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Prenatal Development of Muscle and Adipose and Connective Tissues and Its Impact on Meat Quality

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Abstract: The abundance of intramuscular fat (marbling) and tenderness are 2 key determining factors of beef quality, whereas muscle growth determines the meat production efficiency. Marbling accumulation is due to both hyperplasia and hypertrophy of intramuscular fat cells (adipocytes). On the other hand, intramuscular fibroblasts are major contributors for the formation of connective tissue and its cross-linking, which are responsible for background toughness of beef. Interestingly, muscle cells, adipocytes, and fibroblasts are derived from a common pool of mesenchymal progenitors during embryonic development. In the early embryos, a portion of progenitor cells in anlage commit to the myogenic lineage, whereas nonmyogenic cells become adipo-fibrogenic cells or other cells. These myogenic cells proliferate extensively and further develop into primary and secondary muscle fibers and satellite cells, whereas adipo-fibrogenic cells form the stromal-vascular fraction of muscle where intramuscular adipocytes and fibroblasts reside. Strengthening prenatal myogenesis and muscle development enhances lean growth, whereas promoting intramuscular adipocyte formation elevates marbling. Because the abundance of progenitor cells in animals declines as their development progresses, it is more effective to manipulate progenitor cell differentiation during early development. Maternal nutrition and other environmental factors affect progenitor cell commitment, proliferation, and differentiation, which programs muscle growth and marbling fat development of offspring, affecting the quantity and quality of meat production.

Key words: skeletal muscle, intramuscular fat, fibroblasts, marbling, beef, quality
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Introduction

Enhancing muscle growth increases the lean-fat ratio and production efficiency of meat animals. On the other hand, marbling (intramuscular fat) and tenderness are top quality problems associated with beef. For meat animals, all muscle fibers are formed before birth, and enhancing prenatal myogenesis and muscle development form more muscle fibers, which promotes lean growth of subsequent animals (Zhu et al., 2006). Marbling fat formation is due to both hyperplasia and hypertrophy of intramuscular adipocytes. The formation of adipocytes mainly occurs during the fetal and neonatal stages, and better maternal nutrition improves intramuscular adipocyte formation, resulting in adipocyte hyperplasia. In addition, intramuscular connective tissue and its cross-linking are responsible for the background toughness of meat. Fibroblasts mainly contribute to the formation of connective tissues, and their reduction improves beef tenderness (Liu et al., 2021). As a result, changes in the cellular abundancy and composition of muscle affect meat production efficiency and quality.

The prenatal stage is critical for the formation of myogenic, adipogenic, and fibrogenic cells (Du et al., 2010). During the embryonic stage, a portion of progenitor cells (PCs) in the dermomyotome first differentiate into myogenic cells, which further mature into

muscle fibers and satellite cells during the fetal stage and after birth (Zhao et al., 2021). On the other hand, nonmyogenic cells in the dermomyotome form intramuscular adipocytes, fibroblasts, and other cells. Their lineage commitments and differentiation are sensitive to changes in maternal nutrition and other factors and, thus, the prenatal stage provides a unique opportunity to enhance lean growth and intramuscular adipocyte formation while reducing connective tissue accumulation, improving the production efficiency and meat quality (Zhao et al., 2023).

In this review, we first discuss the embryonic commitments of PCs to myogenic, adipogenic, and fibrogenic cells and their effects on fetal and postnatal development. Then, we summarize the effects of maternal nutrition on prenatal muscle, fat, and connective tissue formation and their subsequent effects on beef production and quality.

Prenatal Muscle Development

Skeletal muscle development

During embryonic development, somitogenesis sequentially occurs along the body axis (Tam, 1981). Following formation, somites further split into the dermomyotome and sclerotome (Venters et al., 1999). Next, a portion of PCs within the dermomyotome start to express myogenic factor 5 (*Myf5*), committing PCs to myogenic cells, which further develop into muscle fibers and satellite cells at later stages (Seale et al., 2008; Murphy and Kardon, 2011; Chal and Pourquié, 2017). Besides forming dermis and subcutaneous fat, nonmyogenic PCs in the dermomyotome, referred to as primary fibroblasts (Saga et al., 1997; Fazilaty et al., 2019; Leavitt et al., 2020), are precursors of fibro-adipogenic progenitors (FAPs), fibroblasts, and adipocytes in adult muscle (LeBleu and Neilson, 2020). Biologically, fibroblasts and other cells synthesize connective tissues and other components, which form the stromal tissue for muscle structural integrity and muscle fiber connection to bones; on the other hand, they have critical impacts on the tenderness and marbling fat formation and, thus, the eating quality of meat (Fig. 1).

Myogenesis can be separated into 2 steps: commitment and differentiation. Myogenic commitment is initiated by the expression of *Myf5*, which then induces the expression of other myogenic regulatory factors (MRFs) including MyoD, myogenin, and MRF4, converting committed PCs into differentiated muscle cells (Rudnicki et al., 1993; Relaix et al., 2005; Tapscott, 2005; Bajard et al., 2006; Sato et al., 2010; Bentzinger et al., 2012). Myocyte enhancer factor 2 partners with MRFs to drive myogenic differentiation (Grifone et al., 2005; Buckingham, 2006; Shen et al., 2006; Potthoff and Olson, 2007; Taylor and Hughes, 2017).

The primary muscle fibers formed *de novo* in the embryonic stage serve as scaffolds for the formation of fetal muscle fibers (Swatland, 1973); these embryonic myogenic cells and PCs proliferate and provide myogenic cells for secondary muscle fiber formation during the fetal stage. In addition, these cells contribute to the formation of satellite cells in offspring muscle (Gros et al., 2005; Murphy and Kardon, 2011; Chal and Pourquié, 2017). Thus, embryonic myogenic process has critical roles in determining fetal and postnatal muscle growth and development.

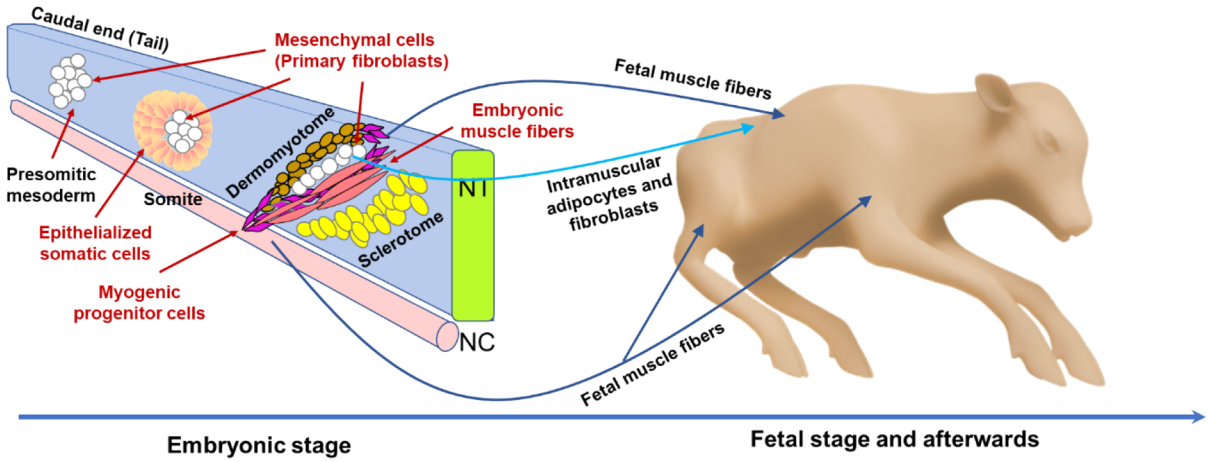

Figure 1. Diagram showing the development of embryonic muscle and fibro-adipogenic progenitor (FAP) cells, which subsequently develop into fetal muscle and intramuscular adipocytes, fibroblasts, and resident FAPs. Of note, embryonic cells have high plasticity and, thus, myogenic and fibro-adipogenic commitments are not exclusive. NC = notochord; NT = neurotube.

The secondary myogenesis that occurs during the fetal stage forms most muscle fibers. Depending on fetal maturity at birth, the occurrence of secondary myogenesis is slightly different among different animal species, which occurs during mid- to late gestation in pigs (up to around 90 d, term 114 d) (Wigmore and Stickland, 1983) and mid-gestation in cattle (up to around 200 d, term 284 d) (Bonnet et al., 2010). Therefore, the prenatal stage, especially mid-gestation, is critical for skeletal muscle development (Greenwood et al., 2000). Because muscle fibers are derived from the fusion of myogenic cells, higher abundance of myogenic cells results in more muscle fiber formation (Zhu et al., 2004). The source of fetal myogenic cells includes the proliferation of myogenic cells derived from embryos and the continued myogenic differentiation of proliferating PCs. Maternal nutrition and growth factors profoundly affect the proliferation and formation of myogenic cells and thus the number of secondary muscle fibers (Zhu et al., 2004, 2008; Tong et al., 2009; Yan et al., 2010). On the other hand, myostatin inhibits myogenic cell proliferation, and its mutation dramatically enhances prenatal muscle fiber formation, resulting in "double muscling" cattle (McPherron and Lee, 1997).

Postnatal muscle growth is mainly due to hypertrophy, in which muscle fibers increase in size and length (Brameld et al., 2000), wherein satellite cells have critical roles. Muscle satellite cells, originated from the embryonic myotome, lie between the sarcolemma of myofibers and surrounding basal lamina in adult skeletal muscle (Reznik, 1969). Their proliferation and myogenic differentiation provide the majority of nuclei in adult muscle fibers (Allen et al., 1979), showing their critical roles in postnatal muscle growth. Insufficient prenatal myogenesis will not only reduce the number of muscle fibers but also the density of satellite cells, persistently reducing lean growth. In support of this, runt piglets have suppressed fetal muscle development because of insufficient placental delivery of nutrients and have lower muscle mass permanently (Aberle, 1984; Handel and Stickland, 1987).

Adipose and Connective Tissue Development

Adipose tissue development

There are 4 major fat depots, including visceral, subcutaneous, intermuscular, and intramuscular depots, of which only intramuscular fat is highly desirable; the accumulation of other fats is a liability to producers because of their low commercial value. During prenatal development, these 4 fat depots do not form at the same time. Instead, the first detection of adipocytes is in the perirenal fat of beef cattle, followed by subcutaneous fat and intermuscular adipocytes (Bonnet et al., 2010). In perinatal fat, adipocytes were detected as early as 80 d of gestation (dG), whereas adipocytes in the intermuscular fat are detectable at 180 dG (Taga et al., 2011). The appearance of discernable intramuscular adipocytes occurs much later. Most adipocytes are formed during the fetal and early postnatal stages, and adipocyte hyperplasia largely ceases in the visceral fat after birth (Bonnet et al., 2010). Adipocyte hyperplasia is ongoing lifelong but reduces as animals become older (Robelin, 1981; Cianzio et al., 1985) because of the declining density of PCs in fat depots. Therefore, changes caused by maternal nutrition during gestation and other physiological conditions during the fetal, postnatal, and early postweaning stages affect adipogenesis and the total number of adipocytes in each depot of meat animals.

The delayed formation and maturation of intramuscular adipocytes provide an opportunity to specifically enhance intramuscular adipogenesis and marbling fat. Intramuscular adipogenesis mainly occurs during the late fetal/neonatal stage to about 250 d of age in beef cattle. Because adipogenesis is ongoing in neonatal calves, early weaning to 250 d of age is a unique time window to specifically enhance marbling with less effect on the fatness of other depots, termed as the "marbling window" (Wertz et al., 2001, 2002; Pyatt et al., 2005; Du et al., 2013). Supplementation of nutrients or other bioactive compounds to enhance adipogenesis during this stage may specifically enhance intramuscular adipogenesis and marbling.

Adipogenesis can also be separated into 2 stages: commitment and differentiation (MacDougald and Mandrup, 2002). For the adipogenic commitment of PCs into preadipocytes, zinc finger protein 423 (ZFP423) is a key transcriptional factor (Gupta et al., 2010). ZFP423 further induces the expression of peroxisome proliferator-activated receptor (PPAR) γ, which is a key transcription factor initiating the adipogenic differentiation (Gupta et al., 2010, 2012). PPARγ cooperates with CCAAT/enhancer-binding proteins to induce the expression of adipogenic-specific genes (Spiegelman and Flier, 1996; Rosen and MacDougald, 2006). These cells then accumulate lipid droplets and become mature adipocytes (Brun and Spiegelman, 1997). Feedlot fattening with high corn feeds enhances intramuscular adipocyte hypertrophy and increases marbling, but its effectiveness depends on the presence of intramuscular adipocytes formed during the earlier developmental stage.

Connective tissue development

Connective tissue, mainly collagen, is responsible for the background toughness of meat, and tender beef, such as ribeye steak, has low collagen content (McCormick, 1999). Moreover, not only content but collagen cross-linking is even more important for tenderness. Cross-linking increases as the animal age increases and, thus, only young animals produce high-quality beef. In addition, collagen content and cross-linking are positively correlated (Archile-Contreras et al., 2010). Fibrogenesis, referring to connective tissue formation by fibroblasts, is highly active during the fetal and neonatal stages, which form a connective tissue network for maintaining muscle integrity. Transforming growth factor (TGF)-β is the critical factor stimulating fibrogenesis (Liu and Pravia, 2010). Three isoforms of TGF-β have been identified, which are TGF-β1, TGF-β2, and TGF-β3; TGF-β1 is primarily expressed in muscle (Ghosh et al., 2005). All TGF-β isoforms activate downstream SMAD signaling to enhance fibrogenesis (Attisano and Wrana, 1996; Letterio and Roberts, 1998). The SMAD signaling not only activates the expression of fibrogenic genes such as procollagen but also lysyl oxidase catalyzing collagen cross-linking (Massagué and Chen, 2000).

Collagen turnover reduces cross-linking (Archile-Contreras et al., 2010). However, collagens have a very low turnover rate, and their turnover is regulated by matrix metalloproteinases (MMPs) (Visse and Nagase, 2003; Huang et al., 2012b). Collagen turnover is accelerated by compensatory growth and extracellular remodeling, which increases tenderness (Hill, 1967; Archile-Contreras et al., 2011). In our studies in sheep and cattle, the expression of collagens, lysyl oxidase, and MMPs is correlated, showing their coordinated roles in the formation of intramuscular connective tissue (Huang et al., 2012b).

Adipocytes and fibroblasts share a common pool of progenitor cells

During embryonic muscle development, PCs first diverge to either myogenic PCs or nonmyogenic cells. Of these nonmyogenic cells, a major portion become adipo-fibrogenic PCs, which are precursor cells for intramuscular adipocytes, fibroblasts, resident FAPs, and other cells in muscle. Postnatally, intramuscular adipocytes and fibroblasts are developed from resident FAPs (Joe et al., 2010; Uezumi et al., 2010, 2011). As a result, intramuscular adipogenesis and fibrogenesis can be considered as a competitive process; enhancing adipogenic differentiation of adipo-fibrogenic PCs and FAPs can reduce their fibrogenic differentiation, which may increase intramuscular adipocytes and reduce fibroblasts, improving both marbling and tenderness. Based on available studies, ZFP423 is a key transcriptional factor enhancing the adipogenic commitment of PCs and FAPs into adipocytes. On the other hand, enhancing TGFβ signaling increases fibrogenic differentiation and collagen synthesis (Huang et al., 2012a).

Manipulating Progenitor Cell Differentiation Through Maternal Nutrition

Maternal nutrition and muscle development

Fetal developmental programming, also called the Barker hypothesis, refers to the profound impacts of maternal nutrition on fetal development, which permanently affect metabolic health of offspring (Drake and Walker, 2004). During fetal development, essential organs and tissues such as the brain and heart have higher nutrient partitioning priority compared with skeletal muscle and adipose tissue. As a result, maternal nutrient deficiency and stress preferentially affect skeletal muscle and adipose tissue development (Zhu et al., 2006). Most studies on maternal nutrition and fetal development in livestock were conducted in sheep, in which both maternal nutrient restriction and overnutrition were used (Stannard and Johnson, 2004; Quigley et al., 2005; Tong et al., 2008, 2009; Zhu et al., 2008; Yan et al., 2010). These studies demonstrated the lasting effects of maternal nutrient deficiency on muscle growth in lambs (Zhu et al., 2006), pigs (Dwyer et al., 1994), and guinea pigs (Ward and Stickland, 1991).

For ruminant animals, fetal muscle development mainly occurs during early to mid-gestation, and maternal nutrient restriction limits the proliferation and formation of myogenic cells, resulting in reduced muscle fiber formation. On the other hand, muscle fiber formation largely stops at late gestation in ruminant animals, and nutrient restriction does not affect muscle fiber numbers but reduces fiber sizes (Greenwood et al., 1999) as well as satellite cell density (Woo et al., 2011). After birth, there is no further increase in muscle fiber numbers, and muscle grows through hypertrophy of individual muscle fibers, for which satellite cells are critically important (Russell and Oteruelo, 1981). Therefore, reduction in fetal myogenesis negatively affects long-term growth of muscle (Stannard and Johnson, 2004; Zambrano et al., 2005; Zhu et al., 2006).

Consistently, 50% nutrient deficiency during early to mid-gestation of ewes suppressed the formation of secondary myofibers (Zhu et al., 2004), which correlated with reduced muscle mass in subsequent lambs (Zhu et al., 2006). Correspondingly, maternal 60% caloric restriction in cows during 30 to 140 dG reduced muscle fiber size at 140 dG (Gonzalez et al., 2013). In addition, both restricted (60% of nutrient requirement) or overfed (140%) ewes during 30 to 90 dG decreased secondary muscle fiber formation and the density of PAX7+ myogenic cells (Gauvin et al., 2020). Therefore, both nutrient deficiency and overfeeding alter fetal muscle development, including the number and size of fibers, muscle mass, and satellite cell density in offspring muscle.

Up to now, studies on maternal nutrition and fetal development have been focused on mid- to late gestation (Du et al., 2015). However, accumulating studies show the importance of periconceptional period on embryonic development, which alters fetal and offspring development (Velazquez et al., 2019). The embryonic development is characterized by morphogenesis; at the cellular level, extensive epigenetic remodeling occurs in PCs during this stage, which persistently alters their differentiation and cellular properties in later stages (Velazquez, 2015; Dunford and Sangster, 2017; Velazquez et al., 2019).

In beef cattle, the embryonic stage is up to 50 dG (Lonergan et al., 2016), and the periconceptional period mainly includes 60 d pre- and post-breeding (Caton et al., 2020; Copping et al., 2020). Sheep gestation lasts about half of cattle gestation, and thus, the periconceptional periods is around 30 d before and after mating (Reynolds et al., 2014; Caton et al., 2020). Both under- and overnutrition of ewes before conception reduce oocyte quality, which compromises embryonic development (Lozano et al., 2003; Borowczyk et al., 2006; Grazul-Bilska et al., 2012). In cows, nutritional restriction postconception delayed embryonic development (Kruse et al., 2017). In heifers, maternal nutrition during the first 50 dG alters the expression of nutrient transporters in placenta, generating long-term changes in fetal and postnatal development (Crouse et al., 2017, 2021; Greseth et al., 2017). Maternal nutrient restriction during the first 50 d of pregnancy in heifers alters gene expression of the hind limb muscle of the 50 dG conceptus (Crouse et al., 2019; Diniz et al., 2021).

Primary myofibers form between 21 to 60 dG in cattle (Russell and Oteruelo, 1981), and impairment of embryonic myogenesis affects fetal and offspring muscle development. Nutrient deficiency (60%) during 30 to 85 dG of cows reduced the number of PAX7+ myogenic progenitors in fetal muscle (Gonzalez et al., 2013). Additionally, 50% nutrient deficiency 1 wk before and after mating in ewes increased the size but reduced the number of fetal myofibers (Sen et al., 2016).

Finally, maternal nutrition also affects the muscle fiber composition of offspring. Muscle fiber composition affects postmortem glycolysis and thus the water-holding capacity of meat. Oxidative Type I fibers contain higher intramyocellular lipids and other compounds, increasing meat flavor, whereas glycolytic fibers increase postmortem glycolysis. Unlike rodents and pigs, type IIx is the dominant fast fiber type instead of type IIb in ruminant animals. Fifty percent nutrient deficiency during 30 to 70 dG in ewes reduced the density of glycolytic myofibers while increasing oxidative myofibers at birth (Fahey et al., 2005). But in well-nourished lambs, maternal nutrient restriction increased glycolytic myofibers, likely because of the compensatory growth (Zhu et al., 2006). Consistently, in sows, a maternal high-fat diet starting from 60 dG increased glycolytic fibers in neonatal muscle (Hu et al., 2021). Therefore, maternal nutrition affects muscle fiber composition of offspring.

Maternal nutrition regulates prenatal adipogenesis and fibrogenesis

Depending on adipose depots, the developmental sources of adipocytes are different. Although intramuscular adipocytes and fibroblasts are mainly derived from PCs inside dermomyotome, adipocytes in other depots are derived from the lateral plate mesoderm and others. The formation of adipose tissue occurs slightly later than embryonic myogenesis, and the major formation of adipose and connective tissue occurs during the late gestation stage and early postnatal stage in calves. As a result, maternal nutrition during pregnancy and lactation affects the adipose tissue development of calves and the resulting quality of beef (Du et al., 2011).

Maternal undernutrition during late gestation and lactation reduces overall adipocyte formation in neonates. However, after these offspring grow up, they are fatter because of the simultaneous reduction in muscle mass, which reduces energy consumption, driving excessive energy for lipid storage and profoundly increasing adipocyte hypertrophy. In alignment, 20% nutrient restriction during the fetal development increased the 12th rib fat thickness of cattle (Mohrhauser et al., 2015). Maternal nutrient restriction during 28 to 80 dG in ewes increased neonatal fat mass

in sheep (Bispham et al., 2005). Maternal nutrient restriction in sows increases intramuscular connective tissue in offspring (Karunaratne et al., 2005), likely because of a reduction in muscle development, which increases the PC differentiation into fibro-adipogenic cells.

On the other hand, a high energy diet during gestation and lactation increases adipocyte formation, which stimulates adipocyte hyperplasia, translating into a higher proportion of adipose tissue in offspring (Rattanatray et al., 2010; Nicholas et al., 2013). Consistently, in ewes, 150% overnutrition from 60 d before conception to birth increased intramuscular fat and connective tissue contents in offspring lambs (Yan et al., 2011; Huang et al., 2012b). In addition, runt piglets that had experienced nutrient deficiency during gestation have higher adipose and connective tissue contents compared with the largest piglet (Karunaratne et al., 2005). Feeding early weaned calves with a high-grain diet increased intramuscular fat and marbling (Moisá et al., 2015), consistent with the "marbling window" concept.

Intramuscular adipocytes and fibroblasts are developed from muscle resident FAPs, which are descendants of embryonic fibro-adipogenic PCs. In beef cattle, the density of fibro-adipogenic PCs and FAPs declines as animals become older (Du et al., 2017). The density of FAPs differs because of genetics and nutrition. Wagyu, the Japanese Black cattle, are well known for their very high marbling (Gotoh et al., 2014). Previously, we found that Wagyu cattle have both elevated adipocytes and fibroblasts, likely because of the genetic effects that predispose the cattle to fibro-adipogenesis during early development (Duarte et al., 2013). In addition, maternal nutrition, especially overnutrition, increases the density of embryonic fibro-adipogenic PCs, which elevates the accumulation of both intramuscular adipocytes and connective tissue. In our studies, maternal overnutrition increased intramuscular fibrogenesis and adipocytes in skeletal muscle of sheep (Huang et al., 2010). In agreement, maternal overnutrition increased connective tissue and intramuscular fat in fetal and offspring cattle (Duarte et al., 2014).

Besides maternal nutrient deficiency or overnourishment, vitamins may also affect adipose development. Retinoic acid (RA) binds to RA receptors, which is required for adipogenesis. RA is a ligand of RA X receptor, which partners with PPARγ to initiate adipogenesis. We previously found that neonatal vitamin A administration increased intramuscular fat content by 45% without an increase in overall fatness (Harris et al., 2018; Yu et al., 2022). Consistently, vitamin A injection at birth enhanced beef marbling in Montana × Nellore steers (Maciel et al., 2022). Vitamin A increases proliferation of FAPs and promotes their adipogenic differentiation (Harris et al., 2018; Maciel et al., 2022; Yu et al., 2022). On the other hand, RA also stimulates lipid oxidation through activation of PPARα and β/δ in mature adipocytes (Wang et al., 2016). Therefore, during the fattening stage, vitamin A restriction is used to reduce lipid oxidation, which increases adipocyte hyperplasia and marbling fat deposition (Pickworth et al., 2012; Gotoh et al., 2014).

Summary and Conclusions

During embryonic development, uncommitted PCs in dermomyotome first commit to the myogenic lineage, whereas nonmyogenic cells develop into adipo-fibrogenic PCs, which further differentiate into intramuscular adipocytes, fibroblasts, and resident FAPs in mature muscle. Maternal nutrition and other physiological conditions alter PC commitments, which generate persistent effects on fetal and offspring muscle development and beef quality. Nutrient restriction during the fetal stage reduces muscle fiber formation, whereas restriction at late gestation and lactation suppresses intramuscular adipocyte formation. Wagyu cattle, known for their extremely high marbling, have lower myogenesis but elevated adipo-fibrogenesis, which increases FAP density and boosts intramuscular adipocyte hyperplasia, forming extremely high marbling during the fattening stage. Therefore, maternal nutrition profoundly affects the early development of progeny, which is one of the most efficient and effective stages for nutritional management to enhance meat production efficiency and quality.

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