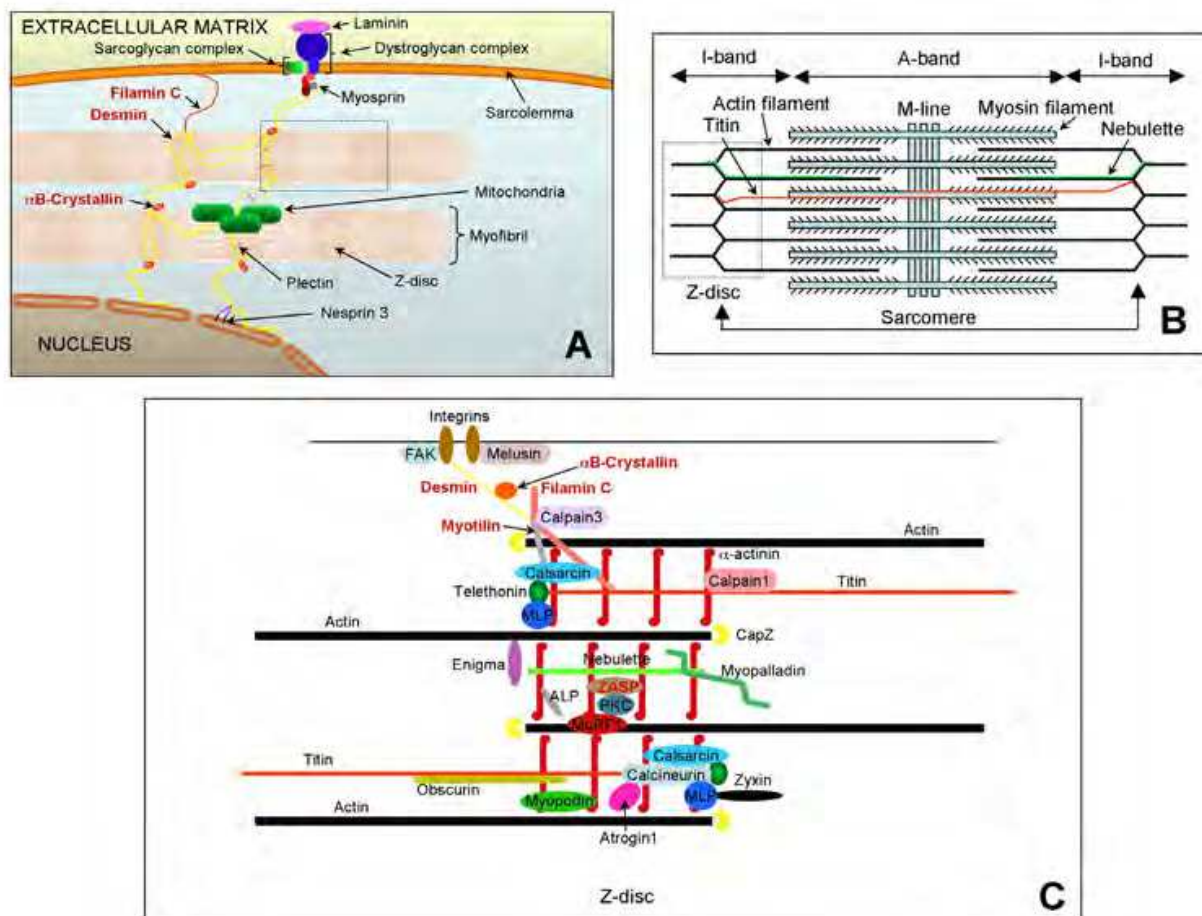
Fig. 2. Schematic representation of the general organization of muscular fibers (A), sarcomere (B) and schematic localization of the major proteins involved in the cardiac Z-disc structure (C).

Figure 2B represents the enlarged dotted rectangle in figure 2A, and Figure 2C the enlarged representation of the dotted rectangle in Figure 2B. Names in red and bold correspond to proteins involved in myofibrillar myopathies, excepted for Bag3 which is not represented. Not all proteins participating to the Z-disc structure or signaling are represented, due to the complexity of this structure. For more details, see text. Figure C is adapted from Frank et al., 2006.

Another essential component is CapZ, a heterodimer composed of α and β subunits, which caps the barbed ends of actin filaments. CapZ is proposed to regulate actin dynamics at the barbed end, thereby anchoring the thin filament system to the Z-disc (Schafer et al., 1996).

The costameres are multiproteic complexes which link the marginal Z-discs at their circumferences to the sarcolemma, the specialized membrane of the individual myofibers. Costameres have been described as transmitters of contractile force to the sarcolemma and extracellular matrix. This lateral force transmission ensures identical sarcomere length, thereby minimizing shear stress. However, desmin, filamin C, dystrophin, sarcoglycans, integrins, melusin and focal adhesion kinases have been involved in its structure (reviewed in Bloch et al., 2002).

Many other proteins (myopalladin, obscurin, Enigma, telethonin, zyxin, ...) participate to the Z-disc structure (Table 1), but their study is beyond the scope of this review (reviewed in Frank et al., 2006). The six genes held responsible for MFM are involved at various degrees in Z-disc structure and force transmission (Figure 2C). Desmin forms a continuous network that maintains a spatial relationship between the contractile apparatus and other structural elements of the cells, and is believed to provide maintenance of structural integrity, force transmission, mechanosignaling, and resistance to external mechanical stress. Myotilin constitutes the core of a network of proteins, including actin, α-actinin and filamin C, that are part of the force transmission mechanism. In turn, filamin C provides a scaffold for signaling proteins at the Z-disc, and may be part of a mechanosensing device.

3.3 Energy metabolism

In this part, we will focus on specific effects of the alteration of genes causing MFMs on energy in muscle. The main effects have been studied on the localization and function of mitochondria. Structural studies of intracellular arrangements of mitochondria into functional complexes with myofibrils and sarcoplasmic reticulum demonstrate their importance in mitochondrial oxydative activity and membrane permeability (Andrienko et al., 2003; Appaix et al., 2003). There are findings with pathological respiratory chain enzyme activities in patients with MFM (Reimann et al., 2003). Desmin intermediate filaments (IFs) might participate in mitochondrial positioning to areas of high energy demand, respiratory function, and calcium cycling in cardiac and skeletal muscle (Capetanaki, 2002).

3.4 Dynamic view of the sarcomere

While often described as a static structure, the sarcomere is actually dynamic and undergoes constant turnover, allowing to adapt to physiological changes while still maintaining its function. New factors have been identified that play a role in the regulation of protein quality control in the sarcomere, including chaperones that mediate the assembly of sarcomere components and ubiquitin ligases that control their specific degradation. The Z-disc has additional important roles as it houses or anchors many additional proteins, which have various roles, including stretch sensing and signaling or protein quality control. The Z-disc can therefore be considered as a nodal point in signaling and disease (reviewed in Frank et al., 2006). In MFMs, the Z-discs are abnormal, the arrangements of myofibrils are in disarray, or aggregates of proteins are present, often near the Z-disc. The highly ordered arrangements of proteins in the sarcomere, which persists even as contractile force is generated, suggest that binding interactions between Z-disc proteins are strong and very stable (Sanger & Sanger, 2008). Thus, the continual remodelling of the cardiac sarcomere allows efficient adaptation to physiological stresses, including exercice or metabolic variations, but also initial efficient adaptation to starting pathologies such as ischemic heart disease and myofibrillar myopathies. Since this dynamic turnover is the basis of homeostatic mechanism of sarcomere maintenance, it is essential to better understand it.

NAME	Size (kDa)	BINDING	FUNCTION	REMARKS
Obscuring	868	M-line, calmodulin, titin	Rho-GEF domain signaling	Giant protein
Myopalladin	145	Nebulette, α-actinin cadiac ankyrin repeat proteins (CARP)	Intra-Z-disc meshwork binds nebulette (directly) and titin (via α-actinin) to actin, CARP signaling ?	Palladin familly
ALP	39	Spectrin repeats of α-actinin	enhances cross-linking actin to α-actinin	PDZ and LIM domain protein 3 (PDLIM3)
Enigma	50	Ret kinase, actin, insulin receptor β tropomyosin	anchor for LIM proteins	PDLIM7
ENH	64	α-actinin 2, PKCε (brain)	hypertrophic program	PDLIM5
CLP36	36	α-actinin 2, Clik1 kinase	stress fibers control, FA	PDLIM1
Zyxin	61	binds actin to MLP α-actinin	close to Z-disc and FAK signalling / antiapoptotic	LIM protein family Nucleoplasmic shuttling
MLP	21	α-actinin, telethonin calcineurin, β spectrin	cardiac stretch receptor and mechanosignalling, negative regulator of cardiac hypertrophy	Nucleoplasmic shuttling
Telethonin	19	Titin N-terminus K+ channels, calsarcin	cardiomyocytes passive tension	negative regulator of myostatin = T-Cap
Calsarcin	27 – 32 *	Calcineurin, α-actinin telethonin, Filamin C, α-actinin	crosslinks Z-disc and Ca^{2+}/ calcineurin signalling, inhibits hypertrophic genes sensor for biomechanical stress	= synaptopodin-2
Myopodin	118 – 136 *	α-actinin colocalization	multiadaptator protein ?	nucleoplasmic shuttling

Table 1. Proteins involved in the Z-disc structure as well as in Z-disc signaling, and not detailed in the text.

Other structural and signaling molecules are described paragraphs 3.1, 3.2 and paragraph 3.4.6, respectively. ALP: Actinin-associated LIM Protein. PDZ: PSD-95 / SAP90 / ZO-1 proteins common domain. LIM domains: LIN-11 / Isl1m / MEC-3 proteins common domain. ENH: Enigma Homologue protein. MLP: Muscle LIM Protein. FA: Focal Adhesion. FAK: Focal Adhesion Kinase. PKC: Protein Kinase C.

3.4.1 Main contractile protein turnover

The following half-lives have been estimated in myocytes:

Actin: 7 to 10 days (Zak, 1977).

Myosin: 5 to 8 days (Martin et al., 1977).

Tropomyosin: 7 to 10 days (Zak, 1977).

Troponin: 3 to 5 days (Michele et al., 1999).

Titin is subjected to a "rapid" turnover, with a half-life estimated to be 3 days in myocytes (Fong et al., 1996).

3.4.2 Protein quality control: Role of chaperone molecules

Multiple endogenous pathways are engaged in restoring cellular homeostasis, among which one of the best characterized mechanism involves protein folding by the heat-shock family of stress proteins (HSP), also termed chaperones. There are several families of molecular chaperones present in the cytoplasm of mammalian cells, including Hsp90, Hsp70, TCP1 (CCT, TriC) and small HSP (sHSPs). Members of the Hsp90 family are the most abundant chaperones located in the cytosol in non-stressed cells which are inducible with stress.

Hsp70 and Hsc70 (Hsp70 cognate protein) are major players in cardiomyocyte protection: the induction of HSP70 by ischemia, and conversely, overexpression of Hsp70 or Hsc70 promotes substantial cardioprotective benefits (Donnelly et al., 1992; Hutter et al., 1994).

Chaperonin TRiC requires additional components, such as Hsp40, to stimulate the Hsc70 ATPase for protein folding, and is required for folding of actin and tubulin *in vivo*.

Unlike Hsp70, small HSPs, including αB-crystallin, Hsp27, Hsp22 and Hsp20 cannot bind nor hydrolyze ATP, and are not able to refold proteins, but can buffer them against aggregation (Merck et al., 1993). αB-crystallin represents a substantial fraction of adult heart total soluble proteins (1 to 3 %) (Kato et al., 1991). The highest level of αB-crystallin expression in muscles has been found in the cardiac conduction fibers (Leach et al., 1994). Previous studies indicate that αB-crystallin is highly soluble and localized in the cytosolic fraction in unstimulated cardiac myocytes. Heat or ischemia triggers rapid translocation of αB-crystallin into the cytoskeletal and nuclear fraction and specific interactions at the Z-disc (Neufer et al., 1998). HspB8 (Hsp22) and HspB6 (Hsp20) are also expressed in striated myogenic lineages with high oxidative capacity, such as the heart and type I skeletal muscle fibers (Depre et al., 2002).

HSP molecules are assisted by co-chaperones which perform a variety of tasks, including modulation of ATPase activity (DNAJ), substrate protein binding and release (BAG : Bcl-2 –Associated athanoGene), protein folding (Hsp40 family), assembly, and translocation or degradation (CHIP : Carboxyterminus of Hsp70 Interacting Protein). Co-chaperones also bind substrate proteins to modulate folding in a substrate-specific manner (reviewed in Willis & Patterson, 2010). Among many proteins (more than 40 Co-chaperones), only DnaJ, BAG-1, Hop and CHIP have been described in the heart. pDJA1 (DnaJ-like molecule) expression is restricted to cardiomyocytes. Its levels increase four-fold after reperfusion (Depre et al., 2003). BAG-1 is able to inhibit apoptosis and to induce autophagy by interacting with Hsc70, stimulated after ischemia / reperfusion injury (Townsend et al., 2004). The BAG-3 isoform participates in the induction of macroautophagy in association with HspB8 (Gurusamy et al., 2009). Another protein,

CHIP, plays a role as cochaperone of Hsp70 and in the ubiquitin-proteasome system as an ubiquitin ligase. CHIP may exert a critical function in shuttling damaged and oxydized proteins into autophagic pathways after ischemia / reperfusion injury (Zhang et al., 2005). Increased cochaperone expression in the heart has been found to be cardioprotective in ischemia (Benjamin & McMillan, 1998).

During assembling of the sarcomere, molecular chaperones are needed for the correct folding, assembly and prevention of aggregation. Two molecular chaperone GimC (prefoldin) and TriC (TCP-1 Ring Complex) have been found to play a synergistic role during synthesis and incorporation of actin filaments into the sarcomere. In contrast to actin, myosin cannot self-assemble without additional factors, including chaperones such as Unc45, Hsp90 and Hsp70. The assembly of desmin requires the chaperone αB-crystallin, to prevent its misfolding and aggregation (Bennardini et al., 1992). αB-crystallin also interacts with titin and actin. These data suggest a highly cooperative relationship between various chaperones during the assembly of the actin filaments in the sarcomere.

In animal models with targeted deletion of muscle-specific chaperone proteins, there is a clear evidence of sarcomere disorganization. Cardiac chaperones such as Hsp70, αB-crystallin and HspB8 levels are increased during the development of cardiac hypertrophy. Hsp27 and αB-crystallin can protect cardiomyocytes against ischemic damages (Martin et al., 1997). Increase in HspB8 expression also results in the re-expression of the foetal gene program characteristic of cardiac hypertrophy (Depre et al., 2002). The protective role of Hsp22 in ischemia / reperfusion injury appears to be due to its function in activating autophagy, which is critical during the course of this type of injury (Carra et al., 2008b).

3.4.3 The specific ubiquitin – Proteasome system in the sarcomere

The ubiquitin-proteasome system (UPS) recognizes specific proteins and target them for degradation. Ubiquitin ligases recognize proteins to be degraded and interact with E1 (activating) and E2 (conjugating) enzymes to create poly-ubiquitin chains on the substrate. Poly-ubiquitin chains are then recognized by the 20S proteasome prior to degradation. Several ubiquitin ligases integrated to the sarcomere have been identified: the MuRF family proteins (MuRF1, MuRF2 and MuRF3), MAFbx / atrogin-1 and MDM2.

MuRF1 is found mainly in the M-line of the sarcomere where it interacts with the giant protein titin. MuRF1 specifically recognizes and degrades troponin I. MuRF1 and MuRF2 are reported to interact with troponin T, myosin light chain 2, myotilin and telethonin. While single deletion of either MuRF1 or MuRF2 allows a normal development, cardiac hypertrophy develop in mice lacking both genes (Witt et al., 2008). MuRF1 and MuRF3 also interact together with the E2 enzyme to degrade β / slow myosin heavy chains in the heart. Mice lacking both proteins develop a hypertrophic cardiomyopathy and skeletal muscle myopathy (Fielitz et al., 2007). MuRF1 may preferentially poly-ubiquitinate oxydized proteins as previous results suggest it (Zhao et al., 2007). Therefore, MuRF1, in cooperation with MuRF2 and MuRF3 may ensure protein quality control by detecting damaged proteins, to allow continuous optimal functions of the cardiac sarcomere (reviewed in Willis et al., 2009).

Additional ubiquitin ligases are also playing important roles in sarcomere maintenance:
CHIP, which plays a role as co-chaperone of Hsp70 and as ubiquitin ligase has been recognized as an important factor involved in ischemia / reperfusion injury in the heart (Zhang et al., 2005).

MAFbx / atrogin-1 was first identified as an ubiquitin ligase involved in skeletal muscle atrophy (Bodine et al., 2001), possibly by regulating cardiac hypertrophy genes (Li et al., 2007).

MDM-2 is a critical regulator of apoptosis through its ubiquitin-dependent degradation of ARC (Apoptosis Repressor with Caspase recruitment domain). It interacts and mediates telethonin degradation in a proteasome-dependent manner (Tian et al., 2006). Its specific role in the maintenance of sarcomere has to be further explored.

3.4.4 Calpain degradation

The highly integrative organization of the sarcomere does not allow direct degradation of the integrated proteins. Predigestion by proteases such as calpains which are embedded in the sarcomeric structure is therefore required. Calpains are a group of calcium-dependent, non-lysosomal cystein proteases expressed ubiquitously in all cells. Calpains are involved in a variety of cellular processes such as cell-cycle control and cell fusion (Goll et al., 2003). Calpain 1 has been found tightly associated to titin in a calcium-dependent manner. It is required to allow the dissociation of sarcomere proteins from the assembled myofibrils before the ubiquitin proteasome system is able to degrade them (Dargelos et al., 2008; Jackman & Kandarian, 2004). When calpains are inhibited in the heart, protein aggregation occur, ubiquitin ligases such as MuRF1 and MAFbx / atrogin-1 are no longer efficient in mediating proteasome-dependent degradation, and autophagy is increased. However, increased levels of calpain 1 in cardiomyocytes of transgenic models lead to cell lysis, cardiac hypertrophy, inflammation and ultimately heart failure (Galvez et al., 2007). These findings are consistent with a critical role of the calpain system in protein quality control in the heart.

3.4.5 Sarcomere maintenance and autophagy

Autophagy is a process for protein degradation that uses lysosomal hydrolases working at acidic pH. Autophagy begins with the formation of isolation membrane (phagophore). The phagophore then elongates and engulfs a portion of the cytoplasm to form a mature autophagosome, which then fuses with lysosomes to form autolysosomes. Autophagy removes damaged organelles such as mitochondria and aggregates of misfolded or damaged proteins (Beau et al., 2011). Autophagy-mediated degradation also contributes to the maintenance of the sarcomere (Portbury et al., 2011). In cardiomyocytes, autophagy occurs at the basal level and can be further induced by physiological or pathological conditions such as starvation, haemodynamic stress, ischemia / reperfusion, proteotoxicity, and toxins (Gustafsson & Gottlieb, 2008). Inhibition of autophagy leads to global disorganization of the sarcomere, mitochondrial aggregation, with ventricular dilation, cardiac hypertrophy and contractile dysfunction in adult animal models (Nakai et al., 2007). When autophagy is inactivated, there is an increase in poly-ubiquitinated proteins, as well as in proteasome activity, which suggest that despite its compensatory increase in activity, the UPS may be rapidly overwhelmed by the accumulation of toxic proteins (Bennett et al., 2005). Conversely, inhibition of proteasome activity leads to the accumulation of poly-

ubiquitinated proteins and activation of autophagy (Tannous et al., 2008b). These results suggest, therefore, an essential role of cooperativeness between UPS and autophagy in maintaining protein quality control in the heart. Cell signaling pathways, such as PI3K / Akt, and transcription factors like FOXO3 have just begun to be involved as essential mediators in coordinating the proteasomal and lysosomal systems. In addition, sHSP and co-chaperones, like the Hsp22 – BAG3 complex activate autophagy, while BAG1 / BAG3 ratio is important to the balance between proteasomal to autophagic degradation (reviewed in Willis et al., 2009).

3.4.6 Physiological signaling and stress signals

An essential component of cardiac signaling is a process termed mechanotransduction, which translates a mechanical stress into a transcriptional response, and may constitute one of the most important stimuli leading to cardiac hypertrophy. Z-disc-associated proteins appear to play a critical role in this process (Frank et al., 2008). Mechanosignaling results in increased rate of protein synthesis, alteration of cell shape and increased expression of genes that are normally expressed predominantly during fetal life. Nodal points of mechanotransduction are found along the cardiac sarcomere, notably in the Z-disc, I-band and M-band regions (reviewed in Frank et al., 2006). It has been found that separate directional pathways are implicated by static transverse and longitudinal forces applied to cardiomyocytes to activate distinct cell signaling pathways. The mains involved are focal adhesion kinases (FAK), proteins kinase C (PKC) and integrins:

FAK is the primary effector of integrin signaling, and is localized to costameres in myocytes (Tornatore et al., 2011). Mechanical stress leads to disruption of FAK interaction with myosin heavy chain at the A-band to Z-disc, costameres and nuclei. Cyclic stretch induces a FAK-mediated activation of JNK and c-jun as well as of MEF2 (Nadruz et al., 2005). FAK appears therefore to play a critical function in hypertrophy, triggered in biomechanical as well as pharmacological models.

PKCε is a modulator of cardiac hypertrophy that belongs to the groups of "unconventional" PKCs which do not require Ca^{2+} for their activation (Dorn & Force, 2005). PKCε translocate to the Z-disc in cardiomyocytes upon stimulation, in particular by mechanical stress, or in pressure overload (Gu & Bishop, 1994). PKCε is necessary for cardiac hypertrophy induced by G protein receptors coupled agonists (Iwata et al., 2005). CapZ also plays a role in PKC signaling, which subsequent effects on cardiac contractility. Anchors to the Z-disc for PKCε are also provided by ZASP which links them to α-actinin through binding either to PDZ or LIM domains.

Other molecules, including PDE5A (PhosphoDiEsterase 5A), PCAF (P300/CBP Associated Factor), Zyxin, myopodin and HDAC4, ArgBP2, localize to the Z-disc, A-bands and I-bands of myocardial tissue, were found to shuttle between the sarcomere and the nucleus, and modulate the signaling pathways involved in cardiomyopathies (rewieved in Frank & Frey, 2011).

Strains on cultured cardiomyocytes also increases FAK activity and PKCε, which lead to the activation of the Rho/ROCK GTPases/kinase pathway, for which substantial evidences support a role in myofibrillogenesis (Franchini et al., 2000; Torsoni et al., 2003). One of the target of PKCε is the muscle actin capping protein for the barbed end of the actin filament (Schafer et al., 1994). Myocyte contractility, through titin and T-cap may also regulate muscle LIM proteins (MLP) shuttling to and from the nucleus, that may play a further role

in myocyte remodeling and hypertrophy, and is required for adaptation to hypertrophic stimuli (Iwata et al., 2005).

Integrins are transmembrane proteins which transduce signals from the extracellular matrix to the inner cell space and conversely. In the myocardium, integrin signalling plays an important role in mediating hypertrophic signals converging on the kinases Erk 1/2, PKC (Heidkamp et al., 2003), p38 MAPK (Aikawa et al., 2002) or JNK (Zhang et al., 2003). Among the proteins binding to integrins upon signaling, were identified the Integrin-Linked Kinase (ILK), FAK and Melusin.

ILK is a serine/threonine kinase. Its specific cardiac deletion in mice leads to dilated cardiomyopathy (DCM) and sudden death, while cardiac-restricted overexpression of ILK induces cardiac hypertrophy via activation of Erk 1/2 and p38 MAPK, indicating a function in hypertrophic signaling (Bendig et al., 2006; Lu et al., 2006).

Melusin is transiently upregulated in the heart upon pressure overload. Deletion of the Melusin gene show DCM and contractile dysfunction upon stress only, while overexpression leads to pathological hypertrophy (Brancaccio et al., 2003; De Acetis et al., 2005).

The Calcineurin / NFAT pathway is modulated by proteins like CIB1/ MLP/Calsarcin/LMDC1 that play a pivotal role in the mediation of pathologic cardiac hypertrophy (Frey et al., 2004). Calcineurin is linked to the Z-disc via calsarcin and MLP, and directly binds to the L-Type Calcium Channel, the major mediator of calcium influx in cardiomyocytes. Calcineurin activates by dephosphorylation the NFAT (Nuclear Factor of Activated T cells) transcription factors family, one of the major mediators of cardiac hypertrophy and remodelling.

PKA and PKG (cGMP-dependent protein kinase-G) are bound to titin. PKA is stimulated by β-adrenergic stimulation by catecholamines, while PKG is stimulated by nitric oxide and the natriuretic peptide (Wong & Fiscus, 2010). PKA can phosphorylate troponin-I, myosin-binding protein C and titin (Yamasaki et al., 2002; Yang et al., 2001; Zakhary et al., 1999).

4. From healthy to failing heart : Etiology and studies of myofibrilar cardiomyopathies

4.1 Diagnosis

As MFM refers to a group of genetically distinct disorders, common morphologic features observed on muscles are determinant. The following clinical findings should direct the diagnosis to a myofibrillar myopathy.

4.1.1 Clinical signs

Most patients with MFM show progressive muscle weakness. A small proportion of patients show paresthesias, muscle atrophy, stiffness or aching, cramps, dyspnea or dysphagia, or mild facial weakness. In about one third of the cases, the weakness is predominantly distal, in another third it is more proximal than distal, and in the other third it is mixed. In some patients, however, the cardiomyopathy may precede the muscle weakness.

Cardiomyopathy is a "classical" feature in MFM and may precede, coincide or follow the skeletal muscle weakness. Cardiomyopathy includes arrhythmogenic type (with atrio-ventricular blocks, supraventricular and ventricular ectopic beats and tachycardia), hypertrophic, dilated or restrictive features (reviewed in Ferrer & Olive, 2008; Goldfarb & Dalakas, 2009; Schroder & Schoser, 2009; Selcen, 2011).

Serum creatine kinase (CK) is variable, sometimes elevated. Differences depending on the causal gene have been reported (Schroder & Schoser, 2009):

DES, CRYAB and MYOT: normal up to 5 fold (reported maximal 15 fold for MYOT)
FLNC: normal up to 10 fold
ZASP: normal up to 6 fold
BAG3: 3 up to 15 fold

4.1.2 Histopathology

Muscle histology is essential and reveals characteristic features:
- Amorphous, hyaline or granular materials stained by trichrome.
- hyaline structures intensely positive for Congo red staining.
- significant decrease of oxidative enzyme activity in many abnormal fibers regions.
- small vacuoles in a variable number of fibers.

Immunohistochemistry performed on frozen sections (paraformaledehyde-fixed (4%)) from biopsies show abnormal ectopic expression of desmin, αB-crystallin, myotilin and dystrophin (Claeys et al., 2009; Schroder & Schoser, 2009; Selcen, 2011).

4.1.3 Electromyography

Electromyography (EMG) should be performed to confirm the histopathological data. EMG reveals abnormal electrical irritability often with myotonic discharges. The motor unit potentials are mostly myopathic, sometimes in combination with neurogenic features (Schroder & Schoser, 2009).

4.1.4 Electron microscopy

Electron microscopy of muscles showing progressive myofibrillar degeneration reveal abnormalities starting from the Z-disc area: streaming, defects in stacking, accumulation of granulo-filamentous dense materials, sarcomere disintegration, dislocated membranous materials, autophagic vacuoles, abnormal accumulation or location of mitochondria. Ultrastructural observation may allow to differentiate between granulofilamentous accumulation, "sandwich" formation, filamentous bundles, floccular thin filaments, tubular filamentous accumulations, and early apoptotic changes, to allow to direct diagnostic efforts toward the type of gene causing the MFM (Claeys et al., 2008).

4.2 Clinical perspectives and therapeutic considerations

There is currently no specific treatment for myofibrillar myopathies, nor clinical trial investigations (to the best of our knowledge).

MFM share protein aggregation with other aggregate-prone diseases, such as Alzheimer's, Parkinson's and Huntington's diseases. Accumulation of toxic β-amyloid oligomers, impairment of the ubiquitin proteasome system, alteration of the efficiency of the autophagic process have also been reported in studies about these diseases (Aguzzi & O'Connor, 2010). Several treatments have been set up and are currently tested for clinical trials, and may possibly be studied in the case of myofibrillar myopathies. However, caution should be taken because reducing the formation of aggregates may not directly allow to the cure of the disease (Sanbe et al., 2005).

Curcumin, a polyphenol naturally occurring in plant products, has been shown to inhibit α-synuclein aggregates formation involved in Parkinson's disease (Pandey et al., 2008).

Another way to reduce aggregates formation is to activate HSP, which may favour refolding or degradation of mutant proteins, or folding of the WT proteins expressed in the normal allele. Non-steroidal anti-inflammatory drugs, prostaglandins (Amici et al., 1992), Celastrol (Westerheide et al., 2004) or Geranylgeranylacetone (Sanbe et al., 2009) have been shown to activate the heat shock response. However, it is probably not judicious to induce αB-crystallin if this gene is mutated.

Activators of the autophagic pathway of degradation have been reported and could constitute a way to clear aggregates from the cardiomyocytes. Among many compounds actually tested, one can cite starvation, rapamycin, wortmanin, trehalose, etc (Sarkar & Rubinsztein, 2008).

Antioxydant agents, such as vitamin C, N-acetyl cysteine, ROS trapping agents like phenyl-N-tert-butylnitrone may also help to reduce aggregates formation, or help to their degradation (Squier, 2001).

5. Conclusion

There has been considerable improvement in the understanding of myofibrillar myopathies since they were first reported in 1978 (Fardeau et al., 1978). New avenues of discoveries have just opened with concepts of protein quality control, involving chaperone molecules, the ubiquitine proteasome system, and macroautophagy. Moreover, the sarcomere is not only seen now as a passive force generator, but also as a mechanosensor which signals to the nucleus and to the whole muscular fiber, and activates specific programs of renewal of sarcomeric proteins, in case of damages. These new findings will help to integrate more components of the muscle physiology, and to understand how they are modified when MFM-causing genes are mutated. However, only 20 % of MFM have found a "culprit" gene, so it may be necessary to analyze other Z-disc-specific structural, quality control or signaling genes to find new candidates responsible for MFMs.

6. Acknowledgment

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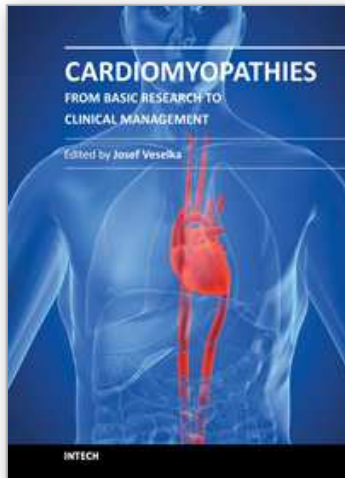
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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