

# Fetal programming in ruminant animals: understanding the skeletal muscle development to improve meat quality

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## Implications

- The intrauterine environment is crucial for the skeletal muscle formation, which depends on maternal supplies for an adequate growth and development.
- Disturbs involving maternal feed restriction or overfeeding directly affect the offspring's skeletal muscle composition, influencing the final meat quality.
- The nutritional manipulation during the intrauterine period contributes to achieving desirable meat quality traits, such as marbling and tenderness.
- Metabolism plays an important role in providing metabolites that are used as substrates in epigenetics mechanisms, which can contribute to phenotypes that are more desirable and establish phenotype inheritance across generations.

**Key words:** epigenetic modifications, livestock, maternal nutrition, skeletal muscle development



**Photo 1.** Representative image of a cow–calf pair in a fetal programming trial.

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## Introduction

The efficiency of livestock production has been largely demanded by population growth, in addition to cost reduction, food safety, and quality. The biggest challenges for the meat industry are to produce good quality meat, which meets the global demand and causes less environmental impact as possible. One of the ways to reach those goals is to shorten the cycle of animal production.

Since the skeletal muscle, which provides meat, begins to develop during the intrauterine stage, manipulating fetal muscle development may help improve the efficiency of production. However, the muscle has lower priority in nutrient partitioning compared to vital tissues during the prenatal development (Long et al., 2009; Meyer et al., 2010). Therefore, its sensitivity to maternal nutrient supply and changes in the intrauterine environment affects the composition of muscle, such as lean muscle mass, connective tissue, and fat, defining the final meat quality. Early to mid gestation is a crucial timeline for increasing the number of muscle fibers, which occurs exclusively during the prenatal period (Du et al., 2010). Concomitantly, the adipose tissue begins to develop during mid to late gestation, and although fat cells continue to form after birth, the ability to form new fat cells decreases over time (Du et al., 2010).

Altering the intrauterine environment may also change the proportion of muscle fibers, which have different metabolic properties (Zhu et al., 2006; Aragão et al., 2014). The type of substrates preferred by the muscle fibers may affect the final meat quality. Due to the forage quantity and quality fluctuation throughout the year, pregnant ruminants raised in pasture are commonly exposed to an undernutrition environment (Duarte et al., 2013a), impairing fetal development, and causing last-long effects. Therefore, in this review, we summarize the impacts of fetal programming on the skeletal muscle development, in addition to management strategies that impact final body composition and meat quality focusing on ruminant animals.

## Skeletal Muscle Development

The skeletal muscle is the major component of the carcass and its components, such as muscle fibers, connective tissue,

and adipose tissue (Figure 1), affect the quality of meat. The processes, by which muscle fibers, adipose, and connective tissue are formed, are termed as myogenesis (formation of muscle fibers), adipogenesis (formation of fat cells), and fibrogenesis (formation of connective tissue), respectively.

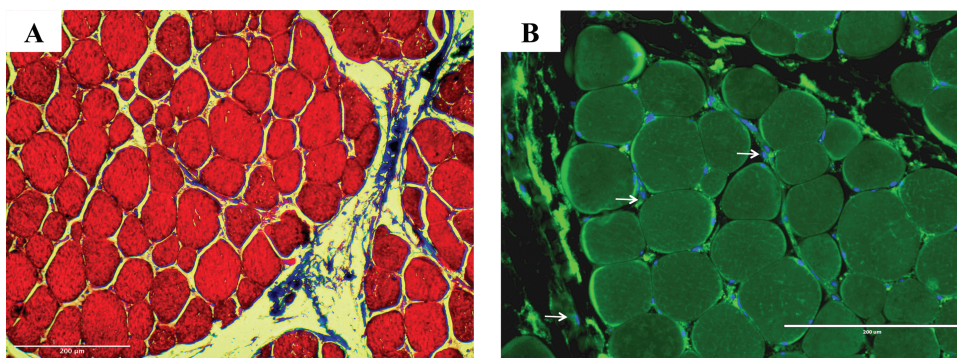
## Myogenesis

The formation of muscle fibers occurs in the prenatal stage and is commonly divided into primary and secondary myogenesis. In cattle, the primary muscle fibers are formed during the embryonic period, within 2 mo after conception, while secondary muscle fibers are formed during the fetal stages between the 2nd and 7th months of gestation (Du et al., 2010). Although the secondary muscle fibers represent the majority of fibers in adults, primary muscle fibers are used as a template for the formation of secondary muscle fibers during the fetal stage (Swatland, 1973).

Muscle mass is determined by the number (hyperplasia) and size (hypertrophy) of muscle fibers. Hyperplasia occurs exclusively in the prenatal period, and the number of muscle fibers is fixed at birth. Moreover, muscle hypertrophy also begins during the prenatal period and extends to the end of pubertal stage. During the course of myogenesis, a population of myogenic cells become quiescent and locates surrounding muscle fibers in mature muscle, which are termed satellite cells. The proliferation and fusion of satellite cells with existing muscle fibers contribute to postnatal muscle fiber hypertrophy (Kuang et al., 2007). Therefore, the establishment of greater number of muscle fibers at birth and increase in the number of satellite cells may positively impact meat production efficiency, which can be achieved through an adequate nutritional and environmental support during the intrauterine stage.

## Adipogenesis

Similar to myogenesis, the adipogenesis involves cell determination and differentiation. As a competitive process, the same population of embryonic stem cells which can develop into muscle fibers can also undergo differentiation into fibro-adipogenic progenitors, a group of undifferentiated cells that can further develop into mature adipocytes and fibroblasts



**Figure 1.** (A) Photomicrograph (20× of magnification) of skeletal muscle of beef cattle showing the muscle fibers (red), and intramuscular collagen (blue). (B) Photomicrograph (20× of magnification) of skeletal muscle of beef cattle showing preadipocytes and adipocytes (indicated by white arrows) within muscle fibers.

(Uezumi et al., 2010). In ruminants, adipogenesis begins around mid-gestation, concomitantly with the secondary myogenesis (Du et al., 2010). Unlike myogenesis, the adipogenesis is not limited to prenatal stages; however, hyperplasia potential of this tissue decreases over time (Du et al., 2013). Visceral fat hyperplasia extends until the neonatal stage, while subcutaneous and intermuscular fat extends until early weaning, and intramuscular fat formation extends until approximately 250 d of age (Du et al., 2013). After the respective period of hyperplasia, the adipocytes undergo hypertrophy contributing to fat storage.

### **Fibrogenesis**

Fibrogenesis begins during the late fetal stage, accompanied by adipogenesis; both fat cells and fibroblasts are developed from fibro-adipogenic progenitor cells. Fibroblasts are responsible for secreting components of connective tissue, including collagen and enzymes that catalyze collagen cross-linking, which occurs slowly, increases with age, and contributes to the background toughness of meat (Zhao et al., 2019).

Since adipose and connective tissue are originated from a common source of progenitor cells during fetal stage, there is an opportunity for manipulation in this period in a way that favors the increase of intramuscular fat cells and decrease of fibroblasts and the accumulation of connective tissue, improving meat quality (Du et al., 2013).

## **Muscle Fiber Types and Meat Quality**

### **Skeletal muscle metabolism**

Skeletal muscle mainly utilizes carbohydrate and fat as energy sources. In ruminants, fermentation by ruminal microbiota produces short chain fatty acids, such as, acetate, propionate, and butyrate. The proportion of these short chain fatty acid is influenced by feed sources, mainly by the roughage:concentrate ratio. Ruminal degradation of diets rich in forages provides an adequate environment for producing high proportion of acetate. While diets rich in grains, favors the production of propionate. Through hepatic gluconeogenesis, propionate is converted into glucose that can be used as carbon sources for many processes. For lipid synthesis, the subcutaneous adipose tissue primarily uses acetate, while the intramuscular adipose tissue uses high proportion of glucose (provided by propionate in ruminants) (Smith et al., 2018). Although intramuscular fat is a desirable meat quality parameter and can be obtained through feed strategies, the achievement of this fat depot without the enhancement in other fat depots remains a challenge (Du et al., 2013).

Another important factor that affects meat quality traits is the energy metabolism of a muscle fiber. Muscle fibers are classified by their contractile and metabolic properties. Type I fibers are characterized by the slow speed of contraction, the oxidative (aerobic) metabolism, which uses fat as the main energy source, possessing a great amount of mitochondria, and are rich in myoglobin that confers red color to the meat (Listrat

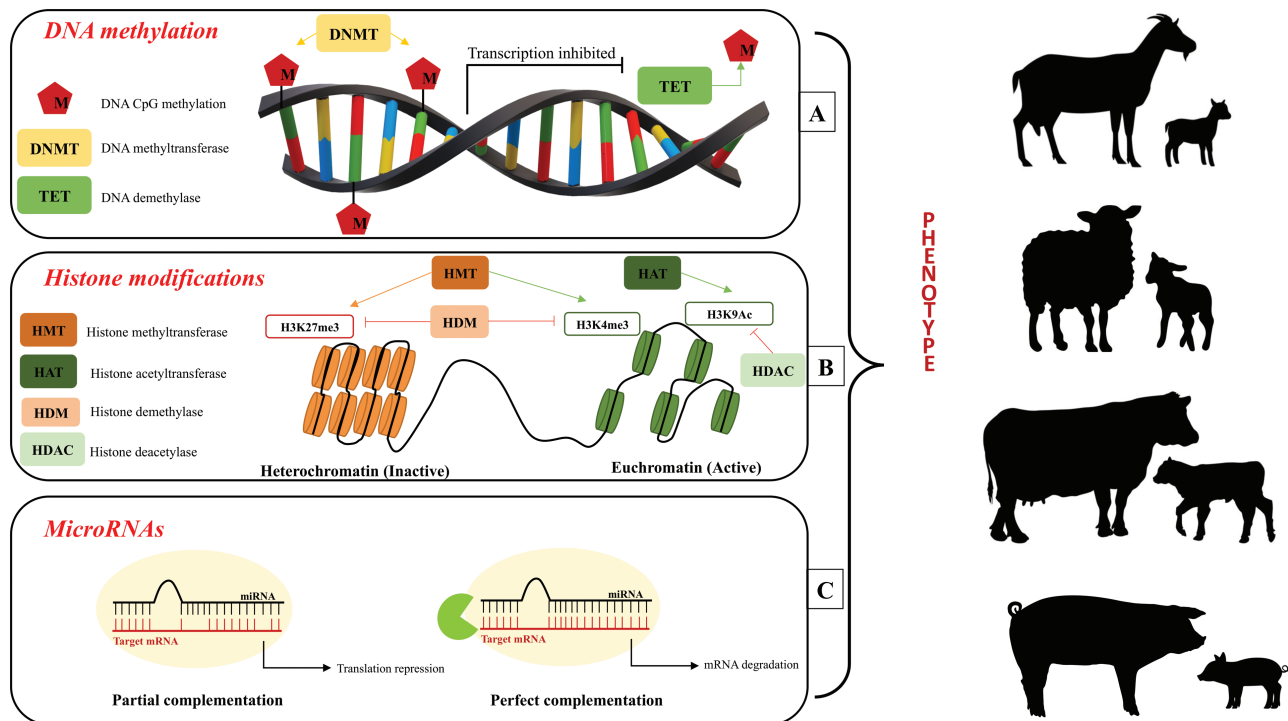
et al., 2016). Based on the greater abundance of intracellular lipid stores, accompanied by the more active hormone-sensitive lipase (HSL) and the efficiency in trans-sarcolemmal transport in type I muscle fibers, there is a greater utilization of free fatty acid, favoring the fat accumulation in comparison with type 2 fibers (for review see: Schiaffino and Reggiani, 2011). Moreover, type I muscle fiber has increased insulin sensitivity, greater capacity of fatty acid uptake, and triglyceride storage (Dyck et al., 1997). Evaluating the correlation of muscle fiber type and meat quality parameter of beef cattle, Joo et al. (2017) reported a positive correlation between intramuscular fat, fiber number percentage, and fiber area percentage of type I muscle fiber compared with type II, demonstrating that muscle fiber type is an important factor that contributes to fat accumulation.

Type II muscle fibers are classified as fibers with fast speed contraction, which uses glucose as the main energy source, and have low myoglobin content, making meat with a white color (Listrat et al., 2016). Besides the meat color, the type of muscle fibers also influences meat tenderness and water holding capacity (Ryu and Kim, 2005). Moreover, the relative proportion of these muscle fiber types varies depending on species, muscle function, breed, gender, age, among others. Genetic selection for increased muscle mass favors the establishment of greater proportion of type II fibers in nonruminant animals (Hocquette et al., 1998). Increased number of fast (type II) muscle fibers were observed in 14-d-old lambs born from ewes fed restricted during the 30 to 70 d of gestation, regardless the sex of the offspring, and consequently, increased lean:fat ratio was also observed (Daniel et al., 2007), impairing fat deposition.

### **Epigenetic regulating muscle growth and development**

Epigenetic is defined as heritable changes in gene expression that may cause phenotypic differences, without changing the DNA sequence. The epigenetic mechanism is very sensitive for nutritional changes, and includes, but is not restricted to, DNA methylation, histone modifications, and noncoding RNAs (Figure 2).

The DNA methylation consists of the inclusion of a methyl group on the 5' position of the cytosine residues located at the CpG islands in the promoter region of the gene, blocking the transcription factor to bind and consequently causing gene transcription repression. The enzymes DNA methyltransferases (DNMT) catalyzes the transfer of a methyl group from the methyl donor S-adenosylmethionine (SAM), synthesized in the methionine cycle from several dietary precursors. In contrast, the  $\alpha$ -ketoglutarate ( $\alpha$ -KG) dependent ten-eleven translocation (TET) family of proteins catalyzes the demethylation and reverting the gene transcriptional silencing. In a maternal obesity model, Yang et al. (2013) reported the enhancement in the expression of the early adipogenic marker *Zfp423* in fetal tissues from obese mothers, regulated by the hypomethylation on the promoter region of this gene. Moreover, DNA methylation caused by nutrient restriction intervention can potentially and permanently influence muscle development. Evaluating



**Figure 2.** Influence of epigenetic marks on livestock phenotype. (A) DNA methylation in CpG islands catalyzed by enzymes DNA methyltransferases (DNMTs) leads to gene silencing, which can be reverted by DNA demethylases, represented by the enzyme ten-eleven translocation (TET). (B) Histone modification influencing the chromatin structure. The mark H3K27me3 result in a condensed chromatin (heterochromatin) and consequently gene silencing, while the marks H3K4me3 and H3K9Ac result in an unpacked chromatin (euchromatin) facilitating transcriptional factors to bind and proceed gene transcription. HMTs and HATs transfer the methyl and acetyl group to the residues of amino acids in the histone tails, respectively. While HDM and HDAC remove the methyl and acetyl group, respectively. (C) Inhibitory role of microRNAs (miRNAs) on the target mRNA. In case of imperfect base pairing with the target mRNA, miRNAs aim to inhibit translation and consequently protein synthesis, while the perfect complementation cause the degradation of the target mRNA.

maternal nutrient restriction during mid-to-late gestation in ewes, [Paradis et al. \(2017\)](#) observed that the skeletal muscle from the maternal nutrient restricted offspring presented hypermethylation levels in the promoter region of *IGF2*, which is an important inducer of cell differentiation.

The histones proteins are responsible for packing the genomic DNA and thus forming the chromatin structure. The N-terminal tails of histone are target of several posttranslational modification (PTM), including acetylation, methylation, phosphorylation, among others. The combination of different PTM in a determined histone can be called histone code. Depending on the histone code, responses of gene transcription or gene silencing will be activated. These modifications directly affect the chromatin structure, taking over the structure of heterochromatin or euchromatin, associated with a compacted (repressing gene expressing) and relaxed (activating gene expressing) state, respectively. The marker histone 3 lysine 27 trimethylation (H3K27me3) is associated with gene silencing and is catalyzed by the Polycomb repressive complex 2 (PCR2). Maternal obesity triggered the decrease in the modification H3K27me3 in fetal mice tissues, resulting in the repression of gene transcription, which combined with the decrease in the DNA methylation in the promoter region of *Zfp423*, enhanced adipogenesis ([Yang et al., 2013](#)). In contrast to the H3K27me3 modification that causes gene silencing, the marks histone 3 lysine 9 acetylation

(H3K9Ac) and the histone 3 lysine 4 trimethylation (H3K4me3) activates gene transcription ([Jia et al., 2016](#)). Throughout the increase in H3K9Ac and H3K4me3 in the promoter region of myostatin, its expression was enhanced in the skeletal muscle of the offspring from maternal fed low protein diets during pregnancy and lactation ([Jia et al., 2016](#)), implying in reduction in muscle mass and muscle fiber size.

MicroRNAs (miRNAs) are single-strand RNAs belonging to the class of small noncoding RNAs, playing roles inhibiting gene expression post-transcriptionally. The inhibitory mechanisms of the miRNAs involve base pairing with the targeted mRNA and cause distinct types of repression, such as blocking the translation, and recruiting complexes to degrade the target mRNA. It has been shown that obesogenic diets during ewe's gestation contributes to the decrease in the expression of the miRNA *let-7g* in fetal muscle, which contribute to enhancing the expression of adipogenic markers and the number of adipocytes ([Yan et al., 2013](#)). Similarly, pro-adipogenic miRNAs (miR-103 and miR-21) were upregulated, while the anti-adipogenic miRNA (miR-34a) was downregulated in the skeletal muscle of calves resulting from cows submitted to a medium plan of nutrition during late-gestation ([Moisá et al., 2016](#)), implying in a possible increase in the adipogenic potential throughout the progeny life.

## Fetal Programming and the Efficiency for the Deposition of Muscle and Fat

### *Muscle fiber number, size, and composition*

As previously mentioned, the potential of muscle growth is based on adequate formation of muscle fibers during the pre-natal period, since there is no increase in muscle fiber number postnatally. The nutrient delivery for embryonic and fetal development is exclusively provided by the dam and therefore assured by a sufficient maternal nutrition. For pregnant ruminants raised in pasture, feed restriction due to forage seasonality may impair the development of the offspring. Under this situation, maternal nutrients are prioritized for the formation of fetal vital tissues instead of secondary tissues, such as skeletal muscle, reducing meat production efficiency. The impairment caused by maternal protein restriction in beef cattle during mid-gestation, imply in a long-lasting reduction of muscle fiber number in the offspring, in addition to alter muscle metabolism to greater proportion of glycolytic type of fiber early in life, which can be reverted depending on the postnatal environment (Costa et al., 2021a). Similarly, the energy restriction during late gestation contributes to the downregulation of genes involved in the oxidative metabolism, and consequently favoring the less efficient glycolytic metabolism in the skeletal muscle of calves (Sanglard et al., 2018). Although no phenotypic differences were observed in the skeletal muscle of the newborn goats, resulting from maternal feed restriction at different stages of gestation (Costa et al., 2019), the skeletal muscle transcriptome profile was altered, resulting in differentially expressed genes that are involved with skeletal muscle development and energy metabolism (Costa et al., 2021b).

In order to solve or nutrient restriction issues, strategies of supplementation during certain periods of gestation may represent an alternative to improve the offspring's skeletal muscle development, in addition to maintain the balance in maternal metabolism. For example, maternal protein supplementation during mid-gestation in cows tends to increase the pregnancy rate in the subsequent breeding season (Rodrigues et al., 2021), while the supplementation during late gestation reduced maternal tissues mobilization (Lopes et al., 2020), and may improve cows' reproductive parameters. Although the costs of supplement are relatively high in a livestock production system, an alternative for decrease the feeding and labor costs may be achieved by reducing the frequency of energy-protein supplementation during prepartum, without causing negative effects in maternal performance and metabolism (Moura et al., 2020).

Regarding the effects of maternal protein supplementation during different stages of gestation on the offspring's performance, Marquez et al. (2017) reported an increased in the number muscle fibers when the supplementation was applied during mid-gestation, and despite the lack of difference in body weight, calves born from protein supplemented dams during mid or late gestation presented greater ribeye area, and consequently improved the postnatal performance. Moreover, protein supplementation during mid-gestation for cows may increase offspring's body weight at birth and provide greater adipogenic



**Photo 2.** Representative image of a male Brahman calf (*Bos indicus*) that was an outcome of a fetal programming trial comparing the effects of maternal supplementation with ruminal degradable and undegradable protein. The trial results are under analyses by the Muscle Biology and Nutrigenomics research group at the Federal University of Viçosa (data not published).

potential in their skeletal muscle (Rodrigues et al., 2021). Taken together, these recent findings show that nutrient supplementation during gestation, ensure the adequate fetal development and, consequently, define the postnatal performance.

### *Meat marbling and tenderness*

The intramuscular fat or marbling is an important parameter that influences meat quality, affecting taste, juiciness, tenderness, and aggregate economic value to the final product. The selection of breeds for lean growth, leded the impairment in the intramuscular fat deposition and consequently reduced the desired marbling of the meat. Moreover, attempting to increase intramuscular fat without increasing the overall body fat accumulation remains challenging for beef producers (Du et al., 2013). The other factor accounting for meat quality is tenderness, which is mainly influenced by the combination of collagen fibrils and the intermolecular cross-linking in the connective tissue, conferring the background toughness of the meat (Zhao et al., 2019).

Both under and overnutrition during pregnancy affects adipogenesis and fibrogenesis and may alter fat deposition potential postnatally, defining the final carcass marbling and the overall composition. Maternal protein restriction during mid-gestation caused a reduction in the intramuscular collagen content in calves' skeletal muscle early in life, in addition to an inefficient collagen remodeling at the finishing phase (Costa et al., 2021a). Overnutrition during mid-gestation may also affect the skeletal muscle adipogenesis, by increasing the expression of adipogenic markers and tended to increase the expression of the fibrogenic marker (COL1) in the skeletal muscle of the crossbred (beef and dairy breeds) fetuses (Gionbelli et al., 2018). In addition, evaluating the effects of maternal overnutrition during different time points of gestation, Duarte et al. (2014) reported the enhancement in the adipogenic markers accompanied by the

accumulation of intramuscular collagen in the fetuses' skeletal muscle from overnourished cows.

Due to the presence of fibro-adipogenic progenitor cells in postnatal period, diet intervention in this period may slightly contribute to improve marbling and tenderness. Feeding cull cows with high-energy diets tended to increase the intramuscular fat content and contributed to increase meat tenderness (Fontes et al., 2021). In contrast, feeding beef cattle with vitamin A during the fattening phase, impaired the lipid biosynthesis in the skeletal muscle and consequently decreased the intramuscular fat deposition (Campos et al., 2020), negatively contributing to meat quality parameters.

Not only dietary interventions may affect the intramuscular fat deposition potential, but also the animal's breed attributes. Comparing distinct beef cattle breeds, Duarte et al. (2013b) showed that the high potential of marbling in Wagyu cattle is accompanied by the enhancement in connective tissue, possibly due to greater abundance of fibro-adipogenic progenitor cells compared with Angus cattle. Similarly, the abundance of fibro-adipogenic progenitor cells may account for difference between Angus and Nellore cattle in marbling fat development. Due to high proportion of these cells, Angus present higher adipogenic potential than Nellore cattle, while the fibrogenesis is not different between these breeds (Martins et al., 2015), which could explain a high level of marbling in Angus.

## Conclusions and Prospects

The embryonic and fetal stages are crucial for the formation of muscle fibers, adipose, and connective tissues. Understanding the specific stages of gestation that affects the final offspring's carcass composition helps to improve beef production efficiency and meat quality. Maternal nutrition during gestation may alter muscle fiber composition and the lean:fat ratio, leading to the production of a desirable body composition. Marbling and tenderness are critical quality characteristics of the meat. The combination of maternal nutrition and postnatal supplementation in a so-called marbling window can result in the elevated number of intramuscular fat cells, leading to more marbled carcasses.

Despite the increasing number of studies and data generated from trials evaluating the effects of maternal nutrition on offspring's development and meat quality, some divergences are still found, possibly due to the time period of nutrient intervention, type of intervention (diet or nutrient specific), breed, multiple pregnancy in case of sheep and goats, and fetal sex. The integration of these data through systematic review and meta-analysis would improve the future practical decision in the field. Moreover, there is a lack of studies on epigenetic mechanisms regarding intrauterine manipulation in ruminant animals. The development of these studies, combined with other omics tools in a system biology, would be beneficial for the establishment of epigenetic biomarkers for meat quality traits and the overall knowledge of cellular mechanisms involved.

## About the Authors



**Thais Correia Costa** is an Animal Scientist and a PhD student in the Department of Animal Science at the Federal University of Viçosa (UFV), Brazil. She earned her B.S. at the Sao Paulo State University (UNESP-Botucatu), Brazil, and a M.S. at the Federal University of Viçosa (UFV), Brazil. Her research focuses on maternal nutrition, ruminant nutrition and production and fetal programming. The main objectives of her

current research are to understand how maternal nutrition (restriction and supplementation) affects the development of the skeletal muscle of the progeny, and the molecular mechanisms behind it. During a year (2020–2021) she was a visiting scholar at Washington State University (WSU) and developed part of her thesis experiments at Nutrigenomic and Growth Biology Laboratory at WSU.

**Dr. Mateus Pies Gionbelli** is currently an Assistant Professor and Director of Graduate Studies in the Department of Animal Science at the University of Lavras (UFLA), Brazil. He earned his B.S. in Animal Science at Santa Catarina State University and his M.S. and Ph.D. from the University of Viçosa, in Brazil. During his Ph.D. he was a visiting scholar in the USDA/MARC, Clay Center, NE. Upon arrival at UFLA, in 2014, he established a



research program focused on maternal nutrition and fetal programming in ruminant animals, where he studies the quantitative, nutritional, and physiological aspects of gestation and lactation in beef cows. His program has been well funded by the Brazilian National Council for Scientific and Technological Development (CNPq), Minas Gerais Research Funding Foundation (FAPEMIG), Coordination for the Improvement of Higher Education Personnel (CAPES), and Industry Companies. In 2020 he was one of the recipients of the Roullier Innovation Awards in a joint fetal programming project with Dr. Duarte. He is very active in teaching and mentoring graduate and undergraduate students.



**Marcio de Souza Duarte** is currently an Assistant Professor at Federal University of Viçosa (UFV). He earned his M.S. (2010) and Ph.D. (2013) in Animal Science with a focus on Meat Science and Muscle Biology at UFV. In 2017, he became a Research Leader of the Muscle Biology and Meat Quality Research Group from the Brazilian National Institute of Science and Technology in Animal Science (INCT-CA). His

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