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# Composition and Function of Extracellular Matrix in Development of Skeletal Muscle

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## Abstract

Skeletal muscle extracellular matrix (ECM), surround of muscle fibers, the amount of which is just <5%, appeals less attention in the field of skeletal muscle physiology. Thus, at one time, the function of skeletal muscle ECM was arbitrarily considered as general structural support that is typical in other tissues. However, an increasing number of recent evidences have indicated that the ECM plays a critical role in muscle fiber force transmission, proliferation, differentiation, migration, and polarization of cells. Alterations of molecules within the ECM are involved in fibrosis, muscle aging, regeneration, and myopathies. In this chapter, we review the composition and functions of ECM in skeletal muscle development.

**Keywords:** extracellular matrix, skeletal muscle, myogenesis, regeneration, fibrosis, myopathies

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## 1. Introduction

The process of skeletal muscle formation in vertebrates begins from myogenic progenitors originating in the somites. However, somitic cells are the source of several cell lineages and only a subset are committed to a muscle fate [1]. Those cells destined for a muscle fate then undergo the process of myogenesis, during which the progenitors become specified and determined as myoblasts, which will proliferate, migrate, and fuse to one another to form multinucleated myofibers [2]. Thus, myogenesis seem to be critical in myoblast alignment and fusion into multinucleated myotubes. And the formation of myotubes is central to skeletal muscle development.

Extracellular matrix (ECM) has been considered as a structural scaffold between cells. It has been clear for many years that the ECM is a dynamic structure that influences cell behavior through the interaction of ECM molecules with each other, interaction with growth factors, and through cell–ECM signal transduction pathways [3]. Although the compositions of the ECM differ between tissues, all ECMs share the common function of structural support, cell adhesion, cell-to-cell communication, and differentiation [4]. Since the discovery that skeletal muscle ECM participate in the conversion of myoblasts to myotubes [5], the field of skeletal muscle physiology begins to focus on the relationship between muscle cells and ECM. In this review, we will give more details about the compositions of skeletal muscle ECM and how they affects muscle's normal functions.

## 2. Composition of skeletal muscle ECM

Anatomic studies indicate that vertebrate skeletal muscle can be typically classified into three layers: skeletal muscle fibers, enclosed by endomysium; muscle fasciculus, enclosed by perimysium; and entire muscle enclosed by epimysium. Thus, skeletal muscle ECM can also be organized into hierarchical structure: endomysial, perimysial, and epimysial connective tissues. According to the structure topology studies, the ECM can be classified into two layers: the interstitial matrix and the basement membrane. Interstitial matrix appears in the intercellular spaces, while basement membrane is a static structure on which cells rest. The interstitial matrix is filled by fibrous proteins and fibroblasts which is responsible for producing collagen, fibronectin, proteoglycans (PGs) and glycosidase, and matrix metalloproteinase (MMPs) [6–8]; while basement membrane is composed of basal lamina and fibrillar reticular lamina [9]. Muscle ECM is made up of numerous macromolecules including collagens, glycoprotein and matricellular proteins, PGs, and matrix remodeling enzymes [10].

In common with other tissues, the major protein of skeletal muscle ECM is collagen [11], synthesized and excreted by fibroblasts, including types I, III, IV, VI, XI, XII, XIII, XIV, XV, and XVIII [12–15]. According to their structure and functions, these types can be divided into several groups. Fibrillar collagens: collagens that have the ability to self assemble into fibrils including types I, III, XI. Network-forming collagens: collagens that have the ability to form a network including types IV and VI. Association collagens: collagens that have the ability to associate with fibrils including types XII and XIV. Transmembrane collagens including type XIII. Multiplexin: multiple triple helix domains with interruptions including types XV and XVIII [16]. Among these isoforms, the predominant distributors in ECM are types I and III as type I appears in perimysium, whereas type III prefers to distribute between endomysium and epimysium [17]. Types IV, VI, XV/XVIII, and XIII collagen are ingredients of the basement membrane [12, 18, 19]. Types XII and XIV collagen are perimysial fibril-associated collagens with interrupted triple helices [14].

Basement membrane, the specific region of ECM, is a reticular lamina knitted by collagen IV and glycoproteins including laminins, fibronectins, and entactin/nidogen [20]. Specifically, laminins bind to integrins and  $\alpha$ -dystroglycan, while fibronectins bind to integrins and

laminins. Laminins and collagen type IV are linked to each other by entactin/nidogen [21–25]. Besides, there are other functional matricellular proteins appear in skeletal muscle ECM including tenascin-C, tenascin-Y, osteopontin, thrombospondin. Particularly, only during muscle regeneration can osteopontin be detected. And Tenascin-C appear to be located to the neuromuscular junction [26–31].

PG is heavily glycosylated proteins that is composed of a central core protein with one or more covalently attached glycosaminoglycan (GAG) chain(s) [32, 33]. Typically, the GAG is a polymer of disaccharide repeats including hyaluronan (HA), chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), and keratan sulfate (KS). Most of the PGs appeared in skeletal muscle ECM belongs to the small leucine-rich proteoglycan (SLRP) family. And the majority of SLRP family present in muscle ECM is decorin that is covalently attached by CS/DS and biglycan [34]. Decorin can associate with fibrillar collagen, types I and III collagens [3]. Moreover, heparan sulfate proteoglycans (HSPGs) including types XV, VIII collagen, perlecan, and agrin are intrinsic constituents of basement membranes that are famous for its interaction with growth factors [35, 36]. Matrilins are a novel family of oligomeric ECM proteins. The matrilin family has four members, which are named matrilin 1, 2, 3, and 4 that all share a structure made up of von willebrand factor A (VWA) domains [37, 38]. In skeletal muscle ECM, matrilin-2 is widely distributed while other members are rarely present. Matrilin-2 has two VWA domains that are connected by ten epidermal growth factor (EGF)-like modules and is believed to be involved in the development and homeostasis of the ECM network by participating in filamentous network forming [38–41].

Dynamic equilibrium of skeletal muscle ECM is maintained by degradation enzyme and cells that can secrete ECM productions. It is well known that the majority of ECM components are secreted the fibroblast. Besides, myogenic cells can also secrete collagens, MMP-2 and decorin [42–44], and embryonic myoblasts secrete collagens [45]. There are at least six categories of enzymes that can digest ECM compositions: prolinase, serine protease, cysteine protease, asparagine proteinase, glycosidase, and matrix metalloproteinase (MMP). Since MMP can widely degrade collages and PGs, it is regarded as the most important regulator in keeping the integrity and homeostasis of ECM [43, 46–48].

Briefly, ECM is a complicated supermolecular network composed by collagen, glycoprotein, and PGs. Each component contains different isoforms and form complicated complexes by connecting with each other. Thus, it is hard to characterize skeletal muscle ECM constructors fully, and for much more details about these components, new techniques are needed.

### **3. Role of ECM in skeletal muscle development**

As a fundamental component of the microenvironment of muscle fibers, the functions of ECM are traditionally considered as force transmission and structure integrity maintenance. However, an increasing number of evidence demonstrating ECM also plays an important role in myogenesis, cell proliferation, differentiation, migration, and muscle regeneration [49].

As mentioned above, providing structural and biochemical support to the surrounding cells is a common function of ECM in all cells. However, the transmission of force from contractile

elements in the muscle fiber to the resultant movement of a joint seems to be the primary function of skeletal muscle ECM [50]. In order to achieve this function, ECM was linked to cytoskeleton by integrins, dystroglycan, and PGs at the cell surface [51–53]. Specifically, integrins can convert mechanical signals to adaptive responses in the cell [54–56] and dystrophin–glycoprotein complex is critical in mechanotransduction of muscle and tendon tissue [56]. In this way, adhesion complexes composed by ECM and transmembrane proteins establish a mechanical continuum along which forces can be transmitted from inside of the cell to outside, and vice versa.

One generally held idea is that many growth factors bind to their signaling receptors using GAG chains attached to ECM and membrane proteins as cofactors. For example, the binding of fibroblast growth factor (FGF) to FGF receptor depends on a HS chain binding at the same time [57]. Fibronectin and vitronectin bind to hepatocyte growth factor (HGF) and form the HGF receptor complexes to enhance cell migration [58]. And vascular endothelial growth factor (VEGF) binds to fibronectin type III (FN3) domains to promote cell proliferation [59]. Together, these evidences suggested that ECM proteins bind and present growth factors as organized solid-phase ligands. And considering growth factors including HGF, IGF, FGF, and the TGF- $\beta$  superfamily are involved in controlling the proliferation and differentiation of myoblasts. Thus, it seems to be clear that ECM proteins can participate in skeletal muscle development by connecting with growth factors.

In vitro studies have shown that collagen fibrils are necessary during orientation and alignment of muscle fibers [60], and the inhibition of collagen synthesis suppresses the differentiation of myoblasts [49]. The functional importance of collagen network can be further proved through studies of mutant knockout models. Defection of types IV, IX, XIII, XV collagen [61–64] and mutations of collagen type VI will cause myopathy symptomatology [65]. Furthermore, lacking collagen types IX or XI will lead to abnormal collagen fibrils [66, 67], while lacking collagen type X chondrodysplasia will present [68].

PGs can also affect skeletal muscle development by modulating the activation of growth factors. For instance, perlecan can activate basic FGF (bFGF) tyrosine kinase receptors, which is a strong inhibitor of myogenic differentiation [69]. Syndecan-4 and glypican-1 participate in muscle cell proliferation and differentiation by regulating FGF2 [70]. Furthermore, syndecan-1 and -3 can also modulate the biological activity of FGF-2 [71, 72].

Decorin obstructs muscle cell proliferation [73, 74], by inhibiting the activity of transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1). Myostatin, belonging to TGF- $\beta$  superfamily, is a negative factor in muscle development. And decorin can also enhance myoblasts differentiation by restraining myostatin [75]. Moreover, fibromodulin, lumican, and biglycan can stimulate myostatin, insulin-like growth factor (IGF), or HGF [76–78].

Laminin is another critical matrix component that affects myogenesis. Specifically, evidences indicate that laminin can promote myoblast adhesion, proliferation, and myotube formation by regulating myostatin activity [79–81]. And lacking laminin mice characterize growth retardation and muscle dystrophy. On the other hand, laminin and collagen IV provide binding sites for PGs that can regulate growth factors activity. However, fibronectin, another



glycoprotein, prevents myoblast differentiation by selectively promoting adhesion of fibroblasts [81, 82].

TGF- $\beta$ 1 signal pathway is reported to prevent myogenic differentiation partly by inhibiting matrilin-2 expression. In return, the matrilin-2 promotes cell differentiation and regeneration processes in myogenic by binding to other ECM proteins and integrins to regulate the TGF- $\beta$ /BMP-7/Smad and other signaling pathways [83].

Skeletal muscle is a regenerative tissues and such regeneration requires the activity of a population of tissue-specific adult stem cells referred to as satellite cells. The satellite cell reside in mature skeletal muscle and is normally quiescent; however, when injury occurs, these muscle progenitor populations will proliferate, migrate, and fuse into new muscle fibers [84]. These special cells are wedged in basal lamina, of which the most abundant proteins are collagen type IV and laminin-2. In vitro studies showed that when satellite cells will rapidly enter cell cycle and proliferate after leaving basal lamina [85]. What is more, satellite cells cultured on matrigel with collagen VI are more inclined to be quiescence compare to these without collagen VI [86]. Thus, it seems that the basal lamina can prevent satellite cell proliferation and differentiation in the absence of damage [20]. When it comes to muscle regeneration, ECM components will positively participate in cell mitosis and differentiation as we mentioned before. Syndecan-3, one member of HSPGs, can regulate homeostasis of the satellite cell population and myofiber size by cooperating with Notch [87]. Together, these evidences show that ECM compositions play an important role in keeping satellite cells quiescent under normal circumstances and proliferation, differentiation during regeneration process.

#### 4. ECM and myopathies

Abnormal accumulation of ECM is clinically termed “fibrosis”, which is characterized by increased endomysium and perimysium in skeletal muscle. Skeletal muscle fibrosis can be detected in nearly all muscular dystrophies, aging, and muscle injury [88–92]. However, it is hard to precisely quantify skeletal muscle fibrosis as the components are complicated and dynamically changed. Furthermore, in normal muscle, the amount of ECM area fraction is 5%, but this value can dramatically increase in muscle fibrosis cases. This is because the muscle fibers will become atrophic in diseased, such as severe atrophy, chronic inflammation, and dystrophies or injured states even ECM structure remains the same [93]. Whether muscle fibrosis is characterized by excessive production of ECM components remains unclear, but the participation of these components in muscle fibrosis has been proved.

TGF- $\beta$  has long been believed to be a central mediator of the fibrotic response as it can induces fibroblasts to synthesize type-I collagen and fibronectin [94]. Moreover, TGF- $\beta$  can induces the expression of connective tissue growth factor (CTGF), a downstream mediator of the effects of TGF- $\beta$  on fibroblasts [95, 96], and the matrix protein fibronectin, a critical factor in enhancing the expression of collagen type I [97].

In skeletal muscular dystrophies, the expressions of decorin and biglycan are increased [98, 99], which will cause alteration of TGF- $\beta$  signaling and eventual fibrosis [100]. Besides,

treatments using decorin and TGF- $\beta$  inhibitors in injured muscle enhance regeneration and prevent fibrosis [101–103].

Fibrin, a structural component of the ECM, accumulates in areas of degeneration and inflammation in dystrophic muscle, whereas knockout fibrinogen was shown to reduce fibrosis development in mdx mice. Fibrin can induce the expression of TGF- $\beta$  to promote fibrosis [104]. Fibrin can activate fibroblasts to synthesize and secrete collagens by binding to  $\alpha$ V $\beta$ 3 integrin receptor [105]. Considering the synthesis and degradation of collagens is controlled by MMPs, the importance of proteases in muscle fibrosis is absolutely obvious [106].

On the other hand, defects in or deficiencies of ECM molecules will cause myopathies and inherited connective tissue disorders. As we mentioned before, ECM and cytoskeleton are connected by transmembrane proteins named dystroglycan, sarcoglycan, integrin. Dystroglycan has two subunits  $\alpha$  and  $\beta$ ,  $\beta$ -dystroglycan intracellularly binds to dystrophin and extracellularly to  $\alpha$ -dystroglycan, which is associated with the ECM proteins laminin  $\alpha$ 2, biglycan, and perlecan [16, 107]. Defects in  $\alpha$ -dystroglycan can lead to congenital muscular dystrophy (MDC) and limb-girdle muscular dystrophy (LGMD) that can also be caused by deficiency of laminin  $\alpha$ 2 [108]. Sarcoglycans can extracellularly binds to biglycan and is closely associated with the dystroglycan complex [109–111]. Mutations in sarcoglycans result in autosomal-recessive limb-girdle muscular dystrophies. In integrin knocked mice, mild form of muscular dystrophy appears [112]. Furthermore, clinical studies show that collagen VI deficiency lead to Bethlem myopathy and Ullrich congenital muscular dystrophy [61, 113, 114].

Extracellular fat is another pathological response of skeletal muscle to disease or injury that is accompanied by pathological diseases include Duchenne muscular dystrophy, obesity, type-2 diabetes, and aged muscle [115–117]. Recent studies have identified a PDGFR $\alpha$ + progenitor cell population that is responsible for intracellular fat deposition as the cell can differentiate into adipose tissue under nonregenerating conditions [118]. Moreover, these cells were found to distribute more in perimysium than endomysium [119].

## 5. MMPs and skeletal muscle

MMPs are famous for its irreplaceable role in degrading ECM compositions. In skeletal muscle, MMP-2 and MMP-9 [43] can degrade type-IV collagen, fibronectin, PGs, and laminin, while MMP-1 [48] and MMP-13 [120] degrade types I and III collagen. The activities of MMPs are controlled by tissue inhibitors of matrix metalloproteinases (TIMPs). TIMP-1 binds to active forms of MMPs forming noncovalent complexes, whereas TIMP-2 stabilizes the inactive form of the enzyme, and thus inhibits the formation of active proteolytic enzyme [47, 48]. In normal muscle tissues, the expression of MMPs are very low but increased in injured muscles mainly because they are secreted by inflammatory cells [121]. Although studies rarely show the functions of MMPs in skeletal muscle, they have been implicated in many pathological processes including myogenesis, muscle growth, development, aging, and regeneration [122, 123]. MMP-2 knockout mice developed significantly less hypertrophy and ECM remodeling in response to overload compared to a significant increase in MMP-2 activity and upregulation of ECM components and remodeling enzymes in wild-type mice [124]. In vivo study shows

that MMP-2 is essential for myoblast migration [125], while in vitro study indicates MMP-2 is secreted at all stages from cell to myotubes [126]. Acute muscle ischemia results in remodeling of the basal lamina which is accompanied by increased MMP gelatinases [127]. And increased MMPs (MMP-2 and MMP-9) are also responsible to the degradation of ECM in skeletal muscle atrophy [128]. Furthermore, satellite cells are reported to synthesize and secrete MMP-2 and induce MMP-9 activity in human skeletal muscles [129]. During regeneration, MMP-2 activation appears go along with the formation of new myofibers, whereas MMP-9 expression is related to the inflammatory response [43]. Expression changes of MMPs have been involved in different myopathies. Distinctly increased MMP-9 appears in inflammatory myopathies [130], MMP-7 upregulation is prominent in case of polymyositis, whereas MMP-2 is only slightly elevated in inflamed muscle [131].

## 6. Conclusion

Skeletal muscle fibers are surrounded by ECM, and the ECM is an important part of the cellular microenvironment consists of a complex mixture of structural and functional proteins including glycoproteins, collagen, and PGs. These molecules interact with each other and form a super molecular network in order to maintain skeletal muscle integrity and participate in the development of skeletal muscle. Additionally, skeletal muscle fibrosis, characterized by abnormal accumulation of ECM, is an obvious clinical characteristic of myopathies such as age-related sarcopenia, muscular dystrophy, and Duchenne muscular dystrophy. Genetic diseases, dysregulation of TGF- $\beta$  signaling and physical activity can cause defects in or deficiencies of molecules within the skeletal muscle ECM.

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