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Invited review: mesenchymal progenitor cells in intramuscular connective tissue development

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Abstract

The abundance and cross-linking of intramuscular connective tissue contributes to the background toughness of meat, and is thus undesirable. Connective tissue is mainly synthesized by intramuscular fibroblasts. Myocytes, adipocytes and fibroblasts are derived from a common pool of progenitor cells during the early embryonic development. It appears that multipotent mesenchymal stem cells first diverge into either myogenic or non-myogenic lineages; non-myogenic mesenchymal progenitors then develop into the stromal-vascular fraction of skeletal muscle wherein adipocytes, fibroblasts and derived mesenchymal progenitors reside. Because non-myogenic mesenchymal progenitors mainly undergo adipogenic or fibrogenic differentiation during muscle development, strengthening progenitor proliferation enhances the potential for both intramuscular adipogenesis and fibrogenesis, leading to the elevation of both marbling and connective tissue content in the resulting meat product. Furthermore, given the bipotent developmental potential of progenitor cells, enhancing their conversion to adipogenesis reduces fibrogenesis, which likely results in the overall improvement of marbling (more intramuscular adipocytes) and tenderness (less connective tissue) of meat. Fibrogenesis is mainly regulated by the transforming growth factor (TGF) β signaling pathway and its regulatory cascade. In addition, extracellular matrix, a part of the intramuscular connective tissue, provides a niche environment for regulating myogenic differentiation of satellite cells and muscle growth. Despite rapid progress, many questions remain in the role of extracellular matrix on muscle development, and factors determining the early differentiation of myogenic, adipogenic and fibrogenic cells, which warrant further studies.

Keywords

fibrogenesis; intramuscular connective tissue; meat; progenitor cells; muscle

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Implications

Intramuscular connective tissue contributes to the background toughness of meat, which is mainly synthesized by intramuscular fibroblasts. Recent studies show that adipocytes and fibroblasts are derived from a common pool of mesenchymal progenitor cells during the early embryonic development. Due to the bipotent developmental potential of these progenitor cells, enhancing their conversion to adipogenesis reduces fibrogenesis, which provides an opportunity to improve marbling and tenderness of meat, thus the overall palatability.

Introduction

Meat quality is determined by flavor, tenderness, juiciness, color, nutritional value and others. Tender meat, which contains more intramuscular fat and less connective tissue is demanded by consumers. Meat tenderness is determined by both the myofibrillar effects and the presence and cross-linking of connective tissue. Myofibrillar contribution to toughness can be partially addressed by aging carcasses, which results in the fragmentation of myofibrils primarily due to proteolysis by calpains (Koohmaraie and Geesink, 2006). On the other hand, *postmortem* aging is ineffective in improving the tenderness of a meat with high collagen content, due to the resistance of collagen to proteolysis. Thus, meat toughness due to connective tissue is called the ‘background toughness’ of meat (Nishimura, 2010). Consistently, the longissimus muscle in beef cattle contains low collagen and is tenderer while beef from limb muscles possesses higher collagen content and is tougher (McCormick, 1999; Dubost *et al.*, 2013a). In addition, the cross-linking of collagen has even greater influence on meat toughness (McCormick, 1994). Because during cooking, collagen is gelatinized, which is hampered due to the presence of cross-linking, contributing to the toughness of meat from old animals (Dubost *et al.*, 2013b). The detailed effects of connective tissue structure, collagen cross-linking, and their impacts on meat tenderness have been previous reviewed (Purslow, 2014).

Intramuscular connective tissue is mainly derived from fibroblasts, which are generated through fibrogenesis, a process referring to the generation of fibroblasts and their synthesis of proteins and other components composing the connective tissue. Fibrogenesis is active during the whole life of animals, particularly during the early developmental stage *in utero*; connective tissues synthesized inside fetal muscle form primordial perimysium and epimysium of muscle bundles at late gestation (Du *et al.*, 2010). In humans, fibrosis refers to a state of excessive deposition of collagen and other extracellular matrix proteins, which is often elicited by a pathological condition and becomes noticeable during the recovery period (Liu and Pravia, 2010). Lysyl oxidase is a rate limiting enzyme catalyzing cross-linking of collagen fibrils (Borg *et al.*, 1985; Huang *et al.*, 2012b). Available studies demonstrated that the content and cross-linking of collagen are frequently correlated to each other, but the turnover of collagen reduces cross-linking (Archile-Contreras *et al.*, 2010), a process increasing tenderness (Hill, 1967; Archile-Contreras *et al.*, 2011; Purslow *et al.*, 2012).

Intramuscular fat is considered part of the intramuscular connective tissue, and intramuscular adipogenesis is inseparable from fibrogenesis due to closely related

developmental origins. However, knowledge regarding regulatory mechanisms, or specific and effective manipulations to augment progenitor cell differentiation to a particular lineage, such as adipogenesis, remains poorly defined. The intent of this review is to provide an overview of current knowledge regarding intramuscular collagen deposition and associated marbling development, and discuss possible mechanisms regulating mesenchymal progenitor cell differentiation focusing on fibrogenesis, and their impacts on muscle growth and meat quality.

Intramuscular connective tissue structure

Organization of intramuscular connective tissue

All connective tissues (cartilage, bone, blood and interstitial tissue) possess three common components: cells, fibers and ground substance. Extracellular matrix tissue refers to a major portion of intramuscular connective tissues surrounding muscle fibers and other cells, which is composed of collagen, elastin, fibronectin, proteoglycans, and other ground substance components (Purslow, 2014). Embedded in extracellular matrix and connective tissue, there are abundant fibroblasts, adipocytes, immune cells, preadipocytes, mesenchymal progenitor cells, and other stromal vascular cells. Connective tissue and associated proteins organize muscle structure, connect muscle fibers to the bone for locomotion, and also mediate muscle growth and development (Sanes, 2003; Jenniskens *et al.*, 2006). The connective tissues surrounding each muscle fiber, termed endomysium, comprised two layers. The inner layer, termed basal lamina, is a 50 to 100 nm thick layer surrounding the sarcolemma, which connects muscle fibers to extracellular niche environment and regulates myogenesis (Wang *et al.*, 2014), and muscle growth (Velleman, 1999). Outside of the endomysium, a thin layer of connective tissue, which integrates into thicker layers between muscle bundles, termed perimysium, and surrounding each muscle, termed epimysium. These connective tissues connect muscle fibers and bundles together, and maintain muscle integrity. Intramuscular adipocytes, blood vessels and nerves are integrated into the connective tissue matrix of the muscle.

Connective tissue structure

Collagen is the major component of connective tissue. There are a number of different types of collagens, which are derived from more than 30 genes (Myllyharju and Kivirikko, 2004; Veit *et al.*, 2006; Soderhall *et al.*, 2007). However, in muscle, types I and III collagen are dominant (Light *et al.*, 1985). The ratio of type I to III may be altered depending on muscle types, locations and animal ages (Listrat *et al.*, 1999). In mature bovine muscles, type I collagen is more abundant in perimysium, but type III collagen levels are enriched in the endomysium (Mayne and Sanderson, 1985). In rats, during aging, the proportion of type I collagen increased, while type III collagen decreased (Kovanen and Suominen, 1989); an increase in type I collagen was also observed in the intramuscular connective tissue of beef cattle at around 6 months of age (Listrat *et al.*, 1999). Up to now, most studies about connective tissue in muscle have been focused on types I and III collagens (Sato *et al.*, 1994; Sato *et al.*, 1997; Duarte *et al.*, 2013).

Each collagen molecule contains three helical polypeptide chains, which are interwined. At both ends, however, non-helical regions termed telopeptide regions are found. Lysyl oxidase is a critical enzyme regulating collagen cross-linking (Siegel and Fu, 1976; Siegel *et al.*, 1976). Lysyl oxidase oxidizes lysine or hydroxylysine in the non-helical portions of collagen molecules to aldehydes, which then react with neighboring collagen molecules to form divalent bonds. Therefore, the presence of lysine and hydroxylysine in the non-helical regions is critical in determining cross-linking development (Robins, 2007). The degree of collagen cross-linking differs in animals of different breeds. In our study with Wagyu and Angus cattle, we found that the collagen content and cross-linking are higher in Wagyu, which correlates with less soluble collagen content (Duarte *et al.*, 2013). We also observed that early nutrition affects collagen content and cross-linking in sheep (Huang *et al.*, 2010). In addition, collagens of different muscle types have various degrees of cross-linking, with the collagen in longissimus muscle having less cross-linking than biceps muscle (Dubost *et al.*, 2013a), correlated with meat tenderness. Collagen cross-linking is a slow process, which increases as animals age, and the high degree of cross-linking is one of the primary reasons for the toughness of meat from old animals. On the other hand, collagens undergo consistent turnover, albeit slower than other proteins. Because newly synthesized collagens do not contain cross-linking, factors that enhance collagen turnover, reduce cross-linking and improve meat tenderness (Purslow, 2014). Indeed, cross-linking was reduced and soluble collagen content was raised in compensatory growing pigs (Kristensen *et al.*, 2002). Collagen turnover, or remodeling, is regulated by metallo-proteinases (Woessner, 1991; Murphy, 2010). The expression of metalloproteinases and their inhibitors, the tissue inhibitors of metalloproteinases, are regulated by a number of factors (Clark *et al.*, 2008), such as inflammation and oxidative stress, which affect cross-linking and meat tenderness (Purslow, 2014).

Development of connective tissue

Fibrogenic cells and adipocytes share common progenitor cells

During early skeletal muscle development, mesenchymal stem cells first diverge to either myogenic or non-myogenic lineages. Myogenic progenitors further develop into muscle fibers and satellite cells, whereas non-myogenic progenitor cells develop into the stromal-vascular fraction of mature skeletal muscle in which resides adipocytes, fibroblasts and resident mesenchymal progenitor cells (Du *et al.*, 2013). These non-myogenic progenitors have adipogenic and fibrogenic capacity, as well as osteogenic and chondrogenic potential (Joe *et al.*, 2010; Wosczyna *et al.*, 2012). These cells are mainly located in the stromal-vascular fraction of skeletal muscle and are distinct from satellite cells (Joe *et al.*, 2010; Uezumi *et al.*, 2010). Platelet-derived growth factor receptor α (PDGFRα) is a reliable marker for separating these cells, and Sca-1^{+}CD34^{+} appears to label the same cell population (Joe *et al.*, 2010; Uezumi *et al.*, 2010, 2011 and 2014).

The notion that mesenchymal progenitor cells as the common sources of adipogenic and fibrogenic cells are further proven by the co-expression of PDGFRα with fibrogenic markers (Murphy *et al.*, 2011), or PDGFRα with adipogenic markers (Yang *et al.*, 2013). Transcription factor 4 (TCF4), also known as transcription factor 7-like 2 (Tcf7l2), was first

found to be related with limb development by interacting with Wnt signaling pathway (Cho and Dressler, 1998). Subsequent studies demonstrate TCF4 as a fibrogenic marker (Kardon *et al.*, 2003; Mathew *et al.*, 2011). A portion of $TCF4^+$ fibroblasts also express PDGFRα (Murphy *et al.*, 2011), showing the intrinsic relationship between mesenchymal progenitor cells and $TCF4^+$ fibroblasts. Similarly, in our previous studies, we detected the co-expression of PDGFRα with ZFP423, a marker of adipogenic commitment (Yang *et al.*, 2013). The lack of TCF4 + and ZFP423 co-expressed cells show the divergence of the fibrogenic and adipogenic lineages during progenitor differentiation.

Mechanisms regulating fibrogenesis

Transforming growth factor (TGF)-β is the most important profibrogenic cytokine (Liu and Pravia, 2010). TGF superfamily contains several structurally related subfamilies, including TGF-β, bone morphogenetic proteins and activin. Three isoforms of TGF-β have been identified, which are TGF-β1, TGF-β2 and TGF-β3. The TGF-β1 isoform is primarily expressed in endothelial cells, fibroblasts, hematopoietic cells and smooth muscle cells; TGF-β2 mainly exists in epithelial cells and neurons; and TGF-β3 is specifically expressed in mesenchymal cells (Ghosh *et al.*, 2005). All TGF-β isoforms activate down-stream SMAD signaling (Attisano and Wrana, 1996; Letterio and Roberts, 1998). The SMAD family contains five receptor-regulated SMAD (R-SMAD 1, 2, 3, 5 and 8), a common SMAD (Co-SMAD 4), and two inhibitor SMAD (I-SMAD 6 and 7) (Moustakas *et al.*, 2001). The ligand, TGF-β, first binds to TGF-β receptor II (TβRII), which then recruits and activates TβRI. Then SMAD2 and SMAD3 are phosphorylated and subsequently bind to SMAD4 (Suwanabol *et al.*, 2011), and the resulting SMAD complex is translocated into the nucleus where it binds to SMAD-specific binding elements of target genes, thereby activating the expression of fibrogenic genes including procollagen and enzymes catalyzing collagen cross-linking (Massague and Chen, 2000). As an anti-inflammatory cytokine, TGF-β signaling is enhanced by inflammation (Bhatnagar *et al.*, 2010; Voloshenyuk *et al.*, 2011), while inhibited by anti-inflammatory factors (Wang *et al.*, 2012).

Connective tissue growth factor (CTGF) is a crucial switch to regulate downstream fibrotic progress (Grotendorst, 1997; Leask *et al.*, 2004). CTGF is a member of CCN family, which are cysteine rich proteins. CTGF gene expression is induced by TGF-β-activated Smad3 binding to its promoter region (Denton and Abraham, 2001; Holmes *et al.*, 2001). Then, CTGF directly stimulates fibroblast proliferation and ECM deposition (Shi-Wen *et al.*, 2008; Morales *et al.*, 2011). Wingless/int (Wnt) signaling pathway plays a crucial role in cell fate commitment (Dorsky *et al.*, 1998; Ross *et al.*, 2000), and synergizes with TGF-β signaling to promote connective tissue synthesis and fibrosis (Brack *et al.*, 2007; Zhou *et al.*, 2012; Cisternas *et al.*, 2014).

Ski/sno family includes ski and sno, which has four distinct isoforms SnoN, SnoN2, SnoA and Snol (Nomura *et al.*, 1989; Pearson-White, 1993; Pelzer *et al.*, 1996). Ski/sno family acts as negative regulators of TGF-β1 pathway by functioning on the downstream signal molecules R-smad/Co-smad complex (Luo, 2004; Deheuninck and Luo, 2009; Jahchan and Luo, 2010), thus reducing connective tissue deposition.

MicroRNAs regulate cell differentiation through inhibiting the expression of target genes. MiR-101a inhibits fibrosis by targeting the TβRI on cardiac fibroblasts (Zhao *et al.*, 2015). High glucose increases the activity of transcriptional co-activator p300, which subsequently enhances the activity of TGFβ pathway by inducing Smad2 acetylation (Bugyei-Twum *et al.*, 2014). Besides, ERK5, one of the MAPK family members, is a critical regulator in TGF-β1-induced lung fibrosis by enhancing Smad3 acetylation (Kim *et al.*, 2013). A number of cytokines and growth factors, which are involved in the regulation of fibrogenesis are listed in Table 1.

Antagonistic effects of adipogenesis on fibrogenesis

Because fibrogenesis and adipogenesis are considered as a competitive process, enhancing adipogenesis reduces fibrogenesis. Adipogenesis can be separated into two steps, the commitment of progenitors to preadipocytes, and the differentiation of preadipocytes to mature adipocytes. Quite recently, Zfp423 was identified as the key regulator committing progenitors to preadipocytes; in addition, Zfp423 promotes the expression of peroxisome proliferator-activated receptor γ, the crucial transcription factor inducing the conversion of preadipocytes to adipocytes (Gupta *et al.*, 2010; Gupta *et al.*, 2012). Importantly, in cattle mesenchymal progenitor cells, the expression of Zfp423 is negatively correlated with TGF-β1 expression, indicating the mutual exclusion of adipogenesis and fibrogenesis (Huang *et al.*, 2012a).

Connective tissue and muscle development

Satellite cells are critical for muscle growth and regeneration. They are wedged between the basal lamina and the plasma membrane (sarcolemma) of skeletal muscle fibers. Extra-cellular matrix together with growth factors and cytokines sequestered inside and those secreted by interstitial cells, forms the niche environment needed for satellite cell quiescence, activation, migration, myogenic differentiation and muscle development (Rhoads *et al.*, 2009; Dodson *et al.*, 2010; Murphy *et al.*, 2011; Urciuolo *et al.*, 2013).

Muscle regeneration involves extensive proliferation and myogenic differentiation of satellite cells. Shortly after muscle injury, both satellite cells and non-myogenic progenitor cells are activated and proliferate; non-myogenic progenitor cells stimulate satellite cell proliferation and facilitate muscle regeneration (Joe *et al.*, 2010; Murphy *et al.*, 2011). In addition, intramuscular fibroblasts particularly promote slow myogenesis, thus affecting muscle fiber type composition and overall maturation during muscle development (Mathew *et al.*, 2011). Extracellular component, collagen VI, regulates satellite cell self-renewal and differentiation (Urciuolo *et al.*, 2013). Besides, other components of extracellular matrix, such as proteoglycan, regulate proliferation and differentiation of satellite cells (Zhang *et al.*, 2007). Decorin, a small leucine-rich proteoglycan, traps TGFβ to regulate satellite cell activation and muscle growth (Li *et al.*, 2006 and 2008).

Extracellular matrix also interacts with a number of growth factors, including TGFβ, hepatocyte growth factor, fibroblast growth factor 2, myostatin and others to either promote or inhibit muscle growth (Yamaguchi *et al.*, 1990; Rapraeger *et al.*, 1991; Allen *et al.*, 1995;

Miura *et al.*, 2006; Kishioka *et al.*, 2008). Table 2 lists selected growth factors known to interact with extracellular matrix and regulate muscle growth.

Conclusions

Intramuscular connective tissue regulates muscle growth and development, and also is the site for intramuscular fat (marbling) deposition. The abundance and cross-linking of intramuscular connective tissue contribute to the background toughness of meat. Connective tissue is mainly synthesized by intramuscular fibroblasts. Non-myogenic mesenchymal progenitor cells are the common source of fibroblasts and adipocytes. Strengthening progenitor cell formation and proliferation enhances both intramuscular adipogenesis and fibrogenesis, while enhancing progenitor differentiation to adipogenesis reduces fibrogenesis, resulting in the overall improvement of marbling and tenderness of meat. Fibrogenesis is mainly regulated by the TGFβ signaling pathway, and a number of factors affect connective tissue deposition via altering TGFβ signaling. Extracellular matrix, a part of the intramuscular connective tissue, provides a niche environment to regulate myogenic differentiation of satellite cells and muscle growth. Despite rapid progress in our understanding of mechanisms regulating fibrogenesis, many questions remain on the synthesis of intramuscular connective tissue and the role of extracellular matrix in muscle development, which warrants further studies.

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Table 1

Factors enhancing and decreasing intramuscular fibrogenesis

Name	Fibrogenesis	Summary	References
TGFβ	Up	A key pathway driving fibrogenesis through Smad signaling	Poncelet and Schnaper (2001); Liu and Pravia (2010)
Inflammatory cytokines	Up	Inflammatory cytokines, such as TNFα, IL-1α, IL-1β and others, promote fibrogenesis through enhancing TGFβ expression	Bhatnagar *et al.* (2010); Voloshenyuk *et al.* (2011)
Wnts	Up	Wnt signaling synergizes with TGFβ signaling to promote fibrogenesis	Zhou *et al.* (2012); Cisternas *et al.* (2014)
FGF-2	Up	Promotes the proliferation of fibroblasts and fibro/adipogenic progenitor cells	Iannaccone *et al.* (1995); Virag *et al.* 2007
CTGF	Up	Promotes fibroblast proliferation and fibrogenic protein deposition	Shi-Wen *et al.* (2008); Morales *et al.* (2011)
PDGF	Up	Stimulates proliferation of fibroblasts and enhances TGFβ signaling	Zhao *et al.*, (2013); Makihara *et al.* (2015)
Anti-inflammatory factors	Down	Anti-inflammatory factors down-regulate TGFβ signaling through inhibiting inflammation	Wang *et al.* (2012)
Ski/SnoN	Down	Ski/SnoN family of oncoproteins bind to Smad proteins to inhibit the expression of TGFβ responsive genes, including fibrogenic genes	Liu *et al.* (2001)
Zfp423	Down	Zfp423 promotes adipogenic differentiation of adipo/fibrogenic progenitor cells, which reduce fibrogenesis	Huang *et al.* (2012a)
MMPs	Down	Catalyze connective tissue degradation and promote extracellular tissue remodeling	Balcerzak *et al.* (2001)
TIMPs	Up	Inhibits MMPs and connective tissue remodeling	Balcerzak *et al.* (2001)

CTGF = connective tissue growth factor; FGF-2 = basic fibroblast growth factor; MMPs = matrix metablloproteinase; PDGF = platelet-derived growth factor; TGFβ = tumor growth factor β; TIMP = tissue inhibitor of metalloproteinase; Wnts = wingless and ints.

Table 2

Growth factors associated with extracellular matrix and associated cells to regulate activation of satellite cells

Name	Summary	References
HGF/SF	Binds to ECM. It is released during ECM degradation to promote satellite cell activation and proliferation	Poncelet and Schnaper (2001), Liu and Pravia (2010)
FGF-2	Is secreted by fibroblasts, which stimulates satellite cell proliferation	Sheehan and Allen, (1999), Velleman (2007), Zhang *et al.* (2008)
IGF-1, IGF-2	Promotes satellite cell proliferation and muscle anabolism	McFarland *et al.* (1993), Haugk *et al.* (1995)
PDGF-BB	Promotes satellite cell proliferation	Doumit *et al.* (1993)
TGFβ	Antagonizes FGF-2 to inhibit satellite cell proliferation	Shi-Wen *et al.* (2008), Morales *et al.* (2011)
SDF-1	Promotes satellite cell activation, proliferation and myogenesis	Brzoska *et al.* (2012)
EGF	Promotes satellite cell proliferation and protein synthesis	Roe *et al.* (1989), Mau *et al.* (2008)

EGF = epithelial growth factor; FGF-2 = fibroblast growth factor-2; HGF/SF = hepatocyte growth factor/scatter factor; IGF = insulin growth factor; PDGF-BB = platelet-derived growth factor-BB; SDF-1 = stromal-derived factor-1; TGFβ = transforming growth factor β.