

Skeletal Muscle Extracellular Matrix

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The skeletal muscle provides movement and support to the skeleton, controls body temperature, and regulates the glucose level within the body. This is the core tissue of insulin-mediated glucose uptake via glucose transporter type 4 (GLUT4). The extracellular matrix (ECM) provides a scaffold for cells, controlling biological processes, and providing structural as well as mechanical support to surrounding cells. Disruption of ECM homeostasis results in several pathological conditions. Various ECM components are typically found to be augmented in the skeletal muscle of obese and/or diabetic humans. A better understanding of the importance of skeletal muscle ECM remodeling, integrin signaling, and other factors that regulate insulin activity may help in the development of novel therapeutics for managing diabetes and other metabolic disorders.

Keywords: Extracellular matrix ; skeletal muscle ; collagen ; integrin ; laminin

1. Introduction

The skeletal muscle constitutes nearly 40% of body mass and is primarily composed of myofiber, multinucleated contractile cells, and mainly provides mobility, protects and supports the skeleton, and regulates the body temperature and glucose homeostasis within the body. The extracellular matrix (ECM) is composed of structural glycoproteins like collagens, laminin (s), and fibronectin (FN) bound to proteoglycans (PGs), which all help to maintain skeletal muscle integrity and provides constructional support. Collagen is the key component of fibrous protein in SM ECM, accounting for up to 10% of SM by weight and forming a network of intramuscular connective tissue (IMCT) ^[1]. IMCT is organized into endomysium (inner), perimysium, and epimysium (outer) layers. Collagen I and III are abundant in the IMCT, while other types of collagens are also present ^[2].

Collagen I is the main component of epimysium and perimysium, while collagen III is a minor component. Both, collagen I and III are the major components of the endomysium ^[3]. The endomysium shares a boundary with the myofiber sarcolemma at the basal lamina of the basement membrane (BM). The BM is composed of the reticular lamina and basal lamina, which contain collagen IV, nidogen, perlecan, and laminins ^[4]. Collagen VI, XV, and XVIII are also components of SM BM ^[5]. Laminins are the key components of the SM BM surrounding muscle fibers and stimulate proliferation, migration, differentiation, and survival of myoblasts ^[6]. Laminin binds with its transmembrane receptors dystroglycan and integrin $\alpha 7 \beta 1$ in the SM. There are several isoforms of laminins, and among them, laminin-211 is the most abundant isoform found in the adult SM BM ^{[7][8]}.

2. Collagen

Collagens are the most abundant protein in multicellular organisms and are the major component of the ECM ^[9]. The collagen gene family consists of 46 genes encoding 28 different types of proteins comprising different combinations; each type of collagen protein consists of homo- and hetero-trimers made of three polypeptide chains ^[10]. Collagens are the most prominent ECM component in SM as they play a crucial role in the regulation of cell attachment and differentiation, providing elasticity and tensile strength to bones ^[11]. There are 28 diverse forms of collagen, of which 11 types (collagen I, III, IV, V, VI, XII, XIII, XIV, XV, XVIII, and XXII) have been identified in mature SM ^{[11][12]}. Collagen I, III, V, IX, and XI are the fibrillar collagens found in SM, with I and III types being the most abundant, accounting for almost 75% of total SM collagen ^[2]. Collagen IV, a triple-helical molecule, is the key structural component of the basal lamina. Both fibrogenic and myogenic cells are known to secrete collagen IV ^[13].

Collagen type I alpha 1 and 2 chains (COL1A1/2) are fibrillar collagens found in all the three (endo-, peri-, and epimysium) layers; COL1A1/2 forms parallel fibers and determines tensile strength and rigidity in SM. Collagen type III alpha 1 chain (COL3A1) is also a fibrillar collagen that appears in endo- and perimysium as well as the myotendinous junction and forms a loose meshwork of fibers ^[14]. Collagen type V alpha 1–3 chains (COL5A1–3) controls fibrillogenesis ^[14]. Collagen type VI alpha 1–6 chains (COL6A1–6) are the main beaded filaments: the $\alpha 6$ chain is predominantly found in endo- and

perimysium; the $\alpha 3$ chain in basal lamina; and the $\alpha 5$ chain in the myotendinous junction (MTJ) [15]. Collagen VI is known to interact with several ECM components and cell surface receptors, and has a significant role in maintaining the functional integrity of the SM. Mutations in the *COL6A1*, *COL6A2*, and *COL6A3* genes are associated with muscle disorders namely Ullrich congenital muscular dystrophy and Bethlem myopathy [16]. Collagen type XV alpha 1 chain (COL15A1), collagen type XVIII alpha 1 chain (COL18A1), and collagen type XIX alpha 1 chain (COL19A1) are components of the BM of SM [12][17]. Collagen type XXII alpha 1 chain (COL22A1) is found in the MTJ and assimilates ECM components, providing mechanical stability to the MTJ. The knockdown of the *COL22A1* gene results in muscular dystrophy in zebrafish by disruption of the MTJ [18][19].

Generally, collagen is produced by fibroblasts in mature SM, but in fibrosis conditions, it may be produced by other cell types, such as myofibers, MSCs, inflammatory cells, or endothelial cells. Fibrosis is the aggregation of excess ECM components, common in most myopathies. Fibrosis in SM occurs during myopathy, aging, and diabetes, usually characterized by increased endomysium as well as perimysium [1]. Expression of collagen I, III, and IV is reported to be increased throughout diet-induced insulin resistance (IR) [20]. Both the murine model and human patients show that the level of SM collagen is higher in insulin resistance (IR) [21]. In a comparative study, total collagen content was observed to increase in obese insulin-resistant individuals compared with lean individuals [22]. Diabetes-induced alterations in SM concern the structure of the BM and the actions of the enzymes responsible for the synthesis of collagen. Gene expression of several collagen types (I, III, IV, V, VI, and XV) was found to be reduced in streptozotocin-induced diabetic mice in a microarray analysis of SM transcriptome. Additionally, mRNA expression of several non-collagenous proteoglycans and glycoproteins was found to be increased in diabetic muscles [23].

3. Laminin

Laminin is a heterotrimeric glycoprotein and a foremost component of the BM. Laminin-211 (previously named merosin) is the most abundant isoform of laminin in the BM of adult SM. However, other isoforms exist during myogenesis and at junctional regions (e.g., the neuromuscular junction and the myotendinous junction) of the muscle fiber [24]. Laminin-211 is composed of one $\alpha 2$ chain, one $\beta 1$ chain, and one $\gamma 1$ chain. The biological functions of the laminins are typically reliant on binding to the cell surface receptors. Two main groups of laminins receptors are known (i.e., integrins and non-integrins).

Integrin $\alpha 7\beta 1$ has been recognized as the main receptor for laminins in adult SM. The $\alpha 7$ subunit is present as $\alpha 7A$ and B in adult SM of mouse and human, where it attaches with an integrin $\beta 1$ splice form ($\beta 1D$ subunit) [25]. Integrin $\alpha 7\beta 1D$ is expressed throughout the sarcolemma, while $\alpha 7A\beta 1D$ expression is limited to junctional sarcolemma [26]. The foremost non-integrin cell surface receptor of laminins in SM is dystroglycan, a central piece of the dystrophin-glycoprotein complex (DGC) [27]. Laminin-211 binds to dystroglycan through O-linked mannose chains of α -dystroglycan (α -DG). α -DG is non-covalently connected to β -dystroglycan, which binds to dystrophin inside the muscle fiber. Other non-integrin receptors of laminin-211 in SM includes sulfatides and syndecans [28][29]. Laminin-211 also interacts with several other ECM components, for example perlecan, agrin, and nidogen [24].

4. ECM receptors

4.1. Integrin

Integrins are the key receptors of most SM ECM components, facilitating mechanical communication between ECM components and cells; they have several critical roles, such as cell attachment, migration, and differentiation [30]. Integrins also facilitate unique bidirectional signaling between ECM and intracellular molecules ("inside-out" and "outside-in" signaling) [31]. Integrins are heterodimeric, having two subunits (α and β). SM express seven α subunits ($\alpha 1$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\alpha 7$, and αv) in combination with the $\beta 1$ subunit [32][33].

Collagen and laminin in SM bind mostly with the $\beta 1$ subunit of integrin [34]. In vertebrates, collagen binds with four integrin receptors that have $\beta 1$ -subunits in association with any of the $\alpha 1$ -, $\alpha 2$ -, $\alpha 10$ -, or $\alpha 11$ -subunits [35]. Previously it was observed a reduced activation of focal adhesion kinase (FAK) in insulin-resistant SM of high-fat fed rats that specify the role for integrin-collagen interaction in the expansion of IR [36]. Mice with integrin $\beta 1$ subunit-deficient striated muscle show IR, as measured by diminishing insulin-mediated glucose uptake and glycogen synthesis in SM and indicated by a reduction in phosphorylation of protein kinase B (AKT) Ser-473 [37]. Downstream signaling of integrins depends on the involvement of the intracellular kinases, FAK and integrin-linked kinase (ILK). Disrupted signaling of integrin and the subsequent inflection of FAK and ILK are found to regulate insulin sensitivity in SM, possibly via altered capillary density [21][38]. As the muscle capillaries are established in direct contact with the ECM, any defect in the recruitment of these capillaries leads to development of SM IR [39]. Zong et al. suggested a connection between abnormal signaling of integrin and the development of T2DM. They observed a decrease of insulin-mediated glucose infusion rate and clearance of

glucose in the muscle-specific integrin β 1-deficient mice, notwithstanding any changes in the intake of food, weight, glucose (fasting), GLUT4 expression, or insulin levels [40]. Meakin et al. reported that β 2-integrins control homeostasis of glucose during high-fat feeding, mostly through actions on SM, to affect the metabolic phenotype *in vivo* [41]. Furthermore, in an experiment with obese high-fat fed mice, with deletion of α 2 integrin from the whole body, a moderate reverse of diet-induced muscle IR was observed, as confirmed by augmented insulin-mediated uptake of glucose through a hyperinsulinemic-euglycemic clamp, and increased insulin signaling [42].

4.2. Non-integrin ECM receptors

4.2.1. CD44

CD44 is a glycoprotein cell surface receptor for a number of ECM components, such as hyaluronan (HA), osteopontin, collagen I, and fibronectin, which are mostly present in the adipose tissue, SM, pancreas, liver, and endothelium. CD44 plays a significant role in the regulation of diverse cellular functions, including cell aggregation, endothelial cell proliferation, and immune cell migration and activation [43]. A genome-wide association study demonstrated that the *cd44* gene is associated with the pathogenesis of T2DM [44]. Hasib et al. hypothesized that high-fat feeding in mice increases HA content and expression of CD44; this activates CD44 signaling and enables muscle capillary rarefaction, successively leading to the development of IR. Interruption of this pathway at several stages, for example, by reduction of HA via PEGPH20 treatment and/or CD44 deletion, helps in reducing IR in SM. Hasib et al. concluded that HA-CD44 signaling might be a probable therapeutic target for IR and T2DM [45].

4.2.2. Dystroglycan

Dystroglycan, a transmembrane protein comprising α and β subunits, is a constituent of the dystroglycan complex (DGC) that enables an interaction between the ECM and cytoskeleton of muscle cells. The DGC is a key receptor system for the components of the ECM in SM [46]. Dystroglycan confers stability to myotube by binding to its ligand (laminin-211) during muscle contraction [47]. As dystroglycan is a heavily glycosylated protein, any defect in this glycosylation may lead to several forms of muscular dystrophy [47]. The DGC is involved in essential cell-signaling processes and serves as a binding platform for several ligands, including nitric oxide synthase, which is known to stimulate the transport of glucose. Thus, disruption in the DGC or its components may lead to abnormal insulin signaling in SM fibers and result in altered functionality. Collectively, alterations in the DGC may create changes in glucose metabolism; for example, IR in the SM of patients with muscular dystrophy [48][49].

4.2.3. Syndecans

Syndecans are transmembrane proteoglycans that form a core set of proteins linked to linear carbohydrate chains, known as glycosaminoglycans (GAG) [50][51]. In addition to binding growth factors through the glycosaminoglycan chains, Syndecans can bind directly to ECM molecules [52].

4.2.4. Muscle stem cells and Extracellular Matrix

Muscle fibers or myofibers are the functional units of skeletal muscles and are formed during embryogenesis when myoblasts fuse to form myotubes. Under normal conditions, MSCs are usually in the quiescent phase and remain in this phase until they are invoked by injury and exercise. Small injuries may initiate minimal MSC proliferation, whereas major injuries can result in the recruitment of large numbers of MSCs, and subsequent proliferation before differentiation [53]. Many factors regulate MSC activation, some of the more widely explored factors include muscle regulatory factors (MRFs, such as, MYF5, MYOD, and myogenin), hepatocyte growth factor (HGF), and neuronal nitric oxide synthase (NOS) [54]. MSCs are positioned between the sarcolemma (cell membrane) and the basal membrane (basal lamina; BL) of muscle fibers, and the balance between quiescent and activated forms of MSCs is usually sustained in this niche [55]. The ability to regenerate skeletal muscle is primarily dependent upon the interaction between MSCs and their microenvironment. BL is covered by an ECM network, which directly contacts MSCs. The main components of BL are type IV collagen and laminin-2, and their concentrations are muscle fiber type dependent. Other components that comprise BL include collagen VI, perlecan, nidogen, FN and other glycoproteins and PGs [56][57].

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