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The Importance of Extracellular Matrix in Skeletal Muscle Development and Function

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<http://dx.doi.org/10.5772/62230>

Abstract

Skeletal muscle tissue makes up approximately 40% of the total body mass in adult mammals. Contractile muscle fibers building skeletal muscle tissue are coated by an extracellular matrix material (ECM), accounting for 1–10% of the muscle mass. The ECM in skeletal muscle was initially considered as a structure, providing mechanical support for bearing force transmission. Now it is evident that muscle cells adhere to and connect with the ECM, also for signaling, and the ECM provides an appropriate and permissive environment for muscle development and functioning. This chapter summarizes current knowledge on the role of ECM components in skeletal muscle growth and regeneration, which is of great importance for potential therapeutic interventions. It also focuses on the contribution of ECM in the motor function of skeletal muscle as well as on mechanisms mediating muscle ECM remodeling during adaptation to physical activity. The role of the ECM in the metabolic function of skeletal muscle tissue and the ECM disturbances associated with insulin resistance are described. Finally, the attention is paid on potential implications of changes in skeletal muscle ECM assembly and function in health and disease.

Keywords: myogenesis, satellite cell niche, exercise, insulin signaling, myopathies

1. Introduction

Skeletal muscle tissue, making up approximately 40% of the total body mass in adult mammals, is composed of multinucleated contractile muscle cells, myofibers. Intramuscular connective tissue accounts for 1–10% of the skeletal muscle mass and varies substantially between muscles [1]. Muscle fibers are coated by an extracellular matrix material (ECM), called the basement membrane, and composed of two layers: an internal, basal lamina, directly linked to

the plasma membrane of myofibers (sarcolemma), and an external, reticular lamina. Extracellular matrix surrounding muscle fibers is composed of collagens (dominated by collagen IV), laminins, fibronectin, and proteoglycans, formed by glycosaminoglycans bound to a protein core. Initially, it was considered as a structure that provides mechanical support for bearing force transmission [2]. The ECM gives mechanical structure to myofibers during contractions, provides the tissue with elastic properties, and participates in the transmission of force from the myofiber to tendon. It also serves as a basic mechanical support for nerves and vessels present in skeletal muscle tissue, and determines the spatial barrier between endothelium and muscle cell surface. A great progress in cell biology, molecular biology and genetics, gives new insight into skeletal muscle biology, and now it becomes evident that cells adhere to and connect with the ECM not only for structural stability but also for signaling. The integrins, heterodimeric transmembrane receptors comprising unrelated alpha and beta subunits, play critical roles in converting extracellular signals to intracellular responses (outside-in signaling) as well as in extracellular matrix interactions based upon intracellular changes (inside-out signaling) [3]. They bind to ECM or cell surface ligands and link the actin microfilament system with ECM, providing a connection between the ECM, the cytoskeleton, and signaling molecules. Integrins are considered as sensors of tensile strain at the cell surface, and together with the cytoskeleton form a mechanically sensitive organelle. Despite the large overall number of integrin receptor complexes, skeletal muscle integrin receptors are limited to seven alpha subunits, all associated with the beta1 integrin subunit. Integrin signal transmission depends on the activation of focal adhesion kinase (FAK), a nonreceptor tyrosine kinase, localized at focal adhesions. Integrin engagement causes the formation of transient signaling complex, initiated by the recruitment of Src-family protein SH2 to the FAK Tyr-397 autophosphorylation site, and by serving as a signaling element in cytoskeleton-associated networks [4]. Integrin-linked kinase (ILK), initially considered as a kinase, but, in fact, incapable to perform phosphorylation due to pseudoactive domain, mediates interactions of integrins with numerous cellular proteins and regulates focal adhesion assembly, cytoskeleton organization, and signaling [5]. The major enzymes responsible for the ECM breakdown under physiological conditions are matrix metalloproteinases (MMPs, or matrixins), which belong to a family of zinc-dependent and calcium-activated neutral endopeptidases, comprising secreted and membrane-associated members. MMPs are involved in degradation of the ECM and basement membrane; however, they also cleave a variety of other ECM-related proteins, including cytokines, chemokines, and growth factors [6]. There is some specificity of certain MMPs toward collagen types, that is, MMP-2 and 9 (gelatinases) primarily degrade type IV collagen and other compounds of the ECM in muscle, whereas MMP-1 and 8 (collagenases) traditionally are thought to break down types I and III collagen, being more relevant for tendon. MMP activities are regulated by tissue inhibitors of matrix metalloproteinases (TIMPs). Four TIMPs, responsible for the inhibition of over 20 MMPs, are identified; of these, TIMP-1 and TIMP-2 are capable of inhibiting, of all MMPs, preferably MMP-2 and 9, respectively [1]. In addition to MMP-dependent mechanisms, TIMPs can alter cell growth and survival in an MMP-independent manner, mediated by integrins. A good example is TIMP-2, which regulates beta1 integrin expression and the size of myotubes formed during myoblast differentiation [7]. MMPs play an important role in skeletal muscle cell growth and differentiation, as they are engaged in release and activation of cytokines and growth

factors. The main contributors to ECM assembly in skeletal muscle are resident fibroblasts; however, muscle cells also synthesize and secrete numerous ECM components and ECM-related molecules, suggesting their active and direct participation in ECM remodeling. Thus, the composition of the ECM exerts mechanical, metabolic, hemodynamic, and angiogenic effects in skeletal muscle tissue. The extracellular matrix and its receptors also provide an appropriate and permissive environment for muscle development and some ECM components, in addition to muscle-specific factors, can serve as good indicators of skeletal muscle functioning. This chapter summarizes current knowledge on the role of ECM components related to skeletal muscle development and regeneration, which is of great importance for potential therapeutic interventions. It also focuses on the contribution of ECM in motor and metabolic functions of skeletal muscle tissue. Finally, the attention is paid on potential implications of changes in ECM assembly and function in health and disease.

2. Extracellular matrix in regulation of muscle stem cell niche

Fetal stage is crucial for skeletal muscle development, when muscle fibers are formed by fusion of mesodermal progenitor cells, myoblasts. During postnatal period, the number of myofibers remains constant; however, the size of each myofiber can increase by fusion with muscle stem cells, called satellite cells. Skeletal muscle is one of the most adaptive tissues in the body, and the adult regenerative myogenesis after muscle injury depends on satellite cells. These cells are normally quiescent, but in response to overloading or muscle damage, they become activated; that is, they begin to proliferate, and their progeny myoblasts terminally differentiate and fuse with one another or with existing myofibers to restore the contractile muscle apparatus and normal tissue architecture [8].

Proper muscle regeneration depends on the cross-talk between the satellite cells and their microenvironment (cell niche). According to the stem cell niche concept, the structural and biochemical stimuli emanating from surrounding environment determine the fate of stem cells present in tissues. Muscle satellite cells exist in highly specific niches, consisting of the basement membrane of myofibers, different types of resident cells (i.e., fibroblasts, adipocytes, etc.), vascular and neural systems, and extracellular matrix [9]. Each of these niche elements exerts profound effects on satellite cell functioning. Satellite cells reside between the basal lamina and the apical sarcolemma of myofibers, covered in laminin. They bind to collagen type IV and laminin through integrins, which also connect with collagen type VI and several proteoglycans, that is, perlecan and decorin. The ECM protein, nidogen (or entactin), supports cross-links between laminin and collagens. Basal lamina directly contacts satellite cells and separates them from muscle interstitium. It also acts as a mechanical barrier to prevent migration of satellite cells and their loss from normal muscle, and could be involved in repressing satellite cell mitosis and differentiation in the absence of muscle injury [2]. On the other site of the satellite cell niche, the myofiber sarcolemma links to the basal lamina, more particularly to laminin, through the dystroglycan complex [10]. Myofibers influence satellite cell behavior as a result of the physical interactions and by the secretion of paracrine factors. Nerves and associated neuromuscular apparatus exert their effects through the control of

myofiber activity. Fibroblasts primarily contribute to matrix formation and, as adipocytes, secrete paracrine factors. Circulating blood transports hormones and other systemic factors; endothelial cells lining blood vessels serve as a source of growth factors, whereas immune cells, infiltrating muscle tissue upon injury, transiently affect satellite cells through the secretion of cytokines [11].

An important function of muscle progenitor cell niche is maintaining the balance between quiescence and activation. The quiescent satellite cells sense the stiffness of their niche through integrins and express various matrix proteins to maintain the stable ECM structure. Within the ECM, growth factors and other bioactive molecules are sequestered, supporting the “quiet” state [10]. Communication between the ECM and satellite cells is essential in the regulation of cellular events crucial for muscle growth and repair, such as gene expression, cell proliferation, adhesion, and differentiation of activated satellite cells. In response to muscle injury, components of the basal lamina are degraded by matrix metalloproteinases, and growth factors and signaling molecules are liberated, which is essential for regulation of processes ongoing in activated satellite cells. Presence of the ECM is required for muscle stem cells to respond to growth factors [12]. Proteoglycans expressed on the surface of satellite cells function as low-affinity receptors and bind to the secreted, inactive growth factor precursors, including hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), insulin-like growth factor isoforms (IGF-1, IGF-2), originating from myofibers, satellite cells, muscle-residing cells, or serum. All these growth factors play crucial roles in myogenesis, and *in vivo* exist in matrix-associated form. Some ECM molecules, that is, decorin [13], fibronectin [14], and laminin [15], can bind to and suppress the activity of myostatin, a negative regulator of muscle cell proliferation and differentiation. Through interactions with these growth factors, the extracellular matrix regulates the ability of skeletal muscle satellite cells to proliferate or differentiate. Differences in the expression of proteoglycans alter satellite cell responsiveness to the growth factor, that is, overexpression of glypican-1 (heparin sulfate proteoglycan) in satellite cells increases their responsiveness to FGF-2, whereas underexpression diminishes cell proliferation and differentiation [12]. Taken together, the major components of basal lamina orchestrate muscle satellite cell development by presentation of mitogenic and myogenic factors. Muscle cells play an active role in creating their own microenvironment via ECM remodeling. Supporting this idea, numerous studies prove changes in expression and/or secretion of proteoglycans, metalloproteinases, adhesion molecules, and growth factors in regenerating muscle tissue and differentiating myoblasts [8, 16–18]. Activated satellite cells dynamically remodel their niche via transient high expression of fibronectin, and knockdown of this protein expression in satellite cells markedly impaired the ability to repopulate the niche [19].

When satellite cells move to the injured site, the surrounding ECM should be degraded for allowing cell migration. Matrix metalloproteinases degrade extracellular matrix components such as collagens, elastin, fibronectin, laminin, and proteoglycans. MMPs play an important role in creating cell niche in regenerating muscle and are essential for satellite cell activation, migration, and differentiation. Expression of matrix metalloproteases is up-regulated upon satellite cell activation, whereas transcripts for proteinase inhibitors are high in quiescent cells

[20]. Migration of satellite cells underneath the basement membrane requires the expression of MMP-2, 3, 7, 9, and 10. The specific inhibition of these MMPs decreases the migration velocity and increases the sustainability of moving direction of myoblasts *in vitro* [21]. Among the MMPs expressed in skeletal muscle, MMP-2 and 9 appear particularly critical. MMP-2 is secreted by satellite cells and regenerating myofibers, whereas MMP-9 is expressed by leukocytes and macrophages. Upon injury, the release of the nitric oxide synthase (NOS) from damaged basal lamina leads to nitric oxide (NO) production, which in turn up-regulates protein level and activity of MMP-2 and 9. Activated proteases degrade collagen IV, facilitating satellite cell migration across the basement membrane to injured regions [22]. The most important details concerning the ECM structure and cues emanating from cellular elements of muscle satellite cell niche are summarized in **Figure 1**.

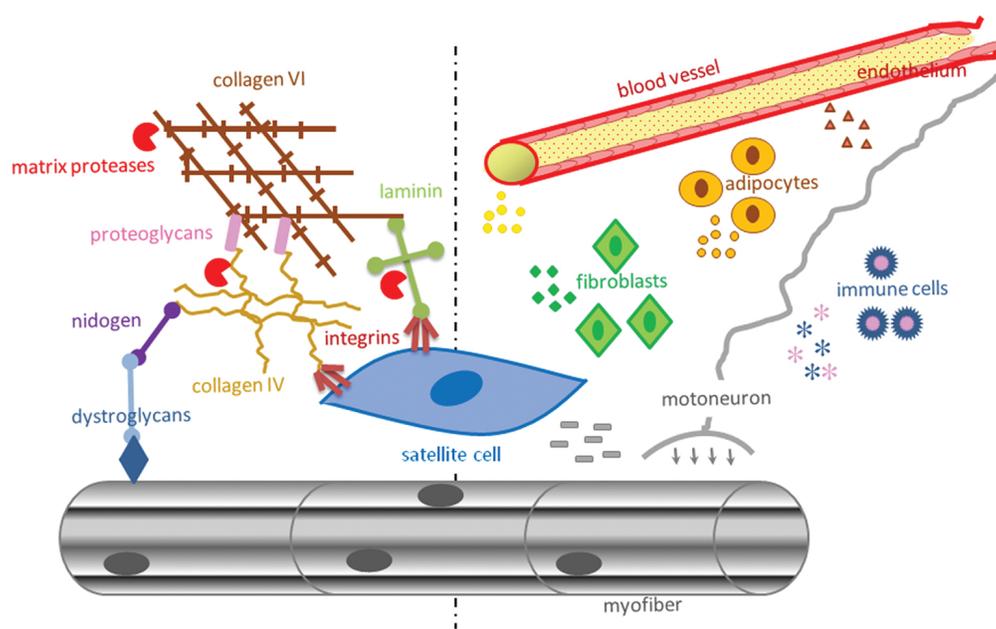


Figure 1. Schematic representation of the complex microenvironment (niche) of satellite cells in skeletal muscle. Left part illustrates the networks and cross-linkings of major ECM proteins in the immediate environment of muscle satellite cells. Right part presents contributions of cellular components in creating the satellite cell niche. The small symbols represent humoral factors released by different types of cells (the colors used correspond with the source of appropriate bioactive factors).

The role of specific niche for muscle stem cell's self-renewal and differentiation is supported by observations, that after removal from the microenvironment, the satellite cells quickly withdraw from quiescence, begin to proliferate, and lose their myogenic properties. On the other hand, myogenic cells cultured on the ECM extracted from large thigh adult muscles manifest enhanced proliferation and differentiation in comparison to standard growth surfaces [23]. In order to study the role of specific ECM components in creating the niche of muscle stem cells, *in vitro* cell culture models are employed, where the environmental conditions can be easily controlled. In such experiments, primary muscle stem cells derived from muscle tissue are cultured *in vitro* on surfaces coated with the ECM components (i.e. collagen, laminin, fibronectin, gelatin, or Matrigel—a balanced mixture of different ECM

proteins) to mimic the muscle extracellular environment. Usually, the primary muscle stem cells show distinct proliferation and differentiation pattern, as well as different muscle-specific and ECM-related gene expressions, dependent on the coating type used [9]. These experiments reveal that the loss of mitogenic and/or myogenic potential of muscle stem cells, due to their transfer from the specific niche to an *ex vivo* situation, could be reduced by using some ECM components/mixture coating. For example, fibronectin and laminin could be used for sorting myoblasts from fibroblasts. Such observations are of great interest and importance in tissue engineering and stem cell therapies.

3. Changes in ECM assembly and function during myogenesis

Skeletal muscle growth and development is a complex process controlled by interactions between muscle cells and surrounding microenvironment. Several cellular events take place during skeletal myogenesis, that is, migration of muscle precursor cells, proliferation of myoblasts, cell cycle arrest, and myoblast terminal differentiation, followed by transcription of muscle-specific genes and myoblast fusion. Muscle cell differentiation is governed by an ordered sequence of the expression of muscle regulatory factors (MRFs) such as MyoD (Myoblast determination protein), Myf-5 (Myogenic factor-5), myogenin, and MRF-4 [24]. The commitment of muscle precursor cells requires MyoD expression, whereas the proliferation arrest and terminal myoblast differentiation are driven by myogenin, a key transcription factor, which activates skeletal muscle-specific genes encoding creatine kinase, myosin heavy chain, and acetylcholine receptor. The formation of myotubes expressing muscle-specific genes is essential for the specialization of myofiber function.

The importance of extracellular matrix molecules as a part of myogenesis signaling mechanism has also been demonstrated. An inhibition of cell-surface transmembrane proteoglycan sulfation results in delayed proliferation and altered MyoD expression, indicating that heparan sulfate is required for proper progression of the early myogenic program [25]. Neither the expression of myogenin nor its localization to myoblast nuclei was sufficient to drive skeletal muscle differentiation, if the cell-ECM interactions were inhibited [26]. Inhibition of proteoglycan sulfation in myoblast cultures strongly affects ECM synthesis and deposition, and induces the expression of the osteogenic markers (alkaline phosphatase and osteocalcin), without alterations in expression of specific muscle transcription factors, such as MyoD and Myf-5 [27]. The above observations support the idea that extracellular matrix provides stimuli for muscle cell development, which are independent of muscle-specific factor expression.

Myogenesis is accompanied by remodeling of ECM proteins as well as by changes in integrin receptor expression pattern [28]. Fibronectin and laminins display an opposite pattern of changes in time during myogenesis, that is, myoblasts secrete a large amount of fibronectin, which is replaced by laminins in myotubes. As a consequence, the location of these proteins in muscle is different, that is, fibronectin is absent in regions manifesting active myogenesis, whereas laminin adjoins myotubes. In myoblasts subjected to differentiation *in vitro*, fibronectin is detected primarily in the extracellular environment as a thick mesh. At the same time, laminin appears ultimately in the cytosolic fraction, which confirms delayed synthesis of this

protein during myogenesis, in comparison to fibronectin [29]. During myogenic differentiation, the laminin synthesis increases, and laminin begins to accumulate in the medium in soluble form, followed by the formation of insoluble cell-associated fraction [30]. Both fibronectin and laminin per se can affect myogenesis. Fibronectin promotes myoblast adhesion and proliferation; however, it inhibits differentiation and participates in collagen fibrillogenesis, thus providing the ECM assembly [1]. Fibronectin also stimulates adhesion of fibroblasts and may facilitate dedifferentiation of myoblasts. This protein is required for somitogenesis, and it may function to regulate fiber organization and limit fast-twitch muscle fiber length [31]. Laminin is crucial for several processes involved in myogenesis, as it enhances myoblast proliferation, migration, and alignment preceding the fusion. Myotube formation is markedly impaired in the absence of laminin [2]. Changes in integrin receptor expression pattern reflect the ECM remodeling during myogenesis. Proliferating and migrating myoblasts express high amounts of the fibronectin-binding $\alpha 5 \beta 1$ integrin, while during myotube formation they switch to the laminin-binding $\alpha 7 \beta 1$ integrin, which is the major integrin receptor in adult muscles [32]. Moreover, there is a negative cooperativity between $\alpha 7$ and $\alpha 5$ integrin subunits. Transfection with integrin $\alpha 7$ resulted in the marked reduction of $\alpha 5 \beta 1$ surface complex expression and its decreased affinity to fibronectin in myoblasts. Such a relationship may play an important role in determining functional regulation of integrins during myogenesis. A critical phase of myogenesis is the fusion of mononucleated myoblasts and the formation of long multinucleated myotubes. Myoblast fusion and myotube formation are associated with increased expression of integrin $\alpha 3$, particularly abundant in myotube membrane [29]. Overexpression of the full-length integrin $\alpha 3$ subunit induces myoblast fusion, whereas the inhibition of integrin $\alpha 3$ extracellular domain impairs this process [33]. Myogenesis is largely normal in the absence of $\alpha 4$, $\alpha 5$, $\alpha 6$, and $\alpha 7$ integrin subunits, indicating the redundancy in integrin functions. In contrast, disruption of the integrin $\beta 1$ in vivo and in vitro profoundly influences myogenesis. Lack of integrin $\beta 1$ had no apparent effect on the migration and proliferation of myoblasts; however, clear alterations occur at the later stages of myogenesis and are manifested by impaired fusion [34]. According to an early study, muscle-specific integrin $\beta 1$, appearing in a doublet form, was used as a marker of differentiation [35]. Integrin $\beta 1$ subunit is also involved in muscle cell survival. In response to the activation of integrin $\beta 1$, focal adhesion kinase phosphorylates tyrosine at residue 397, leading to the activation of cell survival signal transduction and inhibition of apoptosis [36]. Moreover, FAK appears as a mediator by which integrins may regulate myoblast fusion. Specific disruption of gene encoding FAK suppresses the transcription of caveolin 3 and integrin subunit $\beta 1 D$ isoform, both considered as essential for morphological muscle differentiation. As a consequence, the cell fusion and myotube formation are defective, while the expression of muscle terminal differentiation genes, such as sarcomeric α -actin, α -actinin, and vinculin, remain unaltered [37]. It suggests a specific role of FAK in the regulation of cell fusion, as a part of the myogenic differentiation program.

A characteristic feature of proliferating and quiescent undifferentiated myoblasts is the high expression of a disintegrin and metalloprotease, ADAM12, which combines features of adhesion molecules and proteinases [38]. ADAM12 cleaves insulin-like growth factor binding proteins IGFBP3 and IGFBP5, and heparin binding-EGF. The cysteine-rich domain of

ADAM12 supports cell adhesion by binding to syndecan-4, whereas the cytoplasmic domain interacts with signaling proteins, that is, tyrosine kinase Src phosphatidylinositol-3-kinase, and cytoskeletal alpha-actinin 1 and 2 [38]. ADAM12 is transiently upregulated at the onset of differentiation, whereas other ADAMs, such as ADAM9, 10, 15, 17, and 19 are expressed at all stages of myogenesis [35]. Inhibition of ADAM12 by siRNA approach in myogenic cell cultures was accompanied by lower expression of both quiescent markers (p130 and p27 proteins) and differentiation markers (cell cycle inhibitor p21 and myogenin). Overexpression of ADAM12 induces a quiescent-like phenotype and does not stimulate differentiation. Possible role of ADAM12 in myogenesis is associated with the preservation of “reserve pool” of myoblasts, which do not trigger the myogenic differentiation program and maintain regeneration potential. A 100 kDa long isoform of ADAM12 is increased in myoblasts differentiating for 3 days in the presence of IL-1beta [39] and IGF-I [29], suggesting similar effects of proinflammatory cytokines and anabolic growth factors on ECM regulation at early stages of myogenesis. On the other hand, there are studies that implicate the involvement of ADAM12 in the fusion of muscle cells. The expression of ADAM12 and integrin alpha9 subunit parallels and culminates at the time of myoblast fusion, and inhibition of ADAM12/alpha9beta1 integrin interaction dramatically impairs this process [40]. ADAM12 is linked to the cytoskeleton via alpha-actinin [35], and thus the cytoskeleton may regulate the distribution of ADAM12 on the cell surface, where localized proteolysis and/or cell–cell contacts occur [41]. The most important modifications of the ECM structure and function associated with skeletal myogenesis are depicted in **Figure 2**.

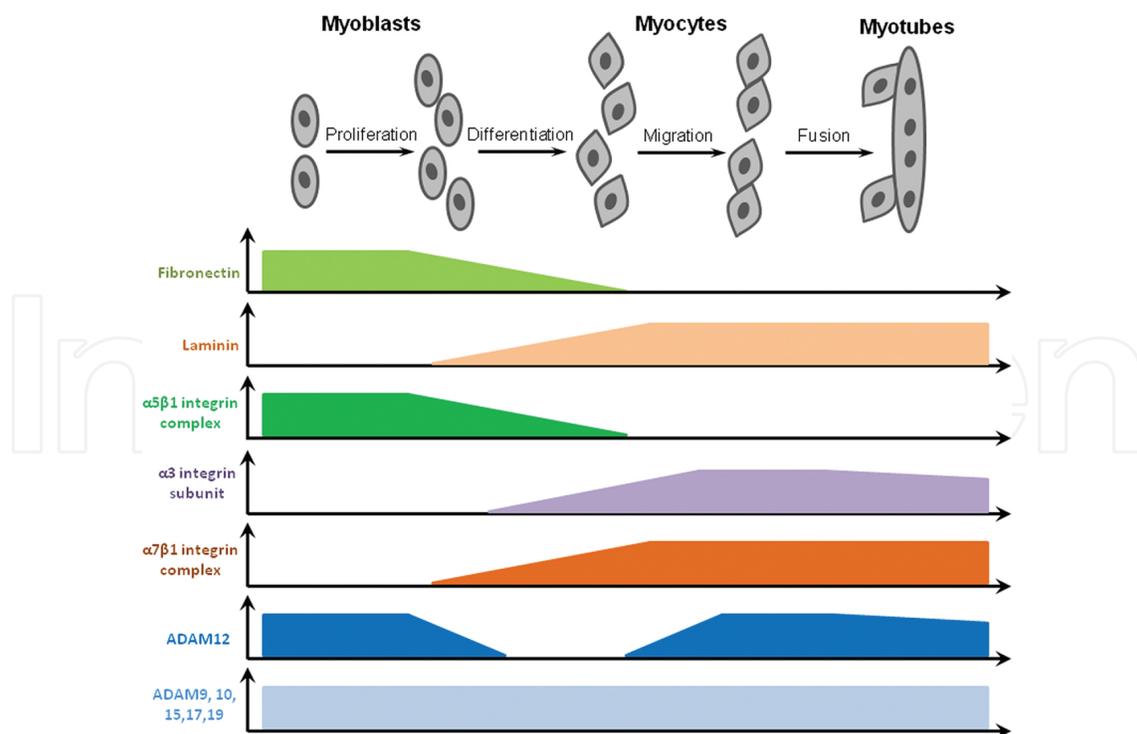


Figure 2. Schematic illustration of ECM remodeling and ECM-related proteins level/activity during skeletal myogenesis. The most important events during myogenic development are presented in the upper panel.

4. ECM and the motor function of skeletal muscle

Skeletal muscle provides structural support, enables the body to maintain posture, and controls motor movements. Muscle tissue is strong, flexible, stress-resistant, and in view of its mechanical properties, it consists of contractile elements (i.e. sarcomeres) and elastic components, supported by extracellular matrix. Majority of ECM elements, which account for muscle strength and elasticity, reside in the basement membrane, especially in basal lamina. The basic structure of basal lamina consists of different networks of triple-helical collagen IV, composed of alpha chains, and the major noncollagenous protein, laminin, which is a heterodimer of alpha, beta and gamma chains. The collagen network contains covalent cross-links; moreover, distinct networks are linked by another noncollagenous protein, nidogen (entactin). These major elements display several further functions: (i) they possess multiple sites binding other protein of basal lamina, (ii) they anchor components of reticular lamina to basal lamina, and (iii) they serve as ligands for membrane-associated receptors (i.e., integrins, dystroglycans, etc.), which interact with cytoskeleton [2]. Taken together, in the context of the mechanical function of skeletal muscle, the extracellular matrix may be considered as a series of networks that connect reticular lamina, basal lamina, sarcolemma, and cytoskeletal structure.

Overload of healthy skeletal muscle leads to myofiber hypertrophy and ECM remodeling, the processes that are thought to contribute to muscle growth. Several ECM components are controlled by the level of mechanical loading, and multiple intracellular proteins involved in mechanotransduction signaling are suggested, including focal adhesion kinase (FAK), paxillin, integrin-linked kinase (ILK), and mitogen-activated protein kinase (MAPK) [1]. The latter is crucial for the conversion of mechanical load to tissue adaptation, transmitting signaling from the cytosol to the nucleus. Laminin, integrin alpha7, and integrin-linked kinase (ILK) are all critical for mechanical stability of skeletal muscle [42]. ILK is recruited to the myotendinous junction, which requires the presence of laminin in the ECM and integrin alpha7 in sarcolemma. Moreover, ILK is essential for strengthening the adhesion of the muscle fibers with the ECM and acts with the dystrophin/dystroglycan adhesion complex in maintaining mechanical stability of skeletal muscles.

Endurance and resistance exercises accelerate the turnover of ECM components in skeletal muscle. Several studies reveal an increase in collagen synthesis and accumulation induced by exercise (summarized in [43]). Transcription of genes encoding types I, III, and IV collagen increases after endurance training. In another study, endurance exercise augments concentration of type IV collagen in slow (soleus), but not in fast (rectus femoris) muscle. Matrix metalloproteinases are activated in human skeletal muscle in response to voluntary exercise, and the expression and time pattern indicate differences between the MMPs in regards of production sites as well as in the regulating mechanism. TIMPs are often activated together with MMPs in response to physical activity, indicating the simultaneous stimulation and inhibition of the ECM degradation. Probably, MMPs' activation precede TIMPs' activation, and the latter serve as "guardians" of degradation termination, providing limits in the ECM breakdown [1]. Levels of MMP-2, 14, and TIMP-1 mRNA in muscle tissue increase after 10

days of training. MMP-2 and 9 proteins were both present in the ECM, around myofibers and capillaries, but MMP-2 was also visible within the skeletal muscle fibers [44].

Mechanical loading induces the secretion of TGF-beta, PDGF, and bFGF in tendon fibroblasts; moreover, it increases the expression of collagen and other ECM components, such as proteoglycans. TGF-beta stimulates collagen formation and reduces its degradation, also via activation of the TIMPs, together with a suppression of MMPs, leading to the ECM accumulation. TGF-beta is known to function as a modulator of ECM proteins and to induce both collagen gene activation and protein formation. In a human model of microdialysis of the Achilles tendon, both local and systemic levels of TGF-beta increase in response to 1 h of running, proving a release of this cytokine from tissues that are mechanically activated during exercise and suggesting a role in the response to mechanical loading in vivo [1]. Mechanical loading induces FGF release from skeletal muscle cells in vitro. Several isoforms of FGFs exist; of these, basic FGF (or FGF2) and, to a lesser extent, the acidic FGF (FGF1) stimulate fibroblast proliferation and collagen synthesis. Interleukin-6 (IL-6) is considered as a physical activity-associated myokine released from working muscles [45]. It can stimulate fibroblasts to increase the synthesis of collagens, glycosaminoglycans, hyaluronic acid, and chondroitin sulfates. Increased expression of IL-6 is necessary for the regulation of ECM remodeling during the hypertrophic response of skeletal muscle to overload [46]. Mechanical activity increases expression of IL-1beta in human and rabbit tendon cells, leading to increased MMPs activity, diminished collagen synthesis, and initiating tissue degradation and remodeling in response to loading. IGF-I is directly involved in skeletal muscle ECM synthesis after mechanical loading. This growth factor increases the expression of types I and III collagen in intramuscular fibroblasts. Bioavailability of IGF-I is controlled by IGF-binding proteins, and increased proteolysis of IGFBPs occurs in response to prolonged training in humans. Interestingly, MMPs can degrade IGFBPs, which provides a possible mechanism of regulation of the free IGF-I in skeletal muscle tissue and circulation.

The blood flow in skeletal muscle is tightly coupled with the metabolic demands of contracting myofibers. During exercise, local mechanisms cause rapid dilation of muscle arterioles to increase the flow of blood to the working muscle. It appears that fibronectin fibrils in the extracellular matrix transduce signals from actively shortening skeletal muscle fibers to local blood vessels to increase blood flow. Skeletal muscle contraction alters the conformation of ECM fibronectin, which results in transient exposure of specific matricryptic sites. These sequences are not exposed in the soluble form of ECM molecules, but may be expressed due to structural or conformational changes, providing "a reserve" of signaling sites activated during ECM remodeling. Matricryptic fibronectin sites (FNIII-1) interact with FNIII-1H receptors on smooth muscle cells and/or skeletal muscle fibers. This activates the neuronal nitrogen oxide (NO) synthase to release NO, which leads to smooth muscle relaxation, vasodilation, and increased blood flow. Thus, FNIII-1 sites in ECM fibronectin serve as important mechanical coupling between skeletal muscle contraction and arteriolar dilation [47]. **Figure 3** summarizes the cellular mechanisms activated during exercise leading to skeletal muscle ECM remodeling.

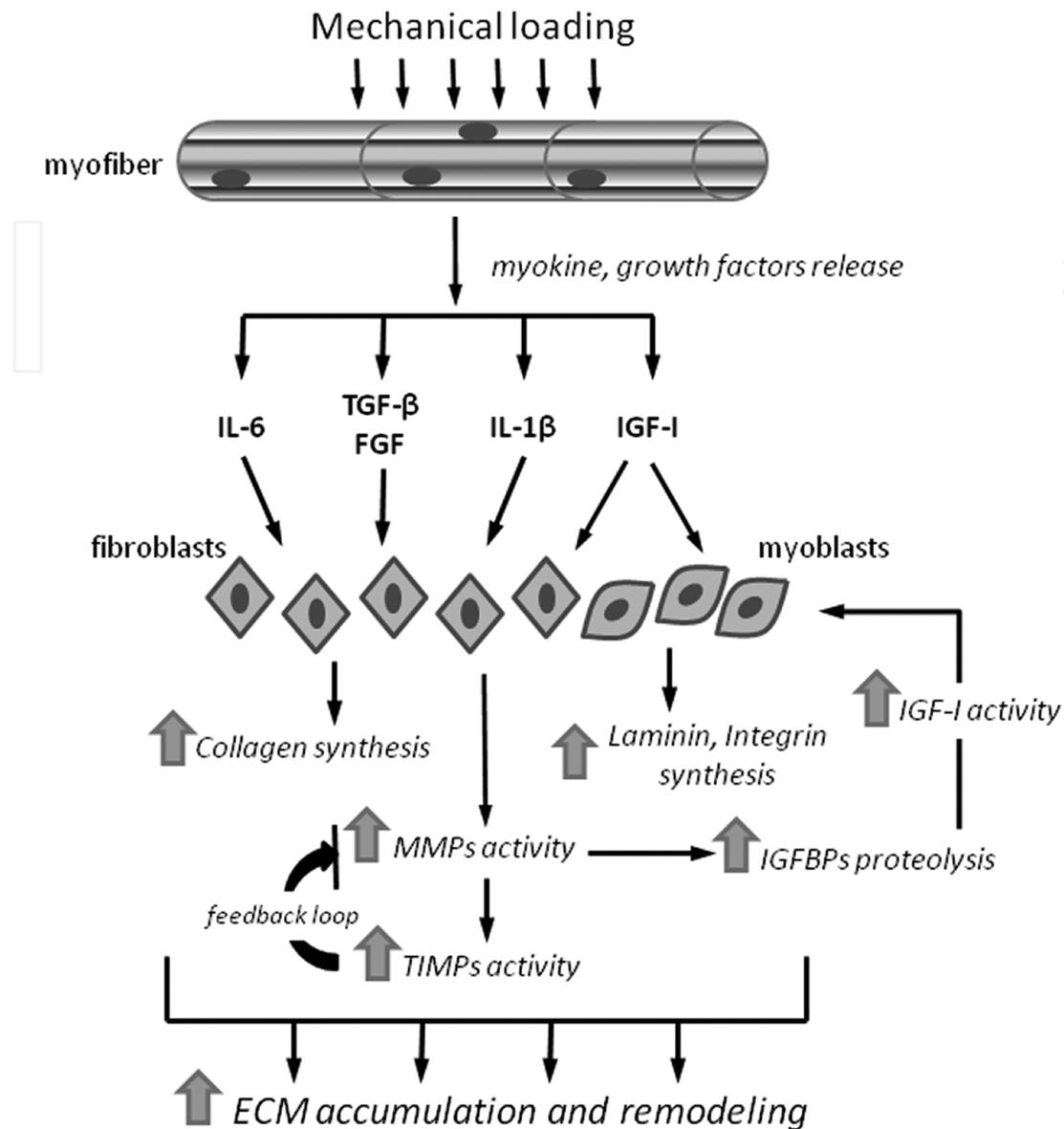


Figure 3. Proposed schema illustrating the mechanisms of alterations in the ECM in skeletal muscle induced by mechanical loading. → means activation/stimulation, ⊥ means inhibition. Gray block arrows indicate total stimulation of particular processes resulting from the regulation of upstream pathways.

5. ECM and the metabolic function of skeletal muscle

Skeletal muscle is a key insulin-sensitive tissue, important in maintaining homeostasis, due to its relatively large mass and energy needs [48,49]. Postprandial, insulin-stimulated glucose disposal in skeletal muscle results from the activation of a complex signaling network with multiple alternative and complementary pathways. Insulin binding to the insulin receptor causes tyrosine autophosphorylation of the receptor beta-subunit, activation of its intrinsic tyrosine kinase, and subsequent phosphorylation of several intracellular proteins, including insulin receptor substrate (IRS) proteins [50]. This leads to the recruitment of further signaling

components such as phosphatidylinositol-3 kinase (PI-3 kinase), the tyrosine phosphatase SHPTP2, the growth factor receptor-binding protein-2 (GRB-2), as well as protein serine/threonine kinases: phosphoinositide-dependent protein kinase (PDK1), protein kinase B (PKB), atypical isoforms of protein kinase C (PKC) lambda and zeta, mitogen-activated protein kinase (MAPK), and others, which support the signal divergency and function as messengers for various biological effects of insulin. Regarding postprandial glucose uptake in skeletal muscle, the activation of insulin signaling leads to the translocation of the insulin-responsive glucose transporter, Glut4, from intracellular storage sites to cell surface membrane, which is a critical step in cellular glucose utilization. Dysregulation of any step of this process in skeletal muscle results in insulin resistance, predisposing for diabetes.

There is an important cross-talk between extracellular matrix and insulin signaling in skeletal muscle. Integrin engagement stimulates both IRS-1-associated PI-3 kinase activity and PKB/Akt pathway. Integrin receptor beta1 subunit increases insulin-stimulated IRS phosphorylation, IRS-associated PI-3 kinase, and activation of PKB (summarized in [51]). Regulation of focal adhesion kinase (FAK) by integrin receptors modulates insulin-dependent cytoskeleton organization, glucose transport, and glycogen synthesis in myoblasts [4]. FAK can interact with IRS-1, PI-3 kinase, PKC, and glycogen synthase kinase-3beta, leading to translocation of Glut4. A decrease in tyrosine phosphorylation and activation of FAK was reported in skeletal muscle of insulin-resistant Sprague-Dowley rats fed with a high-fat diet, as well as in insulin-resistant C2C12 myoblasts [52]. The expression of IRS-1 mRNA is abolished in FAK knockout mouse fibroblasts. Apart from the regulation of skeletal muscle insulin signaling and action by FAK, the reciprocal interaction is documented. It appears that FAK tyrosine phosphorylation, essential for skeletal muscle differentiation, is modulated by insulin. Insulin causes an increase in FAK phosphorylation in proliferating myoblasts, while in differentiating cells, there is an inhibition of FAK phosphorylation [53]. Under insulin resistance, the phosphatase PTEN and SHIP2, usually recognized as negative regulators of insulin signaling, are up-regulated, and they impair insulin action through FAK dephosphorylation [54]. The integrin-linked kinase (ILK) can phosphorylate and activate PKB, and function as its potential upstream regulator. Integrin beta1 knockout mice manifest an impairment of insulin-stimulated skeletal muscle glucose uptake and glycogen synthesis in skeletal muscle, resulting from marked reduction in ILK expression and concomitant decrease in PKB phosphorylation.

Insulin resistance is tightly associated with the ECM remodeling in muscle, and the ECM defects predisposing to diabetes-related symptoms are known. The deposition of collagens, the most abundant structural ECM components, is increased in insulin-resistant muscles, both in humans and rodent experimental models [55]. Synthesis of fibronectin, laminin, and collagen IV is up-regulated by high glucose and diabetes [56], which may lead to basement membrane thickening and the development of diabetes-associated microangiopathy. Similarly, a high-fat diet causes an increase in collagen IV in skeletal muscle [57]. As MMPs are responsible for the degradation of all components of the ECM, their dysregulation is also implicated in the pathology of diabetes and obesity. MMP-9 activity in skeletal muscle is decreased in high fat-fed mice, and it is related inversely to muscle collagen deposition and

directly to muscle insulin resistance [58]. The genetic deletion of MMP-9 worsens diet-induced muscle insulin resistance, indicating that this metalloproteinase is necessary to protect against more serious metabolic disturbances associated with high fat feeding. Collagen V, widely expressed and a less abundant fibrillar protein, which regulates collagen fibril geometry and strength, is important for skeletal muscle glucose homeostasis. Mutant mice lacking *col5a3* gene manifest hyperglycemia, glucose intolerance, and insulin resistance [59]. Skeletal muscle of these mutants is defective in glucose uptake and mobilization of intracellular Glut4 glucose transporter to the plasma membrane in response to insulin.

High-ambient glucose markedly elevates the level of fibronectin in myogenic cells in vitro and causes a decrease in cellular content of the full length 100 kDa form of ADAM12, without affecting integrin alpha5 and integrin beta1 subunit expressions [60]. Such alterations could result in the disturbances in ECM remodeling and accumulation, which in turn contribute to the impairment of the myogenic differentiation, manifested by decrease in MyoD, myogenin,

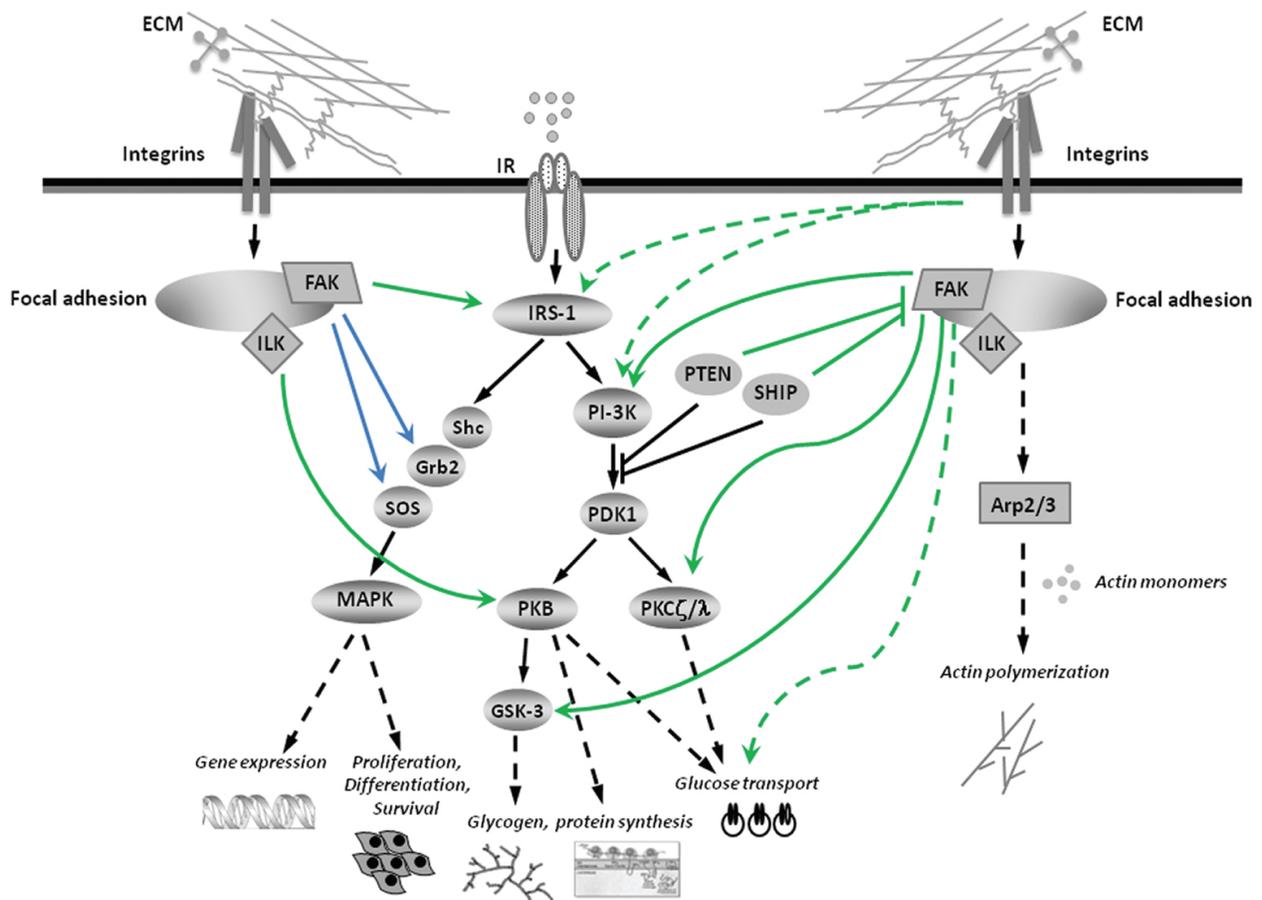


Figure 4. Proposed schema illustrating the cross-talk between insulin signaling and ECM signaling in skeletal muscle. To clarify the picture, both the insulin signaling pathway and ECM signaling are markedly simplified, as they present only the most important linkings and biological effects. Solid lines mean direct connections, dashed lines mean indirect effects. \rightarrow means activation/stimulation, \dashv means inhibition. Green lines indicate interactions between insulin- and integrin-activated pathways (direct or indirect) reported in skeletal muscle. Blue lines indicate interactions described in other cell types [61], and only potentially functioning in skeletal muscle tissue.

myosin heavy chain levels, and fusion index. In view of an important cross-talk between ECM and insulin signaling [4,51], the high-glucose-induced alterations in ECM can, at least partly, contribute to the attenuated insulin and growth factors' action in skeletal muscle under hyperglycemia and diabetes. The ECM turnover also plays a role in the metabolic regulation of skeletal muscle in the pathology of diet-induced insulin resistance. **Figure 4** illustrates the most important points of the cross-talk between insulin signaling and the ECM-related signaling cascades in skeletal muscle.

6. Alterations of muscle ECM components in health and disease

Skeletal muscles have a great ability to adapt and regenerate, and usually injured areas of muscle tissue are replaced with healthy contractile fibers, which results in a full recovery and mechanical function, or even gains in muscle mass and strength. The regenerative potential of skeletal muscle is markedly impaired in aging and several diseases, and is associated with disturbances of muscle ECM.

The efficiency of skeletal muscle regeneration decreases with age, and this phenomenon is primarily associated with the changes in satellite cell functions, that is, the reduction of cell number and/or proliferative capacity. The basal lamina of aged muscle is thicker, and its structure is irregular and amorphous. During aging, type IV collagen abundance increases in slow muscles, whereas laminin increases in fast muscles, which can affect the ability of the basal lamina to store and release growth factors and other bioactive compounds creating the satellite cell microenvironment. Another alteration in the basal lamina during aging is increase in osteopontin, the cytokine, which negatively regulates myogenesis *in vitro* and muscle regeneration *in vivo*. Satellite cell niche during aging also contains other extracellular matrix-associated negative regulators of muscle differentiation, such as transforming growth factor- β and Wnt signaling [10]. The composition of local milieu in aged muscles changes also due to the remodeling of the neuromuscular junction, the functional alterations in endothelial cells (i.e., apoptosis) and in immune cells (i.e. impaired chemotaxis). Taken together, the satellite cell niche during aging shifts toward an increasingly inhibitory influence on satellite cell activity and muscle regeneration potential [11]. Age-related changes in content and structure of ECM in skeletal muscle can also lead to decrease in the local expression or limited access to matricryptic sites in fibronectin [47]. As a consequence, the disturbances of vascular dilation in working muscles can occur and contribute to the impairment of skeletal muscle function in aging.

Muscle atrophy can be divided into primary muscular disease and secondary muscular disorders [62], both of them characterized by pathological changes in muscle ECM. Genetic studies of several primary muscle diseases show that the basement membrane is critical for the maintenance of muscle integrity. In all of these diseases, skeletal muscle tissue development is normal, but they are characterized by progressive muscle weakness, fibrosis, and fatty infiltration [2]. Muscle dystrophy can result from the loss or impairment of any of the elements in the reticular lamina–basal lamina–sarcolemma–cytoskeleton linkage. The examples include

laminin alpha2 and its transmembrane receptors, that is, integrin alpha7 and dystroglycan (congenital muscular dystrophy), dystrophin (Duchenne muscular dystrophy), and the dystroglycan- and dystrophin-associated sarcoglycans (limb girdle muscular dystrophy), collagen IV (Walker-Warburg syndrome), and the alpha chains of collagen VI, which connect reticular lamina to basal lamina (Ulrich congenital muscular dystrophy and Bethlem myopathy). For muscle maintenance, both structural and signaling properties of the basement membrane are required. Signaling from laminin alpha2 provides survival stimuli for myofibers; thus, its absence in congenital muscle dystrophy is associated with high level of apoptosis.

The best known primary muscular disease is Duchenne muscular dystrophy (DMD) resulted from the mutation in the gene encoding dystrophin, which leads to the lack of dystrophin protein at the sarcolemma of muscle fibers. It is characterized by progressive muscle weakness associated with continuous degeneration and regeneration of skeletal myofibers [63]. The loss of satellite cell regenerative capacity due to continuous needs for regeneration may contribute to disease progression in DMD [64]. The absence of dystrophin per se can exert a direct influence on the homeostasis of the ECM by allowing leakage of cellular components to the extracellular space or by abnormal cellular uptake of growth factors, cytokines, and enzymes. This in turn can affect muscle fibroblasts, either directly by altering their adhesion properties or indirectly by interacting with molecules released by muscle or inflammatory cells. Apart from disturbances in dystrophin complex, muscles from DMD patients manifest decreased accumulation of laminin alpha2 and beta1, increased accumulation of collagen IV, higher expression of integrin alpha 7, and profibrotic cytokines, which inhibit myogenesis, that is, TGF-beta and osteopontin [10]. An up-regulation of decorin, myostatin, and MMP-7 transcripts and proteins, as well as a down-regulation of MMP-1 and TIMP-3 expression are reported in DMD fibroblasts [65]; the latter may result in increased ECM deposition leading to tissue fibrosis.

Diabetic muscles are more vulnerable to exercise-induced myofiber damage than healthy muscles. Diabetes-induced changes in skeletal muscle concern the structure of the basement membrane and the activities of the enzymes of collagen synthesis. Microarray analysis of skeletal muscle transcriptom in streptozotocin-diabetic mice show reduced gene expression of types I, III, IV, V, VI, and XV collagen. Moreover, mRNA expressions for some noncollagenous proteins and proteoglycans, that is, elastin, thrombospondin-1, laminin-2, and decorin, as well as connective tissue growth factor (CTGF) increase in diabetic muscles [43]. This can alter the structure of the basement membrane in a less collagenous direction and affect its properties. Patients with congestive heart failure (CHF) experience increased skeletal muscle fatigue. The mechanism underlying this phenomenon involves increased MMPs' activity and collagen content, accompanied by a drop in VEGF expression, which may disturb the normal contractile function of skeletal muscle [66].

Apart from the alteration, loss or impairment of some specific ECM components in physiological and pathological states, the stiffness of the ECM per se, seems to be an important factor regulating muscle cell growth and function. Resting skeletal muscle and myotubes in culture display a similar elastic stiffness (elastic modulus approximately 12 kPa), whereas aged and dystrophic muscles are several-fold stiffer (summarized in [22]). The reason for such alterations

is increased extracellular matrix accumulation, especially collagen deposition by fibroblasts, resulted from repeated muscle degeneration–regeneration events. Another mechanism could be the accumulation of advanced glycation end products (AGEs), nonspecific cross-linkings mediated by condensation of reducing sugars with amino groups, observed in aging and pathological states with elevated glucose levels. Glycated intramuscular ECM has stiffer and more load-resistant structure; however, it also manifests a reduced ability to adapt to altered loading, probably due to decreased collagen turnover. Moreover, AGEs up-regulate the expression of CTGF in fibroblasts, which can promote fibrosis in old and diabetic individuals [1]. Numerous studies using in vitro model reveal that proper myogenesis requires an optimal ECM stiffness and that both softer and stiffer coatings markedly diminish the myoblast's ability to proliferate and differentiate. These results confirm the importance of mechanical and biophysical stimuli in skeletal muscle maintenance and remodeling.

Acknowledgements

This work was supported through funding from the Department of Physiological Sciences, Faculty of Veterinary Medicine, Warsaw University of Life Sciences (SGGW).

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