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Integrins in the Development and Pathology of Skeletal Muscle

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1. Introduction

1.1 Adhesion of muscle fibres to the extracellular matrix

Skeletal muscle is composed of many multinucleated myofibres each of which is surrounded by a connective tissue matrix that is essential for the function and the structural integrity of muscle. Apposed to each myofibre is a basement membrane, composed of a mixture of extracellular matrix (ECM) proteins, including collagen, fibronectin, glycoproteins (laminins, perlecan and nidogen) and proteoglycans. The proteins bind to multiple receptors expressed on the surface of muscle fibres: this is most notable at the level of the Z discs where an assembly of cytoskeletal proteins including dystrophin and integrins maintain continuity between the contractile apparatus, cytoskeleton and the ECM. This association of proteins is commonly referred to as the costamere, which is derived from the Latin word *costa,* meaning rib, because they encircle the whole muscle fibre and are arranged at regular intervals, thus conferring the appearance of a rib-like structure (Ervasti, 2003). Costameres are the means by which mechanical stress generated by contraction is diffused laterally across the myofibre. An additional structure where stress is transmitted to the ECM is the myotendinous junction (MTJ), where a connection to the tendon is made at the termini of muscle fibres (Tidball, 1991). This tight association between the muscle fibre and its surrounding matrix not only confers tensile strength to the entire muscle but also plays an important role in development, regeneration and synaptogenesis (Sanes, 2003). Indeed genetic defects in proteins that localise to the costameres and MTJs are a common cause of muscle disease, underscoring their importance in maintaining normal muscle function (Campbell and Stull, 2003).

The two main adhesion systems recognised in striated muscle are the dystrophin-associated protein complex (DPC) and the integrins. Each system is composed of transmembrane

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proteins that bind to the ECM, and of cytoplasmic proteins that connect to the cytoskeleton and transmit biochemical signals. The DPC is composed of several proteins, which include α- and β-dystroglycan that bind to laminin, dystrophin that connects to the cytoskeleton, and associated proteins such as sarcoglycans and neuronal nitric oxide synthase (nNOS). These proteins have the important function to confer mechanical integrity to the plasma membrane, which otherwise would break following muscle contraction. Indeed, this occurs in patients with mutations in DPC components, and present with several types of severe muscle disease, including Duchenne Muscular Dystrophy (DMD) and various forms of Limb Girdle Muscular Dystrophy (Bushby, 1999; Barresi and Campbell, 2006).

While integrins also establish a connection between the ECM and cytoskeletal and signalling proteins, the two complexes are biochemically distinct. As we will see below, integrins appear dispensable for the mechanical integrity of the sarcolemma, but have important functions during all stages of muscle development.

2. Integrins

Integrins are transmembrane receptors that connect via the extracellular domain to extracellular matrix (ECM) ligands such as collagen, laminin and fibronectin, and via the intracellular domain to the actin cytoskeleton and to a variety of signaling and adaptor proteins. Each integrin is a heterodimer composed of an α- and a β-subunit. In mammalian cells 18 α and 8 β subunits have been characterized, and are known to assemble to form 24 distinct integrin heterodimers, with the combination of α- and β- subunits determining ligand specificity. These play essential functions during development and in adult tissues. Accordingly, genetic ablation of individual subunits in mice leads to defects in tissues including brain, skin vasculature, lung, kidneys, inner ear, placenta, skeletal and cardiac muscle (Hynes, 2002).

The cytoplasmic domain of both the α- and β-integrin subunits is devoid of catalytic activity, but it binds to an array of proteins that mediate integrin effects on cell function. It is currently estimated that over 150 proteins are associated with integrin adhesion sites (Zaidel-Bar et al., 2007). Of these, we will discuss those that to date have been shown to be important in skeletal muscle. Some play structural roles, conferring mechanical integrity to myofibres by connecting integrins to the actin cytoskeleton, and others play signaling roles, by eliciting a biochemical response to mechanical stimuli caused by muscle contraction.

2.1 Developmental expression of integrins in skeletal muscle

Several integrins are expressed in myoblasts and muscle fibres, including αvβ3-integrin, α4-integrin (associated with β1 or β2), and β1-integrin with the α1, α2, α3, α5, α6, α7 or α9 subunits (Gullberg et al., 1998; Mayer, 2003; Thorsteinsdottir et al., 2011). Expression of these subunits is regulated, with regards both to the stage of muscle development and to the localization within muscle fibres (Thorsteinsdottir et al., 2011). Some integrin subunits (β1A, α4, α5, α6, α7b and αv) are detected in the somites and in myoblasts. During myotube formation, expression of most subunits is downregulated, and adult muscle fibres express the β1D subunit, paired with α7a, α7b, and α9. The subcellular distribution of these integrin

subunits is also regulated: α7a is found at the MTJ, α7b at the sarcolemma, MTJ and neuromuscular junction (NMJ), α3- and αv-integrins are localized to the NMJ, and α9-integrin appears to be uniformly distributed along the sarcolemma (Wang et al., 1995; Martin et al., 1996). We will discuss here the functions identified for integrins in muscle, and refer the reader to recent reviews for details on the regulation of somitogenesis and NMJ formation by integrin-ECM interactions (Singhal and Martin, 2011; Thorsteinsdottir et al., 2011).

While the expression pattern of the different subunits is well characterized, the precise function of many remains to be addressed. Genetic ablation of integrins in mice has not always been informative in this regard. For instance, mice with an ablation of α1-, α9- and αv-integrins present no defects in skeletal muscle (Gardner et al., 1996; Bader et al., 1998; Huang et al., 2000). Mice with a genetic ablation of α3- and α6-integrins, die too early to study the long-term functions of integrins in skeletal muscle maintenance (Georges-Labouesse et al., 1996; Kreidberg et al., 1996). The distribution of laminin α5, which is the main ligand for α3-integrin, suggests a possible function in maturation of the muscle fibre and of the NMJ, since its initial expression throughout the basal lamina of developing myotubes becomes restricted to the NMJ in the first 3 weeks following birth (Nishimune et al., 2008). This is also consistent with α3-integrin expression being concentrated at the presynaptic NMJ (Martin et al., 1996).

Muscle defects have also been identified in mice with ablation of α5- and α7-integrins (Taverna et al., 1998; Mayer et al., 1997). α5-integrin is a receptor for fibronectin, and is expressed transiently during myotube differentiation. Ablation of α5-integrin in mice leads to early embryonic lethality with defects in mesoderm, vascular development and neural crest (Yang et al., 1993; Goh et al., 1997), but mice chimeric for this subunit survive postnatally and develop a form of muscular dystrophy (Taverna et al., 1998). No patients have been identified with mutations in α5-integrin possibly because, extrapolating from the data obtained in the mutant mouse models, null mutations are likely to be non viable. α7-integrin has been shown to play important functions in muscle in animal models and human patients, where mutations lead to a form of congenital muscular dystrophy (Mayer et al., 1997; Hayashi et al., 1998). Whilst it is possible that an in-depth analysis of the α-integrin subunit knockout mice would reveal muscle defects, for example in response to stressors such as exercise or mechanical damage, the apparent absence of a reported phenotype for some of these mice might be explained by redundancy. This possibility is supported by the generation of mice with a muscle specific ablation of the β1-subunit, which leads to the concomitant ablation of all αβ1-integrins (Schwander et al., 2003). These mice die shortly after birth, probably because of respiratory failure, with severe developmental defects in the muscle caused by impaired myoblast fusion and altered assembly of the sarcomere.

3. Integrins in skeletal muscle development

Fusion of myoblasts is essential for the formation of a syncytial myofibre, and it occurs in distinct steps: (i) migration of myoblasts to achieve cell proximity; (ii) contact between

myoblasts and alignment of the plasma membranes; (iii) breakdown of the plasma membrane at the site of fusion, leading to the formation of fusion pores (iv) merging of the cytoplasmic contents (Chen et al., 2007). While the identity of the proteins leading to plasma membrane breakdown is unknown, studies in recent years have led to the identification of several components of the fusion machinery, most notably elucidating the importance of actin remodeling (Rochlin et al., 2010).

3.1 β1-integrin and talin

A direct involvement of integrins in the regulation of myoblast fusion in vertebrates has been obtained using genetically modified mice. Ablation of β1-integrin in developing muscle has revealed important functions in cell-cell fusion and assembly of the sarcomere (Schwander et al., 2003). β1-deficient mice died at birth, with histological analysis showing that many myoblasts failed to fuse. *In vitro* analysis showed that fusion defects could be rescued when wild-type and β1-deficient myoblasts were mixed, suggesting that heterophilic interactions of β1-integrin with an unidentified receptor may be important. Analysis of cultured myoblasts by electron microscopy showed that plasma membranes aligned properly, but fusion pores failed to open, indicating that integrins are not essential for the alignment of myoblasts, but affect a subsequent step in fusion. The analysis of mice lacking the integrin effectors talin 1 and talin 2 suggests that signaling to the cytoskeleton may be important in this respect.

Talin 1 and 2 are expressed by two distinct genes (*tln1* and *tln2*) and present a high degree of homology (74% identity in the amino acid sequence)(Senetar and McCann, 2005). They bind to cytoskeletal proteins such as actin and vinculin, and signaling effectors that include focal adhesion kinase (FAK) and PIPK1γ, which regulate the assembly of focal adhesions (Critchley, 2004). The two isoforms are essential to mediate β1-interin functions in myoblasts ablation of talin 1 and talin 2 in muscle (tln1/2-dKO) resulted in defects similar to those observed following ablation of β1-integrin: mice died shortly after birth, with abnormal development of the musculature, including defects in myoblast fusion, sarcomere assembly and in the clustering of α7-integrin, vinculin and integrin-linked kinase (ILK) at the MTJ (Conti et al., 2009). The tetraspanin CD9, which has been implicated in sperm-egg fusion (Kaji et al., 2000; Hemler, 2001), was mislocalised in β1-deficient muscle, but localized normally at the interface of tln1/2-dKO myoblasts, and integrin activation was also normal, suggesting that outside-in signaling mechanisms may be responsible for the fusion defects (Conti et al., 2009). In this respect, it is interesting to note that several of the proteins implicated in myoblast fusion are controlled by integrins, specifically, the Rho GTPases Rac1 and Cdc42, and associated proteins such as Dock180 (Laurin et al., 2008; Pajcini et al., 2008; Vasyutina et al., 2009). In mouse, vinculin, an actin- and talin-binding protein (see below) accumulates at the interface of fusing myoblasts, and genetic ablation of Rac and Cdc42 causes a reduction in this accumulation (Vasyutina et al., 2009). Furthermore, ablation of two other integrin effectors, FAK and filamin C, leads to compromised myoblast fusion (Dalkilic et al., 2006; Quach and Rando, 2006). These data are indicative of a possible involvement of integrins in regulating actin dynamics at the sites of fusion, although this still needs to be demonstrated directly.

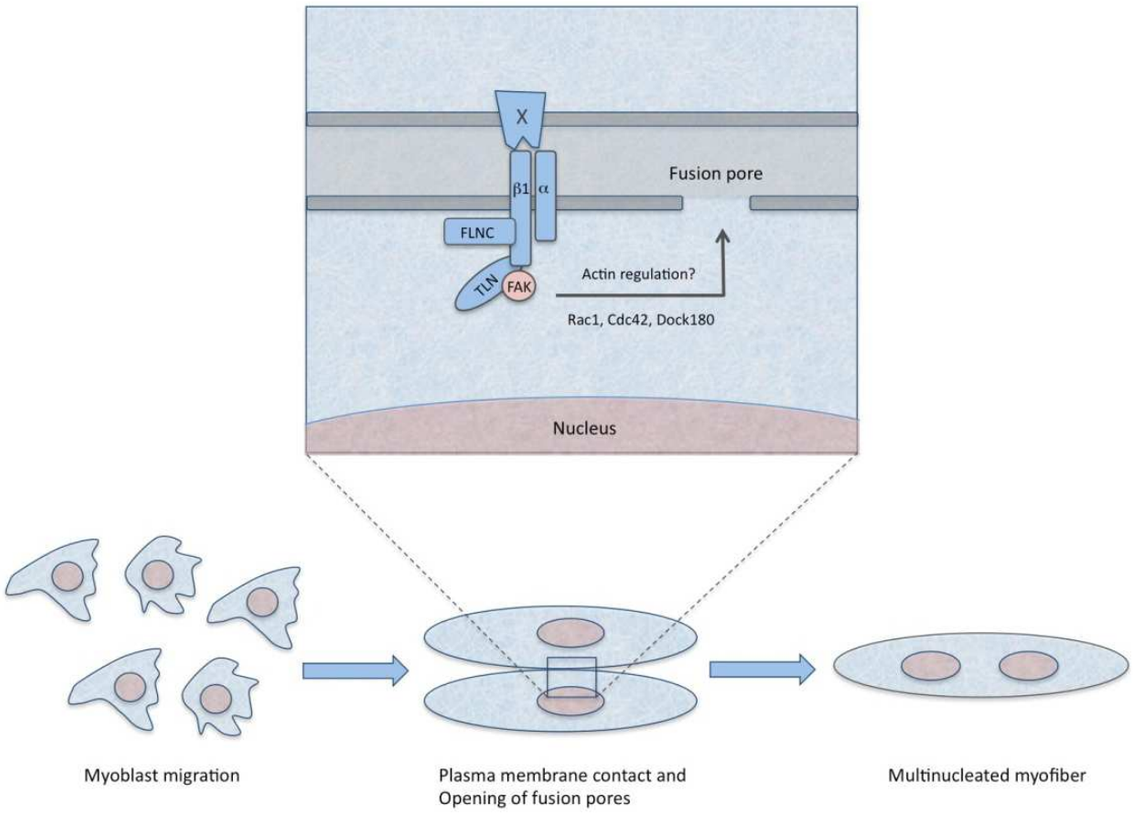


Fig. 1. **Integrins are essential for myoblast fusion.** Prior to fusion, migrating myoblasts elongate and make contact between their plasma membranes. Integrins localise at the cell interface, and are important for the formation of fusion pores, i.e. the breakdown of plasma membrane that precedes mixing of cytoplasmic content. In vitro experiments suggest that integrins interact heterophylically with an as yet unidentified counterreceptor (X in upper image). The mechanisms by which this occurs are unclear, but fusion defects are also observed following ablation of filamin C, talin 1 or talin 2, which are important actin regulators, suggesting that changes in cytoskeletal dynamics are important. Abbreviations: FLNC = filamin C; TLN = talin 1 or talin 2; FAK = focal adhesion kinase; α = as yet unidentified β1-integrin associated α-subunit. X = putative (unidentified) counter receptor for β1-integrin.

3.2 Filamin C

Filamins are actin binding proteins that cross-link actin filaments into orthogonal networks. They bind to over 30 proteins, including integrins and actin, through which they perform many functions, including modulation of cell adhesion to the ECM, cell migration, mechanical strengthening of the plasma membrane, and the activation of signaling networks. Mammalians express three filamin isoforms, termed filamin A, B and C. Filamins A and B are widely expressed, and play essential functions in the development of a variety of tissues. Expression of filamin C is mostly restricted to skeletal and cardiac muscle, where it localizes to the sarcolemma and to the Z-disk, and interacts with several proteins associated with muscular dystrophies, including calpain-3 and sarcoglycans (Zhou et al., 2010).

Downregulation of filamin C in C2C12 myoblasts via siRNA causes an impairment of cell-cell fusion, defective elongation of myotubes, and impaired gene expression during myoblast differentiation, including myogenin, caveolin 3 and α7-integrin (Dalkilic et al., 2006). An important function for filamin C in muscle differentiation was confirmed by analyzing mice in which its expression was genetically ablated. Filamin C-knockout mice died at birth likely because of respiratory failure, and presented with severe defects in myogenesis abnormal morphology of myofibres and a loss of muscle mass. While these defects partly overlap with those of β1-integrin and tln1/2-dKO mice, the phenotypes differ in that fusion and sarcomere defects are less pronounced, indicating that filamin C is not essential for β1-integrin function in muscle and that some of its effects are likely due to the interaction with other binding partners (Dalkilic et al., 2006).

Mutations in filamin C have been identified in patients with late-onset myopathies, characterized by progressive muscle weakness. Mutations in the C-terminal dimerization domain lead to myofibrillar myopathy, characterized by the accumulation of intracellular aggregates constituted of filamin C and various Z-disk associated proteins (Vorgerd et al., 2005; Lowe et al., 2007). The mutations are localized to the dimerization domain of filamin C, and cause the formation of a truncated protein that cannot form dimers, implying that dimerization is important for its function. Recently, mutations in filamin C have also been identified in patients with distal myopathies. These mutations are localized in the N-terminal actin-binding domain of filamin C, and induce increased actin binding. However, unlike the situation in patients where mutations are in the C-terminus, no protein aggregates accumulate in myofibres, suggesting that the pathological mechanisms differs from those observed in patients with mutations in the dimerization domain (Duff et al., 2011).

4. Structural connections of integrins to the cytoskeleton

Given the crucial functions played by integrins during skeletal muscle development, as determined by the studies in vitro and on animal models mentioned above, it is surprising that few defects in integrin function have been associated with muscle disease in patients. In fact, with the exception of α7-integrin and filamin C (Mayer et al., 1997), mutations in integrin effectors have been linked to defects in the heart but not in skeletal muscle. This is in contrast with the mutations in DPC, which have been identified as being the most common causes of muscular dystrophy (mutations the dystrophin gene alone affect approximately 1:3500 male births)(Goyenvalle et al., 2011). This could be due to mutations in integrins or integrin effectors being very rare, or to the pathology not being clearly identified, which would complicate the selection of patients for genetic screening. Although integrins and the DPC provide a similar link between laminin and the actin cytoskeleton, ablation of the two protein complexes leads to a different spectrum of muscle defects, and despite extensive analysis, the specific functions of each protein complex remain unclear.

4.1 α7β1-integrin

α7β1-integrin is a receptor for laminin in the basement membrane, localizes to costameres, NMJs and MTJs, and is the sole integrin known to be expressed in adult skeletal muscle (Bao et al., 1993; Martin et al., 1996). The intracellular domain of α7-integrin is spliced to produce two main isoforms, termed α7a and α7b. Their expression is tightly regulated during

myoblast differentiation and muscle regeneration, and this regulation is conserved across mammals, suggesting that the specific roles played by these isoforms are important (Collo et al., 1993; Ziober et al., 1993; Cohn et al., 1999). The α7b isoform is expressed at higher levels in proliferating myoblasts and adult fibres, while the α7a isoform is expressed upon terminal differentiation. These α7-integrin splice variants bind with equal affinity to laminin, thus differences probably reside in binding to intracellular integrin effectors. It has been suggested that the splice variants may differ in the regulation of myoblast differentiation (Samson et al., 2007), as α7a interacts with Def-6, a guanine nucleotide exchange factor (GEF) for the Rho GTPase Rac-1 that has been implicated in the regulation of myoblast fusion. However, mice in which α7-integrin is ablated (α7-KO) are viable and present with normal muscle development, indicating that α7-integrin is not essential for myogenesis *in vivo* (Mayer et al., 1997). Instead, α7β1-integrin plays an important structural role in skeletal muscle by mediating a connection of actin to the sarcolemma at the MTJ. In α7-KO mice this connection fails, leaving a space filled with vesicular and amorphous material, and the mice developed a progressive myopathy, characterised by muscle weakness and a mild accumulation of centrally nucleated fibres (Mayer et al., 1997; Miosge et al., 1999). α7b-integrin has been shown have a protective effect against mechanical damage. Following exercise, expression of α7-integrin is upregulated in muscle, and exercise-induced damage is increased in α7-KO mice (Boppart et al., 2006). A protective function for α7-integrin is supported by studies in which the α7bX2 splice variant was overexpressed in mice. The transgenic mice showed a reduced activation of the MAPK pathway, associated with injury, and of AKT, mTOR and $p70^{s6k}$, associated with hypertrophy, and presented with reduced muscle damage in response to exercise (Boppart et al., 2008). It is interesting to note that α7β1-integrin is increased in the muscle of patients with DMD and of *mdx* mice (Hodges et al., 1997). Thus, upregulation of α7β1-integrin might be a natural mechanisms to increase the resistance of muscle to injury in the absence of dystrophin and indeed, enhanced α7-integrin expression alleviates muscular dystrophy in transgenic mice lacking dystrophin and utrophin (Burkin et al., 2001; Burkin et al., 2005).

Mutations in α7-integrin have been associated with muscle disease in humans: three Japanese patients were identified with a deficiency in α7-integrin, caused by deletion or frame-shift mutations in the *itga7* gene (Hayashi et al., 1998). Similar to the phenotype of α7-KO mice, the muscle in patients presented with no signs of necrosis and creatine kinase values that were only slightly elevated, indicating no major damage to the sarcolemma. However, the clinical phenotype was severe: patients presented with delayed motor milestones from early childhood, and in one case mental retardation. Follow up of one of the patients showed a severe progression of the disease, comparable to that of DMD, which led the patient to be wheelchair bound by the age of 12 (Nakashima et al., 2009). Thus, while the initial classification was that of a congenital myopathy, patients with a clinical presentation of congenital muscular dystrophy should also be considered for screening for integrin α7-deficiency. As no new patients have been diagnosed with a deficiency of α7-integrin since the initial identification, mutations appear to be rare.

4.2 Talin

Of the proteins that bind to the cytoplasmic domain of integrins, studies have revealed important functions for talin in mediating the connection to myofilaments at the MTJ. In

Drosophila, ablation of the talin gene (*mys*), induces detachment of actin filaments from the integrin cytoplasmic domain at muscle termini (Brown et al., 2002). Two talin isoforms are expressed in vertebrates, with talin 2 being most expressed in skeletal and cardiac muscle, while talin 1 is ubiquitous (Monkley et al., 2001). Muscle-specific ablation of talin 1 was achieved using conditional gene inactivation in muscle, as knockout of the talin 1 gene causes early embryonic lethality. In contrast, mice in which talin 2 was ablated were viable (Monkley et al., 2000; Conti et al., 2009). Both talin1-KO and talin2-KO mice presented with defects in skeletal muscle similar to those obtained following ablation of α7-integrin, consisting in structural failure at the MTJ, and a limited accumulation of centrally nucleated fibres, with no obvious damage to the sarcolemma. Consistent with the expression data, the phenotype was more severe in talin2-KO mice (Conti et al., 2008; Conti et al., 2009). Interestingly, adult muscle expresses a splice variant of integrin β1-integrin, termed β1D, which binds to F-actin with greater affinity than the ubiquitous β1A isoform (Belkin et al., 1997; van der Flier et al., 1997). The data suggest a model whereby a strong connection between the ECM and actin is established at the MTJ by complexes of α7β1D-integrin and talin 2, and, to a lesser extent, talin 1. In the absence of α7-integrin or of talin 2, stress induced by muscle contraction leads to mechanical failure at the MTJ.

4.3 Centrally nucleated fibres in myopathies

The reason for the accumulation of centrally nucleated fibres in muscles lacking integrins or talin is unclear. In muscular dystrophies, central nuclei are associated with regenerating fibres that are thought to form because the absence of DPC proteins causes fragility to the plasma membrane and necrosis of myofibres (Davies and Nowak, 2006). This does not occur when integrins are affected: patients with null mutations in the *itga7* gene have only mildly elevated plasma creatine kinase, and there is no evidence of damage to the sarcolemma in mice deficient in α7-integrin and talin 1 or 2 (Hayashi et al., 1998; Conti et al., 2008; Conti et al., 2009). Thus integrins appear dispensable for maintaining the structural integrity of the sarcolemma and other mechanisms must account for the presence of centrally nucleated fibres. One possibility is that cytoskeletal alterations might affect nuclear positioning. For example, internal nuclei were observed in mouse models lacking proteins that regulated actin organization and membrane trafficking, such as myotubularin 1, dynamin 2 and γ-actin, without evidence of damage to the sarcolemma (Buj-Bello et al., 2002; Bitoun et al., 2005; Sonnemann et al., 2006), but whether integrins regulate nuclear anchorage, it is at present unknown. Alternatively, integrins might be essential to provide survival signals to myofibres. In particular, signaling from FAK, which associates with talin, is important to suppress apoptosis in cultured cells (Lim et al., 2008). These signals might be perturbed in α7-KO and talin2-KO mice, leading to loss of myofibres and regeneration.

4.4 Vinculin

Vinculin is a ubiquitous component of focal adhesions that establishes a connection between integrins and an array of cytoskeletal proteins, including paxillin, talin, actin and the Arp2/3 complex, among others (Ziegler et al., 2006). In skeletal muscle, vinculin localizes to costameres, MTJ and NMJ (Bao et al., 1993), and in cardiac muscle, to costameres and intercalated disks (ICDs). Its expression levels are regulated by mechanical stress, and studies on cells in culture have revealed a function for vinculin in sensing mechanical

stimuli and in reinforcing the connection of integrins to the actin cytoskeleton (Giannone et al., 2003; del Rio et al., 2009; Margadant et al., 2011). Cardiac myocyte-specific excision of the vinculin gene reveals an essential function for the structural integrity of the heart, where ICDs become disorganized and present with an altered distribution of the ICD proteins cadherins and connexin 43. Likely because of these defects, sudden death was found in about half of the transgenic mice, caused by ventricular tachycardia. The mice that survived developed dilated cardiomyopathy and died by 6 months of age (Zemljic-Harpf et al., 2007).

Mutations in the splice variant metavinculin, which includes an additional exon, have been identified in patients with dilated or hypertrophic cardiomyopathy, including deletions and missense mutations (Maeda et al., 1997; Olson et al., 2002; Vasile et al., 2006). A missense mutation in a vinculin-specific exon (L277M) was identified in a patient with hypertrophic cardiomyopathy, which led to a reduction in vinculin levels in ICDs (Vasile et al., 2006). Skeletal muscle problems were not reported for this patient, but the rarity of mutations in vinculin-specific exons, and the fact that the identified mutations are clustered in the metavinculin-specific exon, may be attributed to the fact that mutations in the ubiquitously expressed vinculin splice variant may lead to early lethality, as it occurs in mice (Xu et al., 1998).

5. Integrin signaling: Responses to mechanical stimuli

Integrins are important sensors of mechanical forces applied to cells (Geiger et al., 2009; Moore et al., 2010). For instance, the size of focal adhesions can be modulated by altering the stiffness of the ECM, actomyosin contractility, and by applying forces to specific integrin subunits (Giannone et al., 2003; Jiang et al., 2003; Moore et al., 2010). It is therefore significant that, in skeletal muscle, integrins are expressed specifically at costameres and MTJs, where mechanical stress generated by muscle contraction is transmitted through the plasma membrane to the ECM (Mayer, 2003). As we will see, integrins signaling is important for modultating hypertrophy in the heart in response to mechanical and soluble stimuli. Perhaps surprisingly, it is still unclear whether integrins are also important for regulating hypertrophy in skeletal muscle.

5.1 β1-integrin

No mutations in β1-integrin have been identified in patients, likely because compromised function would result in early lethality, as it occurs in the knockout mouse model (Fassler and Meyer, 1995; Schwander et al., 2003). However, mice with a heart-restricted ablation of β1-integrin present impaired contractility and develop ventricular fibrosis and cardiac hypertrophy in response to transverse aortic constriction (TAC, a procedure in which the lumen of the aorta is artificially restricted)(Shai et al., 2002). These data indicate that β1-integrins are essential for a normal response of cardiomyocytes to mechanical stress, and subsequent analysis identified several proteins associated with β1-integrin that mediate these effects.

5.2 Integrin-linked kinase (ILK)

ILK is closely associated to β1 and β3-integrins (Hannigan et al., 1996; Zervas et al., 2001; Wickstrom et al., 2010), and binds to several proteins that relay biochemical signals and

regulate actin dynamics, including paxillin, α-and β-parvins and PKB. Ablation of ILK in invertebrates leads to detachment of myofibres at the MTJ, a phenotype similar to that obtained following ablation of talin (Zervas et al., 2001; Brown et al., 2002). Thus, in invertebrates, talin and ILK share a common function in the connection of actin to integrins at the MTJ. In vertebrates, however, MTJ defects following ablation of ILK differ from those observed in talin 1- or talin 2-KO mice. MTJ defects in ILK-deficient muscle consisted in discontinuities in the basal lamina and a detachment of actin filaments at the MTJ was not reported (Wang et al., 2008). ILK was important to stabilize MTJs in response to exercise, a process that might involve the relay of biochemical signals in association with the insulin growth factor receptor 1 (IGF-R1), which forms a complex with β1-integrins and plays a role during muscle repair (Musaro et al., 2001). IGF-R1 signaling was impaired in ILK-deficient muscle (Wang et al., 2008). Normally, in response to exercise, the insulin growth factor receptor 1R (IGF-1R) activates PKB/Akt, which in turn activates the kinase mTOR that is involved in the generation of new myofibrils. This activation was impaired in ILK-deficient muscle. Interestingly, β1-integrin was associated with IGF-R1, and this association increased in response to IGF-1. The data suggest a model whereby β1-integrin forms a complex with IGF-R1 that controls activation of ILK, the PKB/Akt and mTOR pathways to regulate skeletal muscle regeneration in response to exercise (Wang et al., 2008).

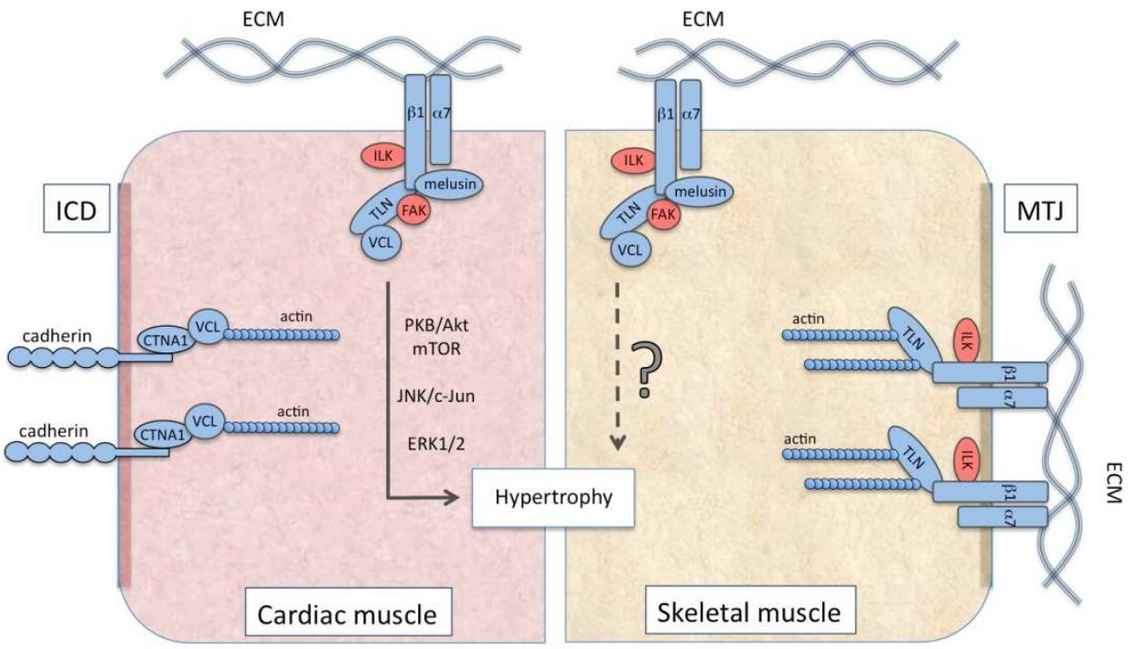


Fig. 2. **Integrin function in skeletal and cardiac muscle.** In skeletal muscle (right), integrins establish a connection between the ECM and actin filaments at the myotendinous junction (MTJ). In cardiac muscle (left), integrins activate hypetrophic signaling pathways, including PKB/AKT and mTOR, JNK/c-jun and ERK1/2, in response to mechanical and soluble stimuli. In addition, vinculin ablation leads to destabilization of intercalated disks (ICD). It is unclear at present whether integrins mediate hypertrophic responses in skeletal muscle. Abbreviations are: ECM = extracellular matrix; ILK = integrin-linked kinase; FAK = focal adhesion kinase; TLN = talin 1 or talin 2; VCL = vinculin; CTNA1 = α-catenin.

ILK is important for the sensing of mechanical stress in the heart. In the Zebrafish main squeeze (*msq*) mutant, isolated through a genetic screen, a missense mutation (L308P) was identified in the ILK gene (Bendig et al., 2006). Fish develop normally, but their hearts loose contractility, resulting in pericardial edema. The *msq* mutation disrupts the interaction with β-parvin, and morpholino-mediated knockdown of β-parvin phenocopies the ILK phenotype. These data suggests that the integrin-ILK-β-parvin complex is essential for transducing mechanical stimuli into signaling pathways important for cardiac contractility. In mice, conditional ablation of ILK in the heart causes dilated cardiomyopathy and sudden death in response to aortic pressure overload, with altered signaling from proteins involved in hypertrophy. A missense mutation in the ILK gene (A262V) has been identified in a patient affected by dilated cardiomyopathy (Knoll et al., 2007), and expression of ILK was elevated in patients affected by pathological cardiac hypertrophy, with a concomitant activation of signaling effectors associated with hypertrophic responses, including Rac, Cdc42, the ERK1/2 pathway and the kinase p70 S6 (Lu et al., 2006). It is at present unclear whether ILK plays any role in regulating hypertrophy in skeletal muscle.

5.3 Kindlin

Kindlin binds directly to β1-integrins and ILK. Three isoforms are expressed in vertebrates, named kindlin 1, 2 and 3. The main isoform expressed in skeletal and cardiac muscle is kindlin 2 (Ussar et al., 2006), which is localized at costameres and ICDs, again suggesting that it may play a structural role in areas of elevated mechanical stress (Dowling et al., 2008a). Mutations in kindlin 1 and 3 have been identified in patients affected by skin and immune disorders, respectively (Jobard et al., 2003; Siegel et al., 2003; Malinin et al., 2009; Svensson et al., 2009), but no mutations in kindlin 2 have been found in humans. *In vitro* studies have shown that kindlin 2 is important for differentiation of myoblasts (Dowling et al., 2008b), and knockdown of kindlin 2 in *Zebrafish* caused defective development of several organs, including skeletal and cardiac muscle, with disruption of ICDs and failure in the attachment of myofibrils to the membrane (Dowling et al., 2008a). Thus, kindlin 2 may be a good candidate gene for screening in patients affected by dilated cardiomyopathy or congenital myopathies.

5.4 FAK

Focal adhesion kinase (FAK) is closely associated with integrins, and following integrin engagement with ECM ligands, it becomes phosphorylated at tyrosine 397 (Y397). This creates a binding site for the SH2 domain of Src family kinases, and leads to the activation of several signaling effectors, including Rho and Rac, PI3K, Akt and the ERK1/2 signaling pathway (Franchini et al., 2009).

The tyrosine phosphorylation of FAK is rapidly increased following pressure overload in the rat heart (Franchini et al., 2000), and FAK activates hypertrophic signaling through PKB/AKT, the ERK1/2 and the JNK/c-JUN pathways. Additionally, FAK signaling regulates expression of the MEF2 transcription factors, which regulate the expression of several sarcomeric proteins (Nadruz et al., 2005). Insights on the function of FAK in striated muscle were obtained by generating mice with a conditional FAK ablation in cardiomyocytes. These mice developed defects that included thinner ventricular walls, ventricular septal defects and reduced cell numbers (DiMichele et al., 2006; Hakim et al.,

2007; Peng et al., 2008). However, the function of FAK in the postnatal heart is still unclear, as studies provide contrasting data on its function in cardiac hypertrophy, reporting either an increase in hypertrophy following mechanical or chemical stimuli (Peng et al., 2008), or an impaired hypertrophic response, with reduced expression of ANF and ERK1/2 (Hakim et al., 2007). The reason for the discrepancy is unclear, but it might be due to differences in the timing of FAK deletion, in the extent of aortic constriction, or in the genetic background of the mice.

The conditional inactivation of FAK in skeletal muscle has not been reported. In myoblasts, the application of mechanical forces to integrins results in FAK phosphorylation, and induction of hypertrophy in skeletal muscle leads to increased FAK expression and activation. Conversely, unloading of skeletal muscle leads to a sharp decrease in FAK activation (Fluck et al., 1999; Carson and Wei, 2000; Laser et al., 2000; Taylor et al., 2000; Gordon et al., 2001; Kovacic-Milivojevic et al., 2001). The inactivation of FAK in skeletal muscle would address its function and clarify whether its activity enhances or inhibits muscle hypertrophy.

5.5 Melusin

Melusin binds directly to β1-integrins and is expressed in skeletal and cardiac muscle, where it colocalises at costameres with integrins and vinculin (Brancaccio et al., 2003). Its domain structure includes in the N-terminus repeats of CHORD domain, which bind Zn2+, and in the C-terminus the integrin binding site and an acidic region resembling domains in calreticulin and calsequestrin that bind to calcium. In addition, while melusin is not endowed with catalytic activity, it includes binding sites for SH2- and SH3-domain proteins. The *itgb1 bp2* gene, encoding melusin, was inactivated in mice (Brancaccio et al., 2003). The mutant mice developed normally and were fertile. The basal structure and function of the heart were normal. However, when subjected to pressure overload via TAC, melusin-null mice presented with an impaired hypertrophic response, characterized by a reduction in myocyte cross-sectional area, ventricular wall thickness and induction of hypertrophic markers such as atrial neuretic factor and β-MHC. These changes led to an enlarged left ventricular chamber, a decrease in contractile function and eventually cardiac arrest, and may involve signaling through GSK3β and Akt, as phosphorylation in these proteins was reduced. Interestingly, unlike what is observed in FAK-deficient mice, infusion with angiotensin II or phenylephrine did not cause an aberrant hypertrophic response in melusin-null mice, indicating that melusin is required to specifically sense mechanical but not biohemical stimuli (Brancaccio et al., 2006; 2003). No overt defects in skeletal muscle were observed in melusing-knockout mice.

6. Conclusions and future perspectives

In recent years integrins have emerged as key players in skeletal muscle, both during development, where they are essential for somitogenesis, myoblast fusion and assembly of the sarcomere, and in the adult, where they play important structural roles, in particular in conferring mechanical integrity to the MTJ of skeletal muscle, and to ICDs in cardiac muscle in the heart. Key questions remain to be addressed. For instance, how do the functions of integrins differ from those of the DPC? While both protein complexes create a link between

the ECM and the actin cytoskeleton, the assortment of proteins that are associated with each complex differs, and it is likely that specific signaling pathways elicit different biochemical responses. Studies in the heart indicate that integrins translate mechanical stimuli into hypertrophic responses. Are they important for regulating hypertrophy in skeletal muscle? It is also unclear how integrins regulate the process of myoblast fusion, for instance whether defects in the function of integrins lead to altered actin organization at sites of cell-cell fusion. Are signaling cascades activated by integrins important for the activation or recruitment of other effectors that mediate the breakdown of plasma membrane occurring during cell-cell fusion? Few patients affected by congenital myopathy have been identified with mutations in an integrin (α7). It is unclear still how defects in integrin function lead to the observed muscle defects, as, unlike for the DPC, breakdown of the sarcolemma is not usually apparent. This may be elucidated with the identification of additional patients, and by an in-depth analysis of α7-KO mice. Also, do mutations in other integrins or associated proteins underlie genetically undiagnosed cases of muscular dystrophy or congenital myopathy? Talin, kindlin and vinculin are good candidate genes, as genetic studies in animal models showed essential roles for these proteins in conferring structural integrity to skeletal or cardiac muscle.

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