Postprint: Ruminant Skeletal Muscle Development and Nutritional Regulation During Gestation

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Abstract

The growth and development of skeletal muscle in ruminants substantially influence their production performance, while gestation represents a critical period for fetal skeletal muscle development. Important signaling pathways and factors, such as Wnt and insulin-like growth factor (IGF), are intimately associated with fetal skeletal muscle development, and maternal nutritional status during this stage exerts a crucial regulatory role in the processes of fetal skeletal muscle fiber development and adipose tissue formation. Therefore, this review summarizes the developmental sequence of various skeletal muscle components in ruminants, the underlying mechanisms, and the effects of maternal nutrition during gestation on fetal skeletal muscle development.

Full Text

Skeletal Muscle Development and Nutritional Regulation During Gestation in Ruminant Animals

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Abstract: The growth and development of skeletal muscle significantly influence the production performance of ruminant animals, with the gestation period representing a critical window for fetal skeletal muscle development. Key signaling pathways and factors such as Wnt and insulin-like growth factor (IGF) are intimately involved in fetal skeletal muscle development, while maternal nutrition during this period exerts crucial regulatory effects on myofiber development and adipose tissue formation. This review synthesizes current knowledge on the

developmental sequence and underlying mechanisms of skeletal muscle components in ruminants, as well as the impact of maternal nutritional status during gestation on fetal skeletal muscle development.

Keywords: ruminant animals; gestation period; skeletal muscle development; muscle fiber; nutrient level

Muscle quality represents the most important economic trait in livestock. Skeletal muscle development encompasses myofiber development, intermuscular/intramuscular fat formation, and fibrogenesis. Muscle size is primarily determined by both the number and size of muscle fibers, with development initiating during embryogenesis and proceeding mainly throughout the fetal period. The prenatal to mid-gestation phase constitutes a particularly critical stage for skeletal muscle development, as myofiber numbers cease to increase after birth. Consequently, ensuring normal skeletal muscle development during the fetal period is essential for improving offspring production efficiency. Since fetal skeletal muscle development depends entirely on maternal nutrient supply, maternal nutrition during gestation profoundly regulates fetal myofiber development, with maternal undernutrition particularly limiting fetal skeletal muscle growth. Skeletal muscle comprises three main components: muscle fibers, adipose tissue, and connective tissue. Muscle fibers constitute the primary component, adipose tissue primarily regulates meat quality, and connective tissue provides essential structural support. The developmental capacity of these three components during gestation determines or substantially influences meat production performance in livestock. While most current research on fetal skeletal muscle development focuses on murine and porcine models, studies on ruminants remain relatively limited. Therefore, investigating the mechanisms and influencing factors of fetal skeletal muscle development in ruminants is crucial for improving meat yield and quality.

1. Myofiber Development

Myofibers, the principal constituent of skeletal muscle, originate from stem cells that differentiate into myoblasts, which subsequently fuse to form multinucleated myotubes that mature into myofibers. In cattle, primary myotubes appear by day 47 of gestation, primary myofibers form around day 100, secondary myofibers develop between months 3 and 7, and myofiber hypertrophy occurs during late gestation. In sheep, myofiber numbers peak around day 105 of gestation, with late gestation primarily characterized by myofiber hypertrophy.

1.1 Fiber Types

Since the 17th century, skeletal muscle has been recognized as having two distinct types: white and red. In the 19th century, Ranvier classified skeletal muscle into slow-contracting, enduring red muscle and fast-contracting, non-enduring white muscle using electrical stimulation methods. Subsequent research categorized mammalian skeletal muscle fibers based on oxidative capac-

ity into highly oxidative fast-twitch (Type I), slow-twitch (Type IIa), and low-oxidative slow-twitch (Type IIb) fibers. Type I fibers exhibit lower growth efficiency but rapid protein turnover, whereas Type II fibers demonstrate higher growth efficiency with lower catabolic rates.

1.2 Developmental Sequence

Myofibers derive from precursor stem cells through a process where mesodermal stem cells differentiate into myoblasts. Myoblast development can be divided into four stages: somitic, embryonic, fetal, and mature. During the embryonic stage, myoblasts differentiate into primary myotubes that form primary muscle cells. In the fetal stage, myoblasts differentiate into secondary myotubes and satellite cells; secondary myotubes develop into secondary myofibers, while satellite cells function primarily after birth. As myotubes develop, nuclei originally positioned centrally gradually migrate to the periphery, transforming myotubes into myofibers. Individual myofibers are enclosed by endomysium, with bundles of 50-150 fibers forming primary fascicles surrounded by perimysium. Several primary fascicles then aggregate to form secondary fascicles enveloped by connective tissue membranes, with muscle masses ultimately comprising multiple secondary fascicles. Satellite cells, distinct from mature skeletal muscle cells in their proliferative and migratory capacities, reside between the basal lamina and sarcolemma of mature myofibers. Upon stimulation, they can divide and proliferate to form new myofibers or fuse with existing ones, playing a critical role in skeletal muscle regeneration, growth, and repair throughout postnatal development.

Skeletal muscle development, initiated during embryogenesis, is regulated by specific biological signals. A subset of mesenchymal stem cells receives signals from adjacent tissues, including Wnt (wingless and int) and Shh (sonic hedgehog), which regulate expression of transcription factors such as paired box 3 (Pax3), Pax7, and glioma-associated oncogene homolog (Gli), thereby inducing myogenic lineage commitment through expression of myogenic regulatory factors (MRFs). During embryogenesis, a population of mesodermal cells first expresses Pax3 and Pax7. Pax3 induces expression of myogenic factor 5 (Myf5), which subsequently induces myogenic determining factor (MyoD), committing cells to the myogenic lineage. MyoD and Myf4 then regulate myocyte differentiation, while Pax7 can bind to the Myf5 promoter to stimulate its transcriptional activation, thereby regulating myogenic development. Myoblasts also form multinucleated myotubes through myogenic MRF expression. In summary, various MRFs cooperate synergistically to form mature myofibers.

2. Adipose Tissue Formation

Adipose tissue, the second most important component of skeletal muscle, significantly influences meat quality and flavor. Adipogenesis lags behind myogenesis, occurring predominantly during mid-to-late gestation in ruminants, with bovine

fetal skeletal muscle adipose tissue beginning to develop at 4 months of gestation.

2.1 Classification of Adipose Tissue in Skeletal Muscle

Muscle fat comprises intramuscular fat and intermuscular fat. Intramuscular fat resides within the epimysium, perimysium, and endomysium, while intermuscular fat exists between muscle fibers. Intramuscular fat represents an extremely important indicator of meat quality in beef and lamb, correlating positively with meat tenderness, flavor, and juiciness, particularly tenderness. Research indicates that meat flavor continuously improves with increasing intramuscular fat content, which enhances tenderness and juiciness. Intermuscular fat also substantially influences meat flavor. During fetal development, most mesenchymal stem cells differentiate into myogenic cells, with a small proportion becoming adipocytes. The fetal period constitutes a critical stage for adipose tissue development in skeletal muscle, providing sites for marbling formation during the fattening process.

2.2 Adipose Tissue Differentiation

Embryonic stem cells such as mesenchymal cells and bone marrow stromal stem cells can differentiate into adipocytes through the following process: embryonic stem cells differentiate into adipoblasts, which develop into preadipocytes, then into immature adipose cells, and finally into mature adipocytes. Adipogenesis is regulated by multiple transcription factors, primarily including CCAAT/enhancer binding proteins (C/EBP), peroxisome proliferator-activated receptor γ (PPARγ), and adipocyte determination and differentiation factor 1 (ADD1). C/EBPβ and C/EBPδ play important roles in early adipocyte differentiation by regulating mitosis and clonal proliferation, while C/EBPα controls terminal adipocyte differentiation, and PPARγ mediates lipid accumulation and expression of adipocyte-specific genes. During the first stage of adipogenesis, C/EBPβ and C/EBPδ induce and directly bind to the PPARγ promoter to stimulate its expression, which subsequently promotes C/EBPα production. Their synergistic action facilitates adipocyte differentiation. ADD1 represents an important transcription factor in adipocyte differentiation that can independently regulate adipogenesis by modulating expression of genes related to lipid metabolism, while also regulating plasma cholesterol content and fatty acid transcription levels. Co-expression of ADD1 and PPARγ substantially increases transcriptional activity of adipogenic nuclear hormone receptors, with their synergistic participation in adipogenesis. Additional research suggests the ADD1 gene can enhance PPARγ activity, potentially participating in adipogenesis by directly binding to PPARγ as an endogenous ligand substitute. Adipogenesis is also controlled by Wnt signaling, with PPARγ activity regulated by glycogen synthase kinase-3β (GSK-3β) and β-catenin from the Wnt pathway. Reduced GSK-3β activity prevents β-catenin degradation, thereby inhibiting expression of PPARγ target genes and impairing adipocyte formation.

3. Connective Tissue Formation

Connective tissue, the minor component of skeletal muscle, includes endomysium, perimysium, and epimysium, serving as a supportive and connecting bridge in muscle. Composed of cells, fibers, and extracellular matrix, its cellular component consists of fibroblasts that generate and synthesize connective tissue constituents. Fibers, polymerized from proteins, include collagen fibers, elastic fibers, and reticular fibers, while the extracellular matrix primarily comprises proteoglycans. During late gestation, endomysium, perimysium, and epimysium form in fetal skeletal muscle. The endomysium consists of fine reticular collagen fibers arranged in regular wave-like patterns, whereas the perimysium is primarily composed of thick collagen fiber bundles. Because connective tissue is hard and resistant to degradation, collagen fibers serve as an important factor in evaluating meat tenderness. Research demonstrates that lower connective tissue content in adult livestock muscle correlates with more tender meat, while higher content results in tougher meat.

4. Signaling Pathways

4.1 Wnt Signaling

The Wnt signaling pathway constitutes a complex protein interaction network that influences development of various cell types through autocrine and paracrine mechanisms, with functions most commonly observed in embryonic development and cancer. The Wnt/β-catenin pathway represents the most classical pathway. Wnt binding to frizzled proteins activates dishevelled (DVL), which inhibits downstream protein complexes including axin, GSK-3β, and APC. These complexes normally promote β-catenin degradation through ubiquitin-proteasome pathways via GSK-3β phosphorylation. Wnt signaling blocks formation of these complexes, preventing β-catenin degradation and maintaining relatively stable cytoplasmic levels, allowing β-catenin to enter the nucleus and interact with T-cell factor/lymphoid enhancer factor family transcription factors to activate specific target genes. Consequently, β-catenin plays crucial roles in regulating embryonic and postnatal growth and carcinogenesis in numerous tissues. In skeletal muscle, β-catenin regulates expression of transcription factors Pax3 and Gli. Pax3 is essential for myogenesis, acting upstream of MyoD during skeletal muscle development, while Gli is important for Myf5 expression. Signals such as Wnt and Shh regulate MRFs by influencing Pax3 and Pax7. Therefore, blocking the β-catenin pathway reduces total myocyte numbers and inhibits skeletal muscle development.

4.2 Insulin-like Growth Factor (IGF)

IGFs are multifunctional cell proliferation regulators named for their structural similarity to insulin, comprising IGF1 and IGF2. Extensive research demonstrates that IGFs are potent stimulators of myocyte differentiation that function by inducing expression of myogenic proteins, precisely regulating skeletal

muscle growth, regeneration, and hypertrophy. IGF2, a 67-amino-acid protein, critically regulates fetal development, tumor cell proliferation, and muscle growth. Functionally complex, IGF2 expression is regulated at multiple levels including transcription from multiple promoters, alternative translation initiation, mRNA stability, and genomic imprinting. In vitro studies show that IGF2 concentration significantly affects spontaneous differentiation rates of myogenic cells. IGF2 serves as an important cofactor for MyoD expression, with research by Dong et al. demonstrating that IGF2 promotes myocyte differentiation and proliferation by upregulating MyoD expression. In tissue cells, IGF1' s growth-promoting effects are primarily mediated through binding to the IGF1 receptor, a cytoplasmic receptor with partial tyrosine kinase activity that plays a key role in growth regulation. IGF1 stimulates amino acid utilization by muscle fibers, promoting muscle protein synthesis while inhibiting degradation, resulting in net protein accretion. Studies examining effects of various IGF1 concentrations on myogenic stem cell proliferation activity revealed that IGF1 promotes stem cell proliferation by increasing the proportion of S-phase cells and activating G0-to-G1 transition into mitosis, with this proliferative effect gradually increasing with IGF1 concentration until reaching saturation at effective concentrations. Additionally, IGF1 participates in regulating skeletal muscle growth by modulating satellite cell proliferation.

5. Effects of Maternal Nutrition During Gestation on Fetal Skeletal Muscle Development

Most terrestrial vertebrates complete the majority of myofiber development before birth, with bovine myofiber numbers fixed by approximately day 240 of gestation and ovine numbers fixed between days 80-125. Postnatal muscle growth results exclusively from myofiber hypertrophy, making proper fetal skeletal muscle development during gestation crucial for livestock meat production performance. Unlike the brain and heart, skeletal muscle is not prioritized in fetal nutrient partitioning, making it highly susceptible to maternal nutritional status. Current research on maternal nutrition effects in ruminants primarily focuses on overall dietary nutritional level, protein content, and energy level.

5.1 Effects on Myofibers

Primary myofibers form during early gestation, while secondary myofibers develop during mid-gestation. Nutritional restriction during early-to-mid gestation impairs secondary myofiber formation, whereas deficiency during mid-to-late gestation affects myofiber hypertrophy. Late gestational maternal nutrient restriction also reduces fetal skeletal muscle satellite cell numbers, compromising postnatal muscle development and regeneration. Myofiber maturation occurs during late gestation, when maternal nutrient restriction does not substantially affect myofiber numbers. Studies comparing muscle growth between singleton and twin fetuses found that nutrient competition in twin pregnancies during late gestation affects fetal skeletal muscle development by limiting myofiber size

rather than number. Maternal nutritional status also influences fetal myofiber numbers, with severe restriction reducing myofiber counts that can be effectively increased by embryo transfer to better-nourished uterine environments. Research in sheep demonstrated that restricting nutrients to 50% of NRC requirements during days 28-78 of gestation reduced total secondary myofiber numbers and decreased the secondary-to-primary myofiber ratio. Subsequent studies found that lambs from nutrient-restricted ewes exhibited fewer myofibers at 8 months of age, indicating that intrauterine nutrient restriction-induced myofiber maldevelopment produces lasting detrimental effects postnatally. Maternal nutrient restriction also affects offspring myofiber type composition, with studies reducing ewe nutrition to 50% of metabolic weight requirements during days 30-70 of gestation, resulting in increased Type I-to-Type II fiber ratios, reduced lean meat percentage, and decreased carcass protein content in offspring lambs. Thus, gestational undernutrition substantially impacts offspring myofiber development with long-lasting consequences for animal growth and performance.

5.2 Effects on Adipogenesis

Adipogenesis occurs during mid-to-late gestation, overlapping temporally with secondary myofiber formation, making this stage critical for maternal nutritional management. Studies demonstrate that supplementing pregnant ewes with 150% of NRC requirements increases fetal adipogenesis. However, maternal malnutrition-induced myofiber developmental impairment may reduce nutrient consumption, diverting excess energy to adipose development and lipid accumulation and thereby increasing overall offspring adiposity. Long et al. fed beef cows diets at 70% NRC, 100% NRC, or 70% NRC plus rumen-protected protein from early-to-mid gestation, finding that nutrient restriction may increase offspring adipocyte diameter. Another study provided pregnant ewes with three energy levels (60%, 100%, and 200% of metabolic energy requirements) during early gestation and two levels (80% and 140%) during mid-gestation, revealing that high energy during early gestation increased offspring perirenal and abdominal fat deposition, while low energy during mid-gestation increased obesity probability. Similarly, nutrient restriction during the first 110 days of gestation promoted fetal fat deposition in ewes, whereas continued restriction beyond 110 days impaired fetal adipogenesis. Additional research suggests maternal nutrition affects fetal skeletal muscle development by altering the glucose environment, with early-to-mid gestational nutrient restriction enhancing glucose exchange capacity and potentially increasing IGF1 sensitivity to promote adipose development. Restoration of normal nutrition during late gestation increases fetal glucose supply, further promoting fat deposition. Underwood et al. also found that increased dietary protein in pregnant beef cows promoted calf fat development, with cows grazing improved pastures (higher crude protein) producing offspring with greater carcass weight, thicker 12th-rib fat, and more adipocytes. Therefore, both gestational nutrient restriction and excess can alter offspring adipose development and deposition.

Skeletal muscle contains abundant pluripotent stem cells capable of differentiating into adipocytes, though these cells decline with animal maturity. Theoretically, nutritional management to increase muscle fat should be most effective during the fetal period, followed by the neonatal period, early weaning stage, and least effective during post-weaning and finishing periods. However, in practical production, the optimal window for nutritional management to increase muscle fat is actually the early weaning stage, because excessive nutrition during gestation can cause dystocia, slow postpartum recovery, and delayed estrus, negatively affecting production efficiency. Before weaning, lambs primarily consume maternal milk, making nutritional supplementation inconvenient. During finishing stages, depletion of pluripotent stem cells limits the effectiveness of nutritional supplements in increasing adipocyte numbers, with only existing adipocyte size being augmentable. Wertz et al. demonstrated that feeding early-weaned beef cattle high-energy corn-based diets significantly increased fat content.

6. Conclusion

Fetal myofiber number and diameter during gestation in ruminants influence lifelong skeletal muscle growth, with myofiber type composition and proportions also established during the fetal period, making this stage critical for determining meat production performance. Wnt and IGF signaling, along with maternal nutrition during gestation, are key factors influencing fetal skeletal muscle development. Therefore, continued in-depth research on these regulatory factors is needed to elucidate mechanisms underlying skeletal muscle development during fetal stages and further explore how maternal nutrition regulates fetal skeletal muscle development in ruminants, thereby providing guidance for improving livestock production efficiency.

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