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GROWTH AND DEVELOPMENT SYMPOSIUM: STEM AND PROGENITOR CELLS IN ANIMAL GROWTH: The regulation of beef quality by resident progenitor cells[1]

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ABSTRACT: The intramuscular adipose tissue deposition in the skeletal muscle of beef cattle is a highly desired trait essential for high-quality beef. In contrast, the excessive accumulation of crosslinked collagen in intramuscular connective tissue contributes to beef toughness. Recent studies revealed that adipose tissue and connective tissue share an embryonic origin in mice and may be derived from a common immediate bipotent precursor in mice and humans. Having the same linkages in the development of adipose tissue and connective tissue in beef, the lineage commitment and differentiation of progenitor cells giving rise to these tissues may directly affect beef quality. It has been shown that these processes are regulated by some key transcription regulators and are subjective to epigenetic modifications such as DNA methylation, histone modifications, and microRNAs. Continued exploration of relevant regulatory pathways is very important for the identification of mechanisms influencing meat quality and the development of proper management strategies for beef quality improvement.

Key words: adipogenesis, beef quality, connective tissue, fibro/adipogenic progenitors, fibrogenesis, intramuscular adipose tissue

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INTRODUCTION

Meat production is a large component of U.S. agriculture, and the beef industry is a staple of U.S. agriculture. Even with the recent increase in beef price, the demand for high-quality beef continues to grow, as evidenced by a specific increase in the sale of premium beef in the United States (Tatum, 2015). Thus, both producer and consumers can benefit from more efficient production of high-quality beef. The grade of beef, as well as the consumer satisfaction, is influenced by multiple factors, among which tenderness and marbling have always been two of the most important ones (Platter et al., 2005; Igo et al., 2013; Gifford et al., 2017). An enormous amount of effort has been made previously to improve these beef quality traits through understanding the underlying regulatory mechanisms (Cafe et al., 2010; Ouali et al., 2013; Mateescu et al., 2015). Even though remarkable progress has been made, further improvement can still be made (McKenna et al., 2002; Garcia et al., 2008; Boykin et al., 2017). For example, the increase in marbling revealed by the recent National Beef Quality Audit was also associated with increases in carcass fatness (Boykin et al., 2017).

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Thus, mechanisms regulating these quality traits remain a major focus of beef cattle research.

The marbling in beef is attributed to intramuscular adipose tissue (Moody and Cassens, 1968). Unlike excessive adipose tissue located in other parts of the carcass, such as subcutaneous and visceral adipose tissues which have relatively low value, intramuscular adipose tissue directly influences the palatability of beef through providing a lubrication effect, increased juiciness, and a source of lipophilic flavor compounds (Thompson, 2004). The intramuscular adipose depot usually develops at the later stage of the animal's life, well behind subcutaneous and visceral adipose depots (Vernon, 1986). Selection for lean growth has reduced overall fat accumulation in cattle, with intramuscular adipose tissue being affected the most (Fiems et al., 2000). These combined facts make the specific accumulation of intramuscular fat a highly desired trait in beef cattle which, however, is usually difficult to achieve. The palatability of meat is also influenced by tenderness. One determining factor of beef tenderness is the amount of myofibrillar protein, which can be largely resolved by protein degradation during postmortem aging (Koohmaraie, 1992; Smith et al., 2006). In addition, connective tissue, especially the collagens and their crosslinking status, is widely believed to negatively influence the beef tenderness (Riley et al., 2005; Lepetit, 2008; Cha et al., 2012), despite some controversies possibly due to the lack of reliable tools (Christensen et al., 2011). Unlike the negative effect of myofibrillar proteins on meat tenderness, the impact of collagen is much more persistent as the crosslinked collagen matrix is highly resistant to proteolytic enzymes and heat, making it very difficult to address the issue through postmortem aging or cooking (Wu et al., 1982; Etherington, 1984; Tornberg, 2005), a possible contributing factor of the low tenderness of Brahman beef (Gonzalez et al., 2014; Phelps et al., 2017).

Even though adipose tissue is currently considered a type of specialized connective tissue, the significant differences between adipose tissue and the fibrous interstitial connective tissue in their morphology and function have led to the development of distinct research areas. In this article, we review recent publications in the field of adipose and connective tissue development and growth, particularly the regulation of progenitor cells differentiation, which will provide some insights for beef quality improvement. In addition, outcomes of recent relevant biomedical research that can be potentially applied in meat animal study are also discussed.

DEVELOPMENT AND GROWTH

Adipose Tissue

Dependent on the anatomical location, white adipose tissues are classified into subcutaneous adipose tissue, visceral adipose tissue, intermuscular adipose tissue, and intramuscular adipose tissue. In most animal species, subcutaneous and visceral adipose depots are the primary white adipose tissues and contain most of the body fat accumulated in the animal. The accumulation of intramuscular adipose tissue is generally very rare in rodents and humans and thus is considered ectopic adipogenesis (Goodpaster et al., 2008; Uezumi et al., 2010). Developmentally, it is currently accepted that both subcutaneous and visceral white adipose tissues are derived from lateral plate mesoderm (Cristancho and Lazar, 2011; Chau et al., 2014). The developmental origin of intramuscular adipose tissue has not been elucidated. However, given the high similarity of intramuscular and subcutaneous adipose tissues, it is very likely that intramuscular adipocytes share the lateral plate mesoderm origin with other white adipose tissues (Sheng et al., 2014). Interestingly, early studies showed that some adipocytes residing in multiple visceral adipose depots in newborn calves, but not in subcutaneous adipose depots were multilocular and positive for uncoupling protein 1 (**UCP1**), which resembled brown adipocytes (Alexander et al., 1975; Casteilla et al., 1987; Casteilla et al., 1989). However, given the distinct dermomyotome origin of brown adipocytes in rodents (Farmer, 2008), it is unlikely that those identified multilocular adipocytes in visceral adipose tissue of newborn calves were truly brown adipocytes. Instead, they were probably more close to the newly identified beige/brite adipocytes (Wu et al., 2012), which were previously considered brown adipocytes residing in white adipose tissue (Lee et al., 2012). Beige adipocytes and white adipocytes share immediate precursors (Lee et al., 2012) and can transdifferentiate into each other depending on the need for nonshivering thermogenesis (Rosenwald et al., 2013).

A major function of white adipose tissue is to store excess energy for use during feed/energy restriction, which is very important for the postnatal survival of the animal. In addition, it is also an endocrine organ secreting hormones and cytokines important for other physiological activities of animals such as metabolism, thermal regulation, and reproduction (Galic et al., 2010). Thus, the development of white adipose tissue usually is initiated

prenatally. In mice, adipose tissue is present in most subcutaneous and visceral white adipose depots at birth and continues to increase in size throughout the animals' lives (Han et al., 2011). The intramuscular adipose tissue is more readily seen in mice with persistent muscle injury (Uezumi et al., 2010). In cattle, the formation of adipose tissue is influenced by breed (Hudson et al., 2015), sex (Prado et al., 2009), and nutrition (Venkata Reddy et al., 2015). Thus, the exact timing of adipose tissue development in cattle may vary. However, it is currently widely accepted that intramuscular adipose tissue is the last adipose depot to develop (Du et al., 2013). A study showed that the precursors of adipocytes remained undifferentiated until midgestation (Vernon, 1986). Visible adipocytes first appeared in visceral fat depots at 110 d of gestation and then in subcutaneous and intermuscular fat depots at 180 d of gestation. Very little intramuscular adipose tissue appeared in longissimus muscle at birth, which became apparent at 5 mo postnatally (Vernon, 1986; Nürnberg et al., 1999). The postnatal expansion of adipose tissue is a combination of de novo adipogenic differentiation of progenitor cells and the hypertrophy of existing adipocytes. The hypertrophy of adipocytes can happen in all stages of the animal's life and normally slows when the sizes of adipocytes approach their size limit (Lemonnier, 1972; Albrecht et al., 2011). In humans, the number of adipocytes is mostly determined during childhood and adolescence (Spalding et al., 2008). Similarly, in cattle, the increase in subcutaneous and visceral adipocyte numbers was shown to be largely completed during the first year of the animal's life with some differences between early and late developing adipose depots (Hood and Allen, 1973). However, a human study indicates that about 10% of white adipocytes are renewed annually (Spalding et al., 2008), suggesting the presence of adipogenic progenitor cells throughout the entire life of the animal. It is worth noting that excessive energy intake has been shown to prolong both de novo adipogenesis and adipocyte hypertrophy, indicating the high plasticity and adaptability of adipose tissue (Lemonnier, 1972; Wang et al., 2013). The study of the contribution of hyperplasia to postnatal intramuscular adipose tissue expansion in meat animal has proven to be difficult. However, multiple studies have indicated that intramuscular adipocyte number in cattle might continue to increase after the first year of their life, evidenced by the presence of small intramuscular adipocytes in older cattle (Hood and Allen, 1973; Albrecht et al., 2011). A more than 4-fold increase in the expression of the adipogenic differentiation gene, peroxisome proliferator-activated receptor-gamma (***PPARG***), was identified in 25-mo-old Wagyu × Hereford cattle when compared with 20-mo-old cattle of the same breed, which was followed by a subsequent increase in the expression of fatty acid binding protein 4 (***FABP4***), a gene involved in lipogenesis and expressed at high level in differentiated adipocytes (Wang et al., 2009), suggesting the ongoing intramuscular adipogenic cell differentiation in mature cattle. Such a conclusion is also supported by a significantly increased number of marbling flecks seen in multiple muscles of cattle during their second year of life (Albrecht et al., 2006). In addition, Wang and colleagues' research also identified that such a change in adipogenic gene expression was less significant in a breed with low levels of marbling (Wang et al., 2009), suggesting that de novo intramuscular adipocyte formation varies among breeds. The stronger de novo intramuscular adipogenesis activity in Wagyu cattle compared with other breeds may be a result of a greater number of muscle-resident preadipocytes (Duarte et al., 2013).

Connective Tissue

Connective tissue is one of the most abundant and widely distributed tissues in the animal, which is mainly composed of fibroblasts and the extracellular matrix proteins secreted by them (Kendall and Feghali-Bostwick, 2014). A developmental study using an avian model indicated that the connective tissue in skeletal muscle is mainly derived from lateral plate mesoderm with some possible contribution from neural crest (Noden, 1983). The connective tissue in skeletal muscle can be classified into endomysium, perimysium, and epimysium, depending on the physical locations. The most abundant matrix proteins in skeletal muscle connective tissue are multiple isoforms of collagens. A previous study reported that the major collagen isoform located in perimysium was type I collagen, whereas epimysium and endomysium were mainly composed of collagen I and III (Gillies and Lieber, 2011). Both collagen I and III are fibrillary collagens, which can form strong networks and directly affect meat tenderness, especially when they are highly crosslinked (Lepetit, 2008).

Even though skeletal muscle connective tissue does not directly generate the muscle contraction force, it plays an important role in the force transmission and maintenance of skeletal muscle structural integrity (Takahashi, 1996; Purslow, 2010) and

is essential for the development and regeneration of skeletal muscle (Mathew et al., 2011; Murphy et al., 2011). The formation of skeletal muscle connective tissue is initiated before the onset of primary myogenesis. A study employing both rodent and avian models showed that the precursors of skeletal muscle fibroblasts migrate from lateral plate mesoderm into developing limb buds before the migration of skeletal muscle precursor cells and are crucial for the patterning of limb muscle (Kardon et al., 2003). In cattle, endomysial fibroblasts are readily identified in 2-mo-old fetuses by electron microscopy (Russell and Oteruelo, 1981). Around 4 mo after conception, individual fascicles are well separated by perimysium (Russell and Oteruelo, 1981). Further study identified that skeletal muscle fibroblasts regulate the development and maturation of skeletal muscle fibers through controlling the expression of different myosin isoforms in a transcription factor 4 (**Tcf4**)-dependent manner (Mathew et al., 2011). Moreover, the process of skeletal muscle regeneration, which is similar to its development process and also involves the proliferation and differentiation of myogenic progenitor cells and the maturation of differentiated muscle fibers (Sabourin and Rudnicki, 2000), also requires the facilitation by skeletal muscle fibroblasts. A study using a mouse line with inducible skeletal muscle fibroblast depletion showed that skeletal muscle fibroblasts are quickly activated after muscle injury, which is critical for the regeneration process of skeletal muscle (Murphy et al., 2011). Mice lacking skeletal muscle fibroblasts showed impaired muscle regeneration characterized by premature differentiation of satellite cells, depleted satellite cell pools, and reduced numbers of regenerated muscle fibers. In normal animals, activated skeletal muscle fibroblasts revert back to a quiescent state and return to their preinjury number once the regeneration process is completed. However, when muscle regeneration is impaired or not sufficient to regenerate damaged muscle fibers due to repeated injury, skeletal muscle fibroblasts may stay in an activated state and cause chronic fibrosis characterized by sustained excessive intramuscular collagen accumulation (Vidal et al., 2008). Previous research about skeletal muscle fibroblasts in meat animals is relatively limited compared with those focusing on myogenic and adipogenic cells, likely due to the unrecognized importance of these cells in the animal growth and development and meat quality determination. However, it is interesting that a study in cattle skeletal muscle fibroblasts identified some variation in the expression of matrix metalloproteinases 2, an enzyme responsible for collagen turnover, among fibroblasts isolated from different muscles (Purslow et al., 2010), which may contribute to the known difference in the tenderness between bovine longissimus and semitendinosus muscles (Otremba et al., 1999).

FIBRO/ADIPOGENIC PROGENITORS—THE COMMON SOURCE OF INTRAMUSCULAR ADIPOSE TISSUE AND CONNECTIVE TISSUE

Given the high similarity in morphology, it was proposed that fibroblasts and intramuscular preadipocytes might be just 2 names of the same group of cells or 2 closely related groups of cells (Darmon et al., 1981; Aso et al., 1995). However, direct evidence was missing until rodent studies showing that intramuscular adipocytes and fibroblasts are derived from a common group of immediate precursors of mesenchymal origin (Joe et al., 2010; Uezumi et al., 2010, 2011; Lemos et al., 2015). These cells express platelet-derived growth factor receptor alpha (**PDGFRα**), have the ability to differentiate into both adipocytes and fibroblasts, and are thus named fibro/adipogenic progenitors (**FAPs**) (Joe et al., 2010). These cells reside in the interstitial space between muscle fibers and stay quiescent in uninjured muscle (Uezumi et al., 2010). In response to cardiotoxin or notexin (snake venom-derived toxins causing skeletal muscle fiber necrosis)-induced muscle injuries, FAPs differentiated into fibroblasts/myofibroblasts. These cells expressed elevated level of collagens to provide a scaffold for regenerating muscle fibers and secreted cytokines and growth factors believed to promote the proliferation and myogenic differentiation of satellite cells (Joe et al., 2010; Uezumi et al., 2010). In contrast, when skeletal muscle was injected with glycerol, which induced a more persistent injury, FAPs quickly differentiated into adipocytes (Joe et al., 2010; Uezumi et al., 2010). After the original report of skeletal muscle FAPs, similar groups of bipotential cells have also been identified in other organs such as lung and heart (Lombardi et al., 2016; El Agha et al., 2017), suggesting common plasticity of these tissue-resident mesenchymal cells. However, a further study of skeletal muscle FAPs showed that despite the common expression of PDGFRα, this group of cells is composed of individual cells with various adipogenic and fibrogenic capacities, indicating that some heterogeneity is present within the FAP population (Uezumi et al., 2011). This may be due to some

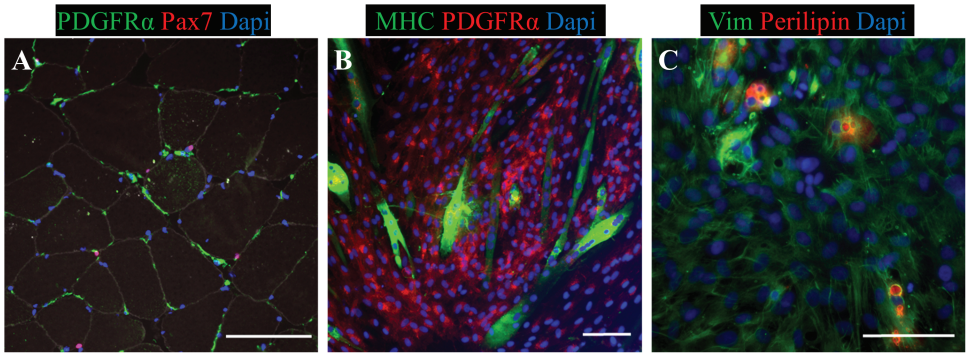

Figure 1. FAPs are present in skeletal muscle of cattle. (A) PDGFRα⁺Pax7⁻ FAPs were identified in skeletal muscle of a Brahman heifer by immunohistochemistry using antibodies against PDGFRα (green), Pax7 (red), and laminin (gray). (B) Cells isolated from skeletal muscle of a Brahman heifer were induced for myogenic differentiation as described previously (Fu et al., 2018b). Immunocytochemistry showed that PDGFRα⁺ FAPs (red) failed to differentiate into myosin heavy-chain (MHC) positive myotubes (green). (C) PDGFRα⁺ FAPs were sorted from cells isolated from skeletal muscle of a Brahman heifer as described previously (Huang et al., 2012) and induced for adipogenic differentiation (Fu et al., 2018b). Immunocytochemistry showed that FAPs gave rise to both adipocytes positive for perilipin (red) and fibroblast-like cells positive for vimentin (Vim, green). Nuclei were stained with Dapi (blue). Scale bar = 100 μm.

differential regulation during the programming and commitment processes. Although most studies about FAPs were conducted in mice, we (Figure 1A–C) and others (Huang et al., 2012; Lewis et al., 2014; Guan et al., 2017) have successfully identified and isolated FAPs from both fetal and adult skeletal muscles of beef cattle and skeletal muscle of pigs using antibodies against PDGFRα. In addition, it has long been known that fibroblast-like cells in bovine skeletal are capable of adipogenesis in response to PPARγ agonist (TORII et al., 1998), strongly supporting the presence of FAPs in bovine skeletal muscle. Similar to rodent FAPs, bovine FAPs seem to be a heterogeneous population consisting of cells with different adipogenic and fibrogenic differentiation efficiencies (Huang et al., 2012). Given the critical role of FAPs in the formation of intramuscular adipose tissue and connective tissue, FAPs can be a novel target for improving meat quality, but which will require a more complete understanding of mechanisms regulating the differentiation of FAPs.

MECHANISMS REGULATING THE DIFFERENTIATION OF FAPS AND SIMILAR CELLS

Transcription Factors and Signaling Pathways

CCAAT-enhancer binding proteins (Cl EBPs), PPARγ, and retinoid X receptors (RXRs). Adipogenic differentiation of progenitor cells giving rise to white adipocytes is affected by multiple cytokines hormones and transcription factors such as insulin, glucocorticoids, and Stat5 (Hauner et al., 1987; Nanbu-Wakao et al., 2002; Kawai et al., 2007). However, most of these factors regulate adipogenesis through acting on PPARγ and C/EBPs, the key immediate regulators of adipogenesis (Wu et al., 1998, 1999; Park and Ge, 2017). In response to adipogenic stimuli, adipogenic cells first express C/EBPβ and C/EBPδ, which in turn activate the expression of C/EBPα and PPARγ (Farmer, 2006; Salma et al., 2006). C/EBPα and PPARγ transactivate each other and promote the expression of adipocyte genes, including those regulating lipid metabolism (Lefterova et al., 2014; Oger et al., 2014). Forced expression of PPARγ was recently shown to promote adipogenic differentiation of progenitor cells in rodent visceral adipose tissue in vivo (Shao et al., 2018). The expression of PPARγ was also observed in mouse FAPs-derived adipocytes in vivo (Uezumi et al., 2010). In addition, pigs treated with PPARγ agonists showed a greater amount of intramuscular adipose tissue (Chen et al., 2013; Jin et al., 2018), possibly due to the enhanced adipogenesis of progenitor cells.

The induction of adipogenesis also requires RXRs. PPARγ and RXR form heterodimers, which bind to PPAR-responsive elements (**PPREs**) in the promoter of target genes. The activation of PPARγ-RXR heterodimer requires the binding of specific ligands to both PPARγ and RXR. Activated PPARγ-RXR heterodimers then attract coactivators and promote the transcription of target genes (Canan Koch et al., 1999). Activation of RXR through binding with its ligands/agonists promotes adipogenesis (Mukherjee et al., 1997; Canan Koch et al., 1999), which is additive with the adipogenic effect of PPARγ (Kliewer et al., 1992; Gearing et al., 1993; Keller et al., 1993). A study showed that mice lacking RXRα displayed impaired adipogenesis (Imai et al., 2001). Consistently, neonatal administration of vitamin A, a ligand of

RXR, in cattle has been shown to enhance intramuscular adipogenesis (Harris et al., 2018).

In opposition to the stimulatory effect of PPARγ on adipogenesis, activation of PPARγ has been shown to inhibit fibrogenesis (Burgess et al., 2005). It was reported that activation of PPARγ attenuated the fibrogenesis in the lung through inhibiting the fibrogenic differentiation of lung fibroblasts (Burgess et al., 2005; Sime, 2008). Similar antifibrogenic effects of PPARγ have been identified in liver (Planagumà et al., 2005; Zhao et al., 2006), kidney (Han et al., 2010), and heart (Hao et al., 2008; Ihm et al., 2010). Even though the underlying mechanism is still not very clear, it appears that PPARγ antagonizes the profibrogenic effect of transform growth factor-beta (**TGFβ**) (Zhao et al., 2006). A similar antifibrogenic effect of C/EBPα was also discovered (Mei et al., 2007). Forced expression of C/EBPα in hepatic stellate cells promoted lipogenesis and ameliorated hepatic fibrosis in mice (Mei et al., 2007).

Transforming growth factor-beta. The fibrogenic differentiation of progenitor cells or fibroblasts is a process characterized by elevated expressions of extracellular matrix (**ECM**) proteins, primarily collagens (Fu et al., 2018a). Due to the common simultaneous expression of smooth muscle alpha-actin assembled into highly organized contractile stress fibers, these differentiated fibrogenic cells are often called myofibroblasts (Contreras et al., 2016). This process is very important in wound healing as the collagen fibers stabilize the damaged tissue and enhance the structural integrity of the tissue during regeneration (Martin, 1997; Gabbiani, 2003). However, in tissues like skeletal muscle, prolonged activation of fibroblasts/myofibroblasts caused by satellite cell depletion-induced regeneration failure (Lepper et al., 2011; Sambasivan et al., 2011) or Duchenne muscular dystrophy-induced repeated muscle injury (Petrof, 1998) also results in pathological fibrosis, which greatly affects the function of affected tissues. It has been shown that TGFβ functions as the key regulator of fibrogenesis-promoting collagen expression in FAPs and other tissue-resident fibroblasts and fibroblast-like cells (Uezumi et al., 2011; Wang et al., 2012; Pan et al., 2013; Khalil et al., 2017). In addition, research has identified that TGFβ promotes the expression of lysyl oxidase (**LOX**; Salazar et al., 2013), a collagen-crosslinking enzyme known to be essential for skeletal muscle connective tissue maturation (Kutchuk et al., 2015) and whose polymorphism was reported to be associated with beef tenderness (Drinkwater et al., 2006). The expression of TGFβ is elevated in the skeletal muscle of patients with muscular dystrophy and is likely a major cause of the excessive fibrotic tissue accumulation in these patients (Bernasconi et al., 1995). Blockage of the TGFβ has been shown to attenuate the fibrosis in dystrophic skeletal muscle (Cohn et al., 2007). It is suggested that the regulation of fibrogenic differentiation of cells by TGFβ is mainly through its canonical signaling pathway composed of TGFβ ligands, their receptors, and Smad proteins (Hu et al., 2003; Khalil et al., 2017). Upon binding with TGFβ, activated TGFβ type II receptor (**TGFβRII**) phosphorylates TGFβRI, which then activates Smad2/3. Activated Smad2/3 forms a complex with Smad4, which translocates into the nucleus, binds to the promoters of target genes, and activates the expression of target genes (Massagué et al., 2005).

Connective tissue growth factor (**CTGF**) is another key component involved in the TGFβ-induced fibrogenesis. Even though the fibrogenic induction efficiency of CTGF is lower than TGFβ, it is a critical mediator required for the TGFβ-induced fibrogenesis (Mori et al., 1999). Increased expression of CTGF was identified in the skeletal muscle of muscular dystrophy patients (Sun et al., 2008). Downregulation of CTGF has been shown to reduce skeletal muscle fibrosis in mice with muscular dystrophy (Morales et al., 2013). Moreover, the stretch-responsive element present in the promoter of CTGF may be responsible for the stretch-induced myofibroblast differentiation (Kessler et al., 2001).

Both TGFβ (Ignotz and Massagué, 1985; Choy et al., 2000; Zhang et al., 2015) and CTGF (Tan et al., 2008) are also strong inhibitors of adipogenesis. A mechanistic study indicated that Smad3/4 complex activated by TGFβ binds to C/EBPβ and δ, which inhibits the transcriptional activity of C/EBPβ and δ (Choy and Derynck, 2003). Another study identified that TGFβ inhibits adipogenesis through a CTGF-dependent pathway (Kumar et al., 2012). Knockdown of TGFβ receptor was shown to promote adipogenic differentiation in porcine preadipocytes (Zhang et al., 2019). A lower expression level of *TGFB* in skeletal muscle of Wagyu cattle when compared with Angus was previously identified, which likely contributes to the greater intramuscular fat content of Wagyu (Duarte et al., 2013).

Transcription factor 4 (TCF4). The expression of TCF4 in skeletal muscle interstitial cells was first identified in chicks and mice (Kardon et al., 2003;

Mathew et al., 2011; Murphy et al., 2011). In mice, its expression is especially abundant in fibroblasts residing in prenatal skeletal muscle and regenerating skeletal muscle and is crucial for skeletal muscle development and regeneration (Mathew et al., 2011; Murphy et al., 2011). Loss of *Tcf4* in skeletal muscle fibroblasts caused a reduction in the expression of slow myosin heavy chain and an increase in the expression of embryonic myosin heavy chain during development (Mathew et al., 2011). Ablation of $TCF4^+$ cells in skeletal muscle resulted in premature differentiation of satellite cells during muscle regeneration (Murphy et al., 2011). Cells positive for TCF4 in skeletal muscle also express PDGFRα (Murphy et al., 2011), indicating that they are possibly the same type of cells as FAPs or their immediate descendants. The expression of TCF4 remains in FAPs-derived myofibroblasts (Murphy et al., 2011; Fu et al., 2016). However, its expression in FAPs-derived adipocytes has not been reported. In addition, TCF4 was identified as an indispensable mediator in the inhibitory effect of tumor necrosis factor α (**TNFα**) on adipogenesis (Cawthorn et al., 2007), suggesting that TCF4 is pro-fibrogenic and is important for the fibrogenic fate determination of FAPs. The expression of *TCF4* in cattle has not been extensively studied possibly due to the presence of large number of *TCF4* transcription isoforms in cattle (Li and Liu, 2017). However, a study reported a possible single nucleotide polymorphism (SNP) effect of *TCF4* on the lean mass of beef cattle (Zhang et al., 2018), which might be related to the reported role of $TCF4^+$ fibroblasts in skeletal muscle development and growth (Mathew et al., 2011; Murphy et al., 2011). The expression of *Tcf4* in progenitor cells residing in other adipose depots has also been reported (Elbein et al., 2007; Kovacs et al., 2008). Even though its exact function in adipose tissue is still unknown, it has been speculated that TCF4 plays a role in the development of type 2 diabetes (Grant et al., 2006; Yao et al., 2015), possibly due to the inhibitory effect of TCF4 on adipogenesis (Cawthorn et al., 2007).

Epigenetic Regulations

DNA methylation. DNA methylation is an important epigenetic mechanism controlling the expression of genes. The methylation and demethylation of DNA are directly controlled by DNA methyltransferases and DNA demethylases, respectively. Hypermethylated DNA is an indicator of transcription silence. Due to its stability, DNA methylation can be passed to the daughter cells (Stein et al., 1982) and even be inherited over generations (Hofmeister et al., 2017). However, programmed active methylation and demethylation of DNA is also required for proper development and growth of the animal. The level of DNA methylation is generally greater in differentiated cells than in undifferentiated stem cells. For instance, active demethylation is required for the zygote-derived stem cells to acquire pluripotency. The progressive specification of stem cells to various cell lineages during the later stage of prenatal development is associated with increased levels of DNA methylation (Guibert and Weber, 2013).

It was reported that the efficiency of bone morphogenetic protein 4 on the adipogenic commitment of C3H10T1/2 mouse embryonic fibroblast cells is greatly enhanced when cells were treated with DNA methylation inhibitor, possibly because of the demethylation of some key adipogenic commitment genes (Bowers et al., 2006). However, proper DNA methylation is also required for the maintenance of the adipogenicity of committed preadipocytes (Sakamoto et al., 2008; Matsumura et al., 2015). Inhibition of DNA methylation reduced the adipogenic efficiency of 3T3-L1 cells, a highly adipogenic mouse cell line, likely due to the disruption of their DNA methylation profile that favors adipogenesis, leading to the loss of adipogenic commitment of these cells (Sakamoto et al., 2008; Chen et al., 2016). The methylation status of DNA regulated by extrinsic factors has also been shown to affect adipogenesis in vivo. The DNA methylation of zinc finger protein 423 (***ZFP423***) gene, a key adipogenic commitment gene, was reduced in the offspring of high-fat diet treated dams, rendering them more susceptible to obesity (Yang et al., 2013a). Exercise was also reported to alter the DNA methylation profile of adipose tissue (Rönn et al., 2013). In addition, increased DNA methylation level at *Pparg* promoter was identified in visceral adipose tissue of diabetic mice, which likely contributed to the reduced adipogenesis activity in these mice (Fujiki et al., 2009).

Like adipogenesis, fibrogenesis is also subject to the regulation by DNA methylation. The TGFβ-induced collagen type I alpha 1 (**COL1A1**) expression in cardiac fibroblasts involves the demethylation of *Col1a1* promoter (Pan et al., 2013). Interestingly, it has also been shown that the transdifferentiation of hepatic stellate cells into myofibroblasts, which is commonly observed after liver injury, requires a DNA methylation-mediated downregulation of the expression of *Pparg* (Mann et al., 2007). This clearly indicates the importance

of DNA methylation in determining the cell fate of multipotent progenitor cells.

Histone modifications. Histone modifications are another well-known category of epigenetic modification, which includes histone methylation, acetylation, phosphorylation, deamination, and ubiquitination. These modifications determine the histone conformation, which regulates the chromatin structure, a determinant of transcription activity. Due to its long tail, histone H3 has the largest number of lysine residues that are susceptible to methylation and acetylation. The methylation at lysine 4 on histone H3 (**H3K4**), and the acetylations at H3K9 and H3K27 are signs of open chromatin. In contrast, methylations at H3K9 and H3K27 are associated with transcription inactivation (Ge, 2012). The methylation status of histone proteins is controlled by residue-specific histone demethylases and methyltransferases, whereas the acetylation status of histone proteins is mediated by histone deacetylases (**HDACs**) and histone acetyltransferases. Transcription factors bound to the promoters of target genes recruit histone modification enzymes, which leads to the expression or repression of these genes (Rezai-Zadeh et al., 2003; Han et al., 2006).

The precise control of the (de)methylation and (de)acetylation of histone proteins associated with adipogenesis regulatory genes is required for proper adipogenesis. It has been shown that knockdown of H3K9 methyltransferase SET Domain Bifurcated 1 (**SETDB1**) significantly enhanced the adipogenic efficiency of 3T3-L1 cells due to increased *Cebpa* expression, whereas knockdown of lysine-specific histone demethylase 1A (**LSD1**), an H3K4/K9 demethylase, in these cells resulted in repression of *Cebpa* and reduced adipogenic differentiation (Musri et al., 2010). Moreover, PAX-interacting protein 1 (**PTIP**), a key component of the mixed-lineage leukemia protein (**MLL**) 3/4-containing histone H3K4 methyltransferase complexes, is required for the expression of PPARγ and C/EBPα during adipogenesis (Cho et al., 2009). Similarly, disruption of histone acetylation machinery also alters adipogenic differentiation. It was shown that retinoblastoma protein-HDAC3 complex recruited by PPARγ reduced the efficiency of PPARγ to activate the expression of target genes, which led to attenuated adipogenic differentiation (Fajas et al., 2002). Elevated HDAC1 activity has been shown to reduce adipogenic efficiency of 3T3-L1 cells (Yoo et al., 2006). Moreover, inhibited acetylation of histone 3 in the promoter of fatty acid binding protein 4 (**FABP4**) in human preadipocytes resulted in reduced adipogenic efficiency (Huang et al., 2017). However, a study using class I and II HDACs inhibitors showed that HDAC activity is also required for proper adipogenesis (Lagace and Nachtigal, 2004). It is possible that HDAC is required to downregulate the expression of antiadipogenic genes (Lagace and Nachtigal, 2004).

Similarly, fibrogenesis also requires coordinated histone modification. Increased recruitment of H3K4 methyltransferase SET7/9 and elevated levels of H3K4 methylations have been identified at the promoters of fibrogenic genes in rat mesangial cells upon TGFβ treatment (Sun et al., 2010). Moreover, TGFβ-induced expression of collagen I in lung fibroblasts requires the activity of HDAC4 (Guo et al., 2009). Similarly, downregulation of HDAC4 in skin fibroblasts through RNA inference or HDAC inhibitor attenuated the differentiation of skin fibroblasts into myofibroblasts (Glenisson et al., 2007).

MicroRNAs. Since their discovery, microRNAs (**miRNAs**) have been reported to be involved in increasing numbers of developmental, physiological, and pathological processes. These RNAs with 20–24 nucleotides bind to target messenger RNAs (mRNAs), which induces the degradation of target mRNAs, leading to reduced gene expression. It has been shown that more than 370 miRNAs are expressed during the adipogenic differentiation of 3T3-L1 cells (Xie et al., 2009). Studies showed that *miR-143* (Esau et al., 2004; Xie et al., 2009) and *miR-103* (Xie et al., 2009) are critical for the adipogenic differentiation of human and mouse preadipocytes. Another study showed that the miRNA *let-7* inhibits adipogenic differentiation through inhibiting the expression of high mobility group AT-hook 2 (**HMGA2**) (Sun et al., 2009), a transcription factor important for adipogenesis in vivo (Zhou et al., 1995). *miR-27a*, another miRNA expressed in adipogenic cells, was shown to inhibit adipogenesis in rodent cells through direct targeting of the 3′-UTR of *Pparg* (Lin et al., 2009; Kim et al., 2010). In addition, *miR-140-5p* was shown to promote adipogenesis in 3T3-L1 cells by targeting TGFβ (Zhang et al., 2015). Moreover, an in vitro adipogenic differentiation study using primary bovine skeletal muscle-derived cells identified that *bta-miR-23a* was down-regulated in response to the induction for adipogenic differentiation and its expression inhibited adipogenesis, possibly through targeting the *ZFP423* mRNA (Guan et al., 2017).

The regulation of fibrogenesis by miRNAs has also been reported. The expression of *miR-145* has been shown to be important in the TGFβ-induced myofibroblast differentiation of lung fibroblasts in vitro and was shown to be elevated in the lungs of idiopathic pulmonary fibrosis patients (Yang et al., 2013b). In skeletal muscle, the intramuscular injection of *miR-1*, *133*, and *206* has been shown to prevent fibrogenesis (Nakasa et al., 2010). Importantly, due to the small size, miRNA can serve as a mediator in intercellular communication. It was recently reported that muscle hypertrophy induced the fibrogenesis of skeletal muscle FAPs, which was regulated by *miR-206* secreted by satellite cells (Fry et al., 2017). In response to mechanical overload, increased ECM deposition was observed along with skeletal muscle fiber hypertrophy. During this process, satellite cells secreted exosomes containing *miR-206*, which were uptaken by FAPs and in turn limited the production of ECM proteins in FAPs, preventing the excessive fibrogenesis that could be deleterious if left uncontrolled (Fry et al., 2017).

SUMMARY AND CONCLUSIONS

Due to their bipotential characteristic, FAPs are an ideal target for altering the tenderness and intramuscular adipose tissue deposition of beef, major goals of beef production. Previous research has demonstrated that the tenderness and marbling of beef can be affected by environmental and management factors such as climate (Gregory, 2010) and feeding (Sitz et al., 2005; Leheska et al., 2008), which might be attributed to the effects of some key transcription regulators and epigenetic regulations on FAPs. Thus, integrated studies of the transcriptomes and epigenomes of FAPs from cattle under different management regimes will likely help identify the mechanisms responsible for the differences in tenderness and/or marbling. These research may result in more feasible and efficient approaches to simultaneously promote the development of intramuscular adipose tissue and inhibit the formation of intramuscular connective tissue. Moreover, significant variations in the tenderness and marbling between different cattle breeds under the same developmental conditions have been noticed (Xie et al., 1996; Kuehn et al., 2010; Albrecht et al., 2011; Walmsley et al., 2015), which might be due to some differences in the differentiation potential of FAPs from cattle of different breeds. Although these differences may be ultimately caused by some variation at the genetic level, the identification and validation of a mutation or a polymorphism are usually very challenging, especially when the mutation or polymorphism is located in the noncoding sequence of a gene. This may affect the expression of the gene instead of directly altering the activity or function of the encoded protein. The situation can become even more complicated when the mutation or polymorphism happens in a gene that indirectly regulates the fate determination of differentiation of FAPs. Attempts to explore the underlying mechanisms may also be benefitted from an integrated study of the transcriptomes and epigenomes of FAPs. Such a study may help us to identify differential gene expression that directly contributes to the differences in the adipogenic and fibrogenic potentials of FAPs from different breeds and identify the epigenetic regulations and other signaling pathways responsible for the differential gene expression. Such a study will also help the selection of candidate genes for further genetic studies, which can eventually lead to the genetic selection for high-performance beef cattle. In addition, similar transcriptome and epigenetic studies, when conducted at single cell level, may help explore the mechanism responsible for the heterogeneity within the FAP population and the identification of genes that can be targeted to enhance the adipogenesis of FAPs.

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