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# Fetal programming of skeletal muscle development in ruminant animals<sup>1</sup>

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**ABSTRACT:** Enhancing skeletal muscle growth is crucial for animal agriculture because skeletal muscle provides meat for human consumption. An increasing body of evidence shows that the level of maternal nutrition alters fetal skeletal muscle development, with long-term effects on offspring growth and performance. Fetal skeletal muscle development mainly involves myogenesis (i.e., muscle cell development), but also involves adipogenesis (i.e., adipocyte development) and fibrogenesis (i.e., fibroblast development). These tissues in fetal muscle are mainly derived from mesenchymal stem cells (MSC). Shifting the commitment of MSC from myogenesis to adipogenesis increases intramuscular fat

(i.e., marbling), improving the quality grade of meats. Strong experimental evidence indicates that Wingless and Int (Wnt)/ $\beta$ -catenin signaling regulates MSC differentiation. Upregulation of Wnt/ $\beta$ -catenin promotes myogenesis, and downregulation enhances adipogenesis. A lack of nutrients in early to midgestation reduces the formation of secondary muscle fibers in ruminant animals. Nutrient deficiency during mid- to late gestation decreases the number of intramuscular adipocytes and muscle fiber sizes. Knowledge of this regulatory mechanism will allow the development of strategies to enhance muscle growth and marbling in offspring, especially in the setting of nutrient deficiency.

**Key words:** adipogenesis, cattle, fetus, mesenchymal stem cell, myogenesis, skeletal muscle

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## INTRODUCTION

The concept of fetal programming originally developed from human epidemiological data linking low birth weight and poor maternal nutrition to an increased incidence of adult diseases, such as coronary heart diseases, stroke, diabetes, and hypertension (Barker et al., 2002). Fetal programming, also called developmental programming or fetal developmental programming, is the response to a specific challenge to the mammalian organism during a critical developmental time window that alters the trajectory of development qualitatively,

quantitatively, or both, with resulting persistent effects (Nathanielsz et al., 2007). Studies linking fetal programming to animal performance in livestock and other experimental species were initiated fairly recently. In these studies, both malnutrition and overnutrition during gestation have been found to affect offspring growth performance (Bispham et al., 2003; Benyshek et al., 2004; Symonds et al., 2004; Desai et al., 2005; Fernandez-Twinn et al., 2005, 2006; Bieswal et al., 2006; King, 2006; Zambrano et al., 2006; Ford et al., 2007). Therefore, in addition to genetic background, proper fetal development is important to maximize the growth potential of animals.

Meat animals are raised for their skeletal muscle. The fetal stage is crucial for skeletal muscle development because there is no net increase in muscle fiber numbers after birth (Stickland, 1978; Zhu et al., 2004). Therefore, a decrease in the number of muscle fibers because of fetal programming permanently reduces muscle mass and negatively affects animal performance.

Marbling (i.e., intramuscular fat) is crucial for meat palatability, and fetal life is a major stage for generation of intramuscular adipocytes (Tong et al., 2008), which provide the sites for intramuscular fat accumulation or

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marbling formation during fattening. Thus, fetal programming also affects marbling in offspring cattle.

In this review, we summarize recent progress in the field of fetal programming of skeletal muscle development, focusing on myogenesis and intramuscular adipogenesis, as well as the effects of fetal programming on the growth performance and meat quality of offspring, and their implications for the beef cattle industry.

## DEVELOPMENTAL PROGRAMMING OF SKELETAL MUSCLE

### *Fetal Skeletal Muscle Development*

Skeletal muscle development is initiated during the embryonic stage (Cossu and Borello, 1999). A portion of mesenchymal stem cells commit to the myogenic lineage as a result of receiving signals from neighboring tissues (Kollias and McDermott, 2008). Signals such as Wingless and Int (**Wnt**) and Sonic hedgehog regulate expression of paired box (**Pax**) 3, Pax7, and Glioma-associated oncogene homolog 1 (**Gli**; Kassarduchosoy et al., 2005), which then initiate expression of myogenic regulatory factors (**MRF**; Munsterberg et al., 1995; Stern et al., 1995; Petropoulos and Skerjanc, 2002). During the embryonic stage, a portion of cells in the mesoderm first express Pax3 and Pax7, and then these cells express the MRF myogenic factor-5 (**Myf5**), and myogenic differentiation 1 (**MyoD**; Buckingham, 2001). Subsequently, the proliferating myoblasts undergo differentiation, a process that includes withdrawal from the cell cycle and expression of muscle-specific genes. Myoblasts also initiate the expression of another important MRF, myogenin, which is necessary for the formation of multinucleated myotubes. Together, the various MRF cooperate to regulate myogenesis, forming a mature muscle fiber (Keren et al., 2006; Kollias and McDermott, 2008).

Primary myofibers form during the initial stage of myogenesis in embryonic development (Figure 1). Secondary myofibers form during the second wave of myogenesis in the fetal stage (Figure 1) and account for the majority of skeletal muscle fibers (Beermann et al., 1978). Postnatal muscle growth is mainly due to an increase in muscle fiber size without forming new muscle fibers (Stickland, 1978; Karunaratne et al., 2005). Satellite cells are located between the basal lamina and the sarcolemma of the mature muscle fibers; their proliferation and fusion with existing muscle fibers are crucial for postnatal muscle growth (Kuang et al., 2007). Satellite cells are a group of cells with different degrees of myogenic commitment. A small percentage of these cells are multipotent and can differentiate into adipocytes or fibroblasts instead of myogenic cells (Aguiari et al., 2008; Kuang et al., 2008; Yablonka-Reuveni et al., 2008).

Because the majority of muscle fibers form during the fetal stage, muscle development during this stage

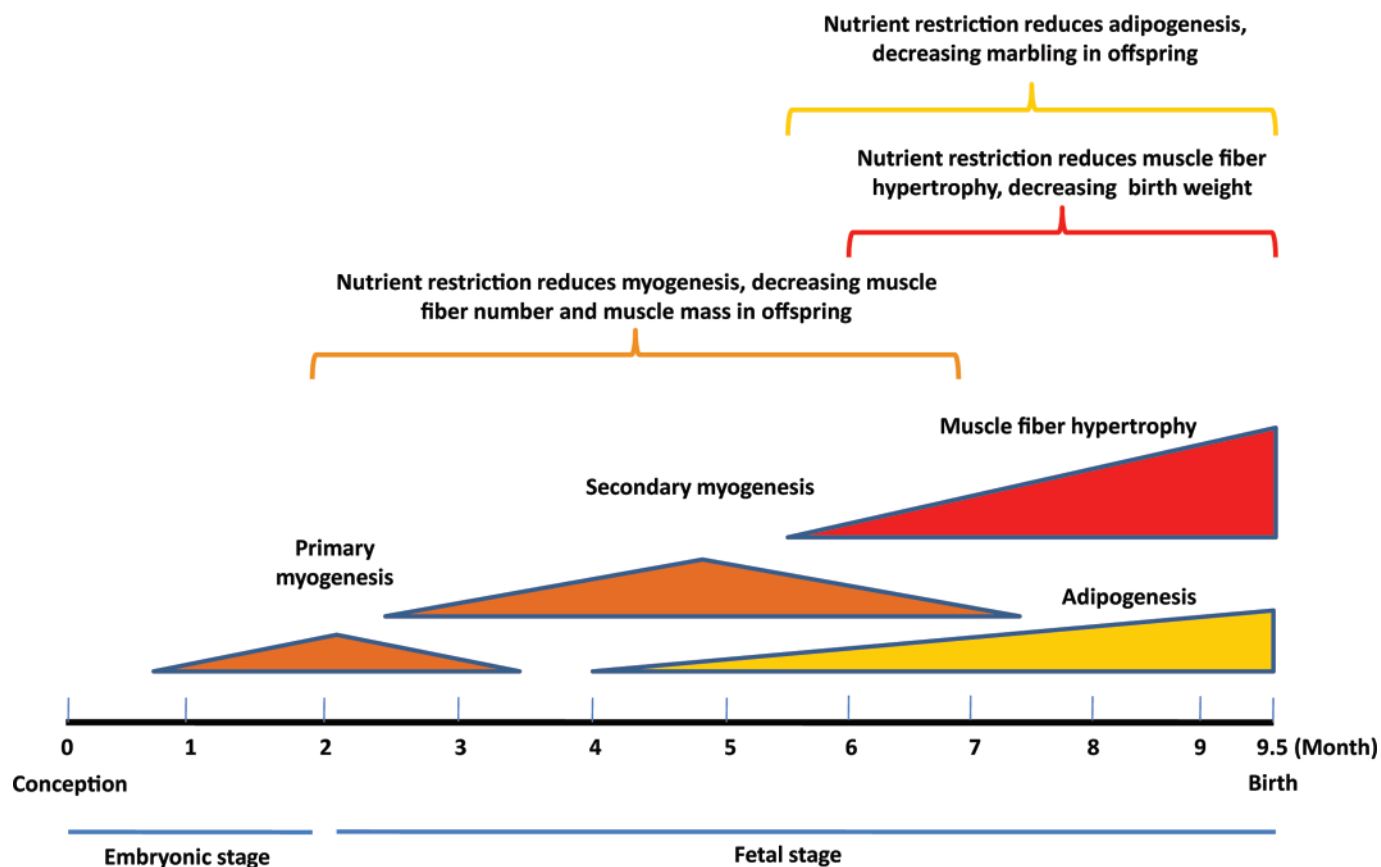
is vulnerable to many perturbations, including nutrient deficiency (Zhu et al., 2004). The formation of secondary myofibers partially overlaps with the formation of intramuscular adipocytes and fibroblasts. Together, these 3 cell types—myocytes, adipocytes, and fibroblasts—produce the basic structure of skeletal muscle. Because the majority of myocytes, adipocytes, and fibroblasts in fetal muscle are derived from the same pool of mesenchymal stem cells in fetal muscle, defining mechanisms regulating mesenchymal stem cell differentiation in fetal muscle is pivotal to improving animal production efficiency.

### *Fetal Developmental Programming of Skeletal Muscle Fiber Size, Number, and Type Composition*

Maternal nutrition programs fetal development, especially skeletal muscle development. Skeletal muscle has less of a priority in nutrient partitioning during fetal development when compared with organs such as the brain, heart, and liver. As a result, skeletal muscle development is particularly vulnerable to nutrient availability (Zhu et al., 2006).

In the bovine fetus, primary muscle fibers form within the first 2 mo postconception (Russell and Oteruelo, 1981). However, because only a very limited number of muscle fibers are formed during this stage, maternal nutrition in early development has negligible effects on fetal skeletal muscle development. Conversely, the majority of muscle fibers form in the fetal stage between 2 mo and 7 or 8 mo of gestation in cattle (Russell and Oteruelo, 1981), and a reduction in the formation of muscle fiber numbers during this stage has long-lasting, irreversible negative physiological consequences for offspring (Figure 1; Stannard and Johnson, 2004; Zambrano et al., 2005; Zhu et al., 2006). A restriction of nutrients to 50% of NRC requirements (NRC, 1985) from d 28 to d 78 of gestation in sheep was shown to reduce the total number of secondary muscle fibers, as well as the ratio of secondary to primary muscle fibers (Zhu et al., 2004). This observation was confirmed in a subsequent study (Quigley et al., 2005). As a consequence, the number of muscle fibers in 8-mo-old lambs born to nutrient-restricted mothers was less than that in control lambs (Zhu et al., 2006). In the pig, undernutrition in utero results in low birth weight and decreased numbers of muscle fibers (Dwyer et al., 1994). Similar results have been observed in guinea pigs (Ward and Stickland, 1991). These results clearly show that nutrient deficiency from early to midgestation in ruminant animals reduces muscle fiber number and muscle mass, negatively affecting the growth performance of offspring.

Skeletal muscle matures during late gestation in sheep (approximately d 105 of gestation) and cattle (approximately d 210 of gestation), and nutrient restriction after this stage has no major impact on muscle fiber



**Figure 1.** Effects of maternal nutrition on bovine fetal skeletal muscle development. The dates are estimated mainly based on data from studies in sheep, rodents, and humans and represent the progression through the various developmental stages. Nutrient restriction during midgestation reduces muscle fiber numbers, whereas restriction during late gestation reduces both muscle fiber sizes and the formation of intramuscular adipocytes.

number (Figure 1). Maternal nutrient restriction during late gestation reduces fetal sheep muscle fiber size, but not number (Greenwood et al., 1999). When the fetal muscle growth of sheep with single and twin pregnancies was compared, the competition between littermates for nutrients during late gestation was found to affect fetal skeletal muscle mass, but to limit only muscle fiber hypertrophy and not hyperplasia (McCoard et al., 2000). A low plane of maternal nutrition during the last two-thirds of pregnancy reduces neonatal calf BW (Freetly et al., 2000), likely as a result of a reduction in muscle fiber size, as well as fiber numbers.

### *The Fetal Stage Is the Most Efficient Stage to Increase Marbling in Beef Offspring*

Intramuscular fat (i.e., marbling) is crucial for the palatability of beef because marbling contributes to both flavor and juiciness. The amount of intramuscular fat is determined by the number and size of intramuscular adipocytes. As discussed previously, during the fetal stage both skeletal muscle cells and adipocytes are derived from the same pool of mesenchymal stem cells, from which the majority develop into myogenic cells. However, a small portion of these cells in fetal skeletal muscle differentiate into adipocytes, to form the sites

for intramuscular fat accumulation that produce the marbling in offspring (Tong et al., 2009). Adipogenesis is initiated around midgestation in ruminant animals (Feve, 2005; Gnanalingham et al., 2005; Muhlhauser et al., 2007), which overlaps with the period of secondary myogenesis (Figure 1). Thus, maternal nutritional management, which enhances the number of mesenchymal cells committed to adipogenesis, will increase the number of intramuscular adipocytes and thus marbling. This stage of fetal development is also associated with fibrogenesis. Fibroblasts developed during this stage synthesize connective tissue that forms the endomysium, perimysium, and epimysium in fetal skeletal muscle at late gestation. Until now, most studies regarding myogenesis have focused on primary myogenesis, whereas the mechanisms regulating the formation of secondary muscle fibers, adipocytes, and fibroblasts have been poorly studied. Considering the importance of intramuscular adipogenesis and fibrogenesis in marbling and connective tissue development, studies to understand their generation and development in fetal skeletal muscle are imperative.

Adipogenesis is regulated by several transcription factors, including C/EBP and PPAR $\gamma$ . During the first phase of adipogenesis, C/EBP $\alpha$  is induced and binds directly to the promoter of PPAR $\gamma$  to induce its ex-

pression (Clarke et al., 1997; Wu et al., 1999). The expression of PPAR $\gamma$  further promotes the expression of C/EBP $\alpha$ , providing a self-reinforcing regulatory loop. Terminal differentiation of an adipocyte requires the concerted action of PPAR $\gamma$  and C/EBP. Peroxisome proliferator-activated receptor  $\gamma$ , but not C/EBP $\alpha$  alone, can stimulate adipocyte differentiation (Rosen et al., 2002). The basic helix-loop-helix protein, adipocyte determination and differentiation-dependent factor 1/sterol regulatory element-binding protein 1, is another important protein induced during the early stages of adipogenesis (Kim and Spiegelman, 1996). This protein can enhance the activity of PPAR $\gamma$  through binding to the response element of PPAR $\gamma$ 1 and PPAR $\gamma$ 2 promoters. Activation of PPAR $\gamma$  promotes terminal differentiation through the induction of a range of genes important for triglyceride uptake and storage, such as fatty acid-binding protein, acyl-CoA synthetase, fatty acid transport protein-1, lipoprotein lipase, and others (Frohnert et al., 1999; Rosen and MacDougald, 2006).

Peroxisome proliferator-activated receptor  $\gamma$  is a ligand-activated transcriptional factor. Fatty acids are ligands for PPAR $\gamma$ . However, PPAR $\gamma$  is less responsive to native fatty acids compared with other PPAR family members (Kliwer et al., 1995; Schopfer et al., 2005); oxidized fatty acids activate PPAR $\gamma$  with greater potency compared with the native fatty acids (Nagy et al., 1998). The potency of PPAR $\gamma$  also depends on the releasing or recruiting coactivators and corepressors. To date, no specific coactivators or corepressors for PPAR $\gamma$  have been identified, but many common coactivators and corepressors of the nuclear receptor family can regulate the activity of PPAR $\gamma$  (Castillo et al., 1999; Hummasti and Tontonoz, 2006). Peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 is an important, highly regulated coactivator that binds to PPAR $\gamma$  in a ligand-independent manner and is highly expressed in brown fat cells compared with white fat cells (Puigserver et al., 1998).

Maternal nutrition affects adipogenesis within fetal skeletal muscle. We have demonstrated that overnourishment of pregnant ewes by feeding 150% of NRC nutrient requirements (NRC, 1985) enhances adipogenesis in fetal skeletal muscle (Tong et al., 2008, 2009). In another study, beef cattle were fed 100, 70, or 70% of NRC (2000) nutrient requirements plus supplementation of ruminal bypass protein from d 60 to 180 of gestation. The steer offspring of the cows fed the 70% nutrient requirement plus supplementation of proteins had numerically less marbling scores compared with steers whose dams were fed 100% of requirements, and the subcutaneous fat thickness was less ( $P < 0.05$ , K. R. Underwood, J. Tong, J. Zhao, M. Zhu, B. W. Hess, and M. Du, unpublished results). These data show not only that global nutrient availability alters adipogenesis, but also that individual nutrients, such as protein, program adipogenesis in fetal muscle.

A limited number of studies have also shown that maternal nutrition changes fibrogenesis in fetal skeletal

muscle and affects the collagen content in the skeletal muscle of progeny. Piglets with less birth weight compared with their littermates may have received fewer nutrients in utero than their littermates. When compared with their littermates, grown pigs that had a reduced birth weight had a greater content of collagen in their skeletal muscle (Karunaratne et al., 2005). Because collagen and connective tissue are the major contributors to the background toughness of meat, more studies on the associations among maternal nutrition, fibrogenesis, and collagen accumulation in offspring muscle are needed.

### *Long-Term Effect of Fetal Programming on Offspring*

Fetal programming has long-term effects on offspring performance. Lambs from dams subjected to nutrient restriction during midgestation were fatter and had a decreased lean-to-fat ratio compared with their counterparts (Zhu et al., 2006). Piglets with reduced birth weight were fatter and were less efficient at growth compared with normal littermates (Wigmore and Stickland, 1983).

In addition to muscle fiber numbers, muscle fiber type composition affects the growth potential of offspring. Type I myofibers have greater protein turnover rates and are less efficient for growth, whereas type II myofibers have reduced catabolic rates and exhibit greater growth efficiency (Therkildsen and Oksbjerg, 2009). In our study on the offspring of ewes that received 50% of NRC (1985) nutrient requirements from d 28 to 80 of gestation, the ratio of type IIx to type I myofibers was significantly increased in the skeletal muscle of lambs exposed to decreased maternal nutrition (Zhu et al., 2006). These findings have been confirmed independently (Daniel et al., 2007).

In addition to maternal undernutrition, maternal overnutrition programs fetal muscle development. Overfeeding of sows from conception to d 50 of gestation was shown to increase offspring fatness at birth, and the muscle fiber type composition of progeny was altered because of maternal nutritional management (Bee, 2004). Rats born to mothers fed a high-fat diet, either during gestation or during both gestation and lactation, exhibited a 25% reduction in muscle cross-sectional area, with approximately 20% fewer fibers compared with pups born to mothers fed a balanced chow diet (Bayol et al., 2005).

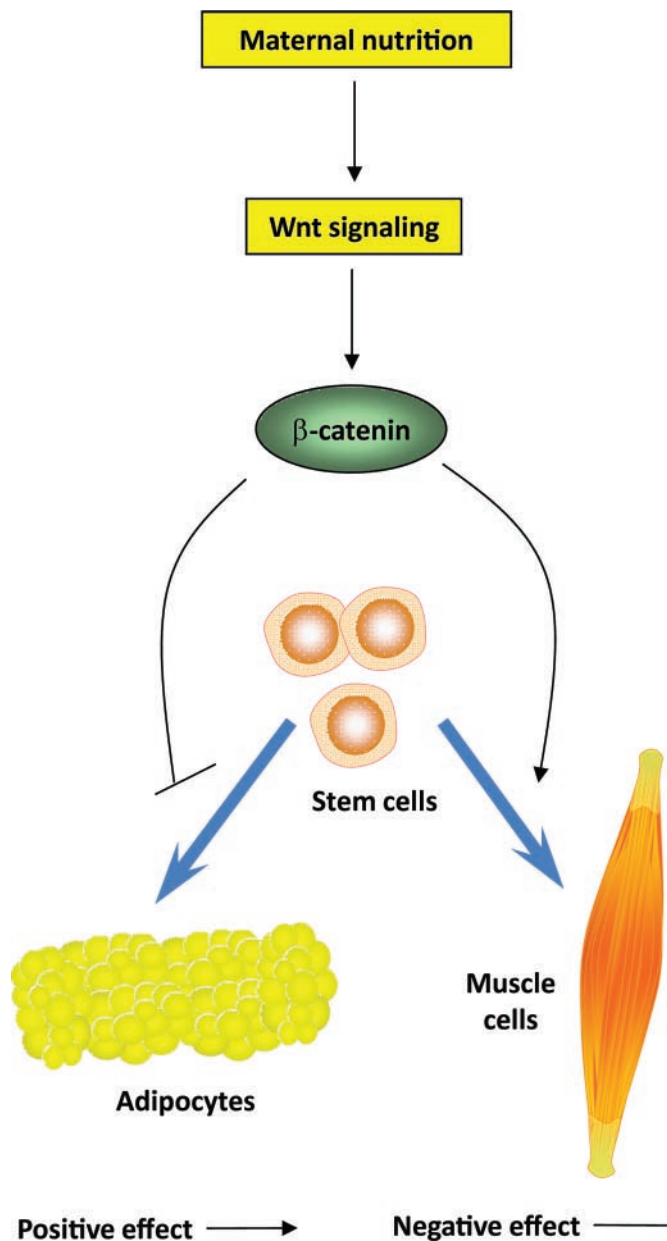
### **WNT SIGNALING AND FETAL SKELETAL MUSCLE PROGRAMMING**

The Wnt family of secreted glycoproteins acts through autocrine or paracrine mechanisms to influence the development of many cell types (Johnson and Rajamanan, 2006). Depending on the context, Wnt signals may cause cell proliferation, differentiation, or maintenance

of precursor cells (Novakofski, 2004). Currently, 19 Wnt genes have been described in vertebrates.

The canonical Wnt pathway, a  $\beta$ -catenin-dependent signaling pathway called the Wnt/ $\beta$ -catenin signaling pathway, is the most studied Wnt pathway (Huelsen and Birchmeier, 2001). Binding of Wnt to Frizzled proteins activates Disheveled “family” proteins. Disheveled, when activated by Wnt binding (Johnson and Rajamannan, 2006), inhibits a complex of proteins that includes axin, glycogen synthase kinase-3  $\beta$  (**GSK-3 $\beta$** ), and anaphase-promoting complex, leading to  $\beta$ -catenin accumulation (Polesskaya et al., 2003; Katanaev et al., 2005). Without Wnt stimulation, the axin/GSK-3 $\beta$ /anaphase-promoting complex promotes the degradation of the  $\beta$ -catenin through phosphorylation by the protein kinase GSK-3 $\beta$  (Liu et al., 2005). As a result of the inhibition of the “ $\beta$ -catenin destruction complex,” a pool of cytoplasmic  $\beta$ -catenin stabilizes, and some  $\beta$ -catenin enters the nucleus and interacts with members of the T-cell factor/lymphoid enhancer factor family of transcription factors to activate specific target genes (Dierick and Bejsovec, 1999; Hecht and Kemler, 2000). Therefore,  $\beta$ -catenin plays an essential role in the regulation of embryonic, postnatal, and oncogenic growth of many tissues (Armstrong and Esser, 2005; Mermelstein et al., 2007). In skeletal muscle,  $\beta$ -catenin regulates the expression of transcription factor Pax3, as well as Gli (Capdevila et al., 1998; Borycki et al., 2000). Paired box 3 is known to be essential for skeletal myogenesis and acts upstream of MyoD during skeletal muscle development, whereas Gli factors play an essential role in Myf5 expression (Ridgeway and Skerjanc, 2001; Gustafsson et al., 2002). The expression of MRF is controlled by signals such as Wnt and Sonic hedgehog (Munsterberg et al., 1995; Stern et al., 1995; Petropoulos and Skerjanc, 2002) via Pax3 and Pax7 (Kassar-Duchossoy et al., 2005). Blocking the  $\beta$ -catenin pathway reduces the total number of myocytes (Pan et al., 2005; Yamanouchi et al., 2007).

Adipogenesis is also under the control of Wnt signaling. The activity of PPAR $\gamma$  is regulated by GSK-3 $\beta$  and  $\beta$ -catenin of the Wnt signaling pathways (Moldes et al., 2003). If GSK-3 $\beta$  activity is attenuated, then  $\beta$ -catenin escapes proteasomal degradation, thereby inhibiting expression of PPAR $\gamma$  target genes (Okamura et al., 2009). In our previous study in which pregnant ewes were fed 150% of NRC (1985) nutrient requirements, the Wnt/ $\beta$ -catenin signaling was downregulated in fetal muscle from overnourished mothers, which should at least partially be responsible for the downregulation of myogenesis but upregulation of adipogenesis in fetal muscle (Tong et al., 2008; Zhu et al., 2008). Activation of the Wnt signaling pathway enhances myogenesis and inhibits adipogenesis in cultured mesenchymal stem cells derived from bone marrow (Figure 2; Shang et al., 2007). Additionally, Wnt signaling may have a role in the regulation of body fat distribution and, to a degree, susceptibility to obesity (Christodoulides et al., 2009). In summary, Wnt signaling is crucial for both myogene-



**Figure 2.** Wingless and Int (Wnt) signaling and fetal skeletal muscle development. Upregulation of Wnt signaling promotes myogenesis, whereas downregulation promotes adipogenesis.

sis and adipogenesis in fetal muscle (Figure 2). Because myogenesis occurs a little earlier than adipogenesis, it should be feasible to enhance both myogenesis and adipogenesis by enhancing Wnt signaling during early to midgestation, when myogenesis is occurring in ruminant animals, and by inhibiting Wnt signaling in late gestation, when adipogenesis is active.

## FETAL PROGRAMMING AND BEEF CATTLE PRODUCTION

Drought, resulting in a significant reduction in forage production, is common in Rocky Mountain states and many other areas in the United States and around the world (National Weather Service, 1988–1989; United

States Geological Survey, 2004). Because of the seasonal nature of cow reproduction, cows in these regions on forage-based production systems frequently experience nutrient deficiency during pregnancy because of limited forage availability on small farms and ranches, because of poor forage quality, and because nutritional supplementation is rarely used on small farms and ranches during early to midgestation (Thomas and Kott, 1995; Enk et al., 2001; Jensen et al., 2002). In contrast, nutrient supplementation of cows is often applied during late gestation (i.e., the final 60 to 90 d before calving; Hall, 1997). The limited availability of forage and its low protein content affect the overall production efficiency of ruminant animals. As discussed previously, periods of maternal nutrient deficiency during pregnancy program fetal skeletal muscle development, potentially reducing muscle fiber numbers and changing the marbling and fatness of offspring cattle.

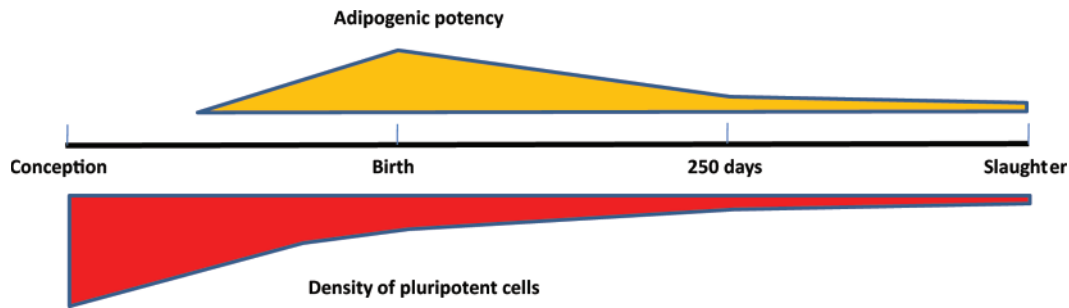
Nutrient supplementation of beef cows during early to midgestation has the potential to improve the muscle development and overall production efficiency of offspring. In a recent study, we demonstrated that protein supplementation from d 60 to 180 of gestation enhanced lean growth and the lean-to-fat ratio in offspring (K. R. Underwood, J. Tong, J. Zhao, M. Zhu, B. W. Hess, and M. Du, unpublished results). Another approach to enhance adipogenesis in fetal muscle is to improve pasture conditions. In a recent study, cows were assigned either to improved pasture ( $n = 8$ ) or to native range pasture ( $n = 7$ ) from 120 to 150 d through 180 to 210 d of gestation. The native range pasture had an average CP of 6.7% and the improved pasture, consisting of irrigated pastures with increased forage production, had an average CP of 8.9%. The chemical ether extract (i.e., fat content) of the LM at the 12th rib was increased ( $P = 0.06$ ) and adipose tissue cell numbers per field were greater ( $P = 0.09$ ) in the steers born to mothers grazing improved pasture compared with the steers born to cows maintained on native range pasture (Underwood et al., 2008). Although these results need to be confirmed and expanded, they indicate that intramuscular adipogenesis and marbling can be increased through improving the plane of nutrition during gestation—in this case, by improving pasture conditions.

Developmental programming can also be extended to the postnatal management of cattle, for example, to the production of grass-fed beef. Grass-fed beef contains greater ratios of unsaturated fatty acids, especially n-3 fatty acids, which are beneficial to human health (Mann et al., 2003; Ponnampalam et al., 2006). In addition, grass-fed beef is produced naturally and has minimal environmental impacts. As a result, interest in grass-fed beef by both consumers and producers is increasing nationwide. However, the poor flavor of grass-fed beef is the major problem hampering its wide acceptance (Mandell et al., 1998; Sitz et al., 2005). The flavor of beef steak mainly comes from intramuscular fat (i.e., marbling), and grass-fed beef lacks marbling,

which decreases the flavor derived from fat and reduces its juiciness. Therefore, if we can effectively enhance marbling in grass-fed beef, we can significantly improve its palatability, further expanding this segment of the beef industry.

Grass-fed beef cattle need to be fed a forage-based diet because it is not practical to use dietary grain supplementation to enhance marbling in this production management system. However, marbling is correlated with the number of adipocytes in skeletal muscle. Increased adipogenesis in fetal muscle leads to an increase in the number of intramuscular adipocytes. These intramuscular adipocytes accumulate fat during postnatal growth, forming marbling. Because grass-fed cattle are not fed a grain-based diet during “fattening” that induces adipocyte hypertrophy, it is less likely that adipocyte size will increase dramatically during the “finishing” phase of grass-fed cattle. Therefore, maternal nutritional management, to increase adipogenesis in fetal muscle, is an alternative and may be the only choice to enhance marbling in grass-fed beef cattle. Our preliminary studies have demonstrated that the fetal stage is crucial for the formation of intramuscular adipocytes, and their formation (i.e., adipogenesis) can be enhanced effectively through maternal nutritional supplementation (Tong et al., 2008). Because producers of grass-fed beef usually are also cow-calf operators, these producers are in a unique position to manage maternal nutrition to increase intramuscular fat in calves.

Nutritional management to enhance marbling in beef cattle will be more effective at earlier stages of development because of the presence of an abundant amount of multipotent cells in skeletal muscle, which wanes as animals mature (Du et al., 2009). Therefore, the effectiveness of nutritional management on altering marbling is fetal stage > neonatal stage > early weaning stage (i.e., 150 to 250 d of age) > weaning and older stages (Figure 3). After 250 d of age, nutritional supplementation becomes less effective in increasing the number of intramuscular adipocytes because of the depletion of multipotent cells, although the size of existing intramuscular adipocytes can be increased and is the major reason for the enhancement in marbling during fattening. Studies in humans show that after childhood, the total number of adipocytes is maintained at a relatively constant level (Spalding et al., 2008). Currently, the marbling window, or the period of time when nutritional management of cattle can enhance marbling, is between 150 and 250 d after birth, which corresponds to the early weaning stage (Wertz et al., 2001, 2002; Pyatt et al., 2005a,b; Corah and McCully, 2007). There are studies indicating that early weaning and feeding grain, especially a corn-based diet, increases marbling (Wertz et al., 2001, 2002; Pyatt et al., 2005a,b). Nutritional supplementation of calves earlier than 150 d of age is more difficult because calves are nursing and consuming significant quantities of milk during this time. On the other hand, fetal stages of development provide a unique, and perhaps the best,



**Figure 3.** Density of multipotent cells and adipogenic potency of bovine skeletal muscle. The dates are approximate and represent the progression through the various developmental stages. Adipogenesis is initiated around midgestation in ruminant animals and peaks near the term. The adipogenic potency gradually declines postnatally because of depletion of multipotent cells.

window for nutritional management. This is due to at least 3 advantages: 1) an abundant pool of multipotent cells exists in fetal muscle; 2) fetal nutrients are derived from the maternal circulation, allowing the potential for these increased maternal-supplemented nutrients to be transferred effectively to the fetus, thus promoting adipogenesis in fetal muscle; and 3) this stage is a very convenient one for cow-calf producers to manage their cows nutritionally.

### Conclusion

Available studies clearly show that maternal nutrition affects fetal skeletal muscle development, exerting long-term effects on the growth performance of offspring. Maternal undernutrition during fetal development reduces skeletal muscle fiber numbers, alters muscle fiber composition, increases fatness, and reduces the growth performance of progeny. Proper nutrient supplementation, however, improves fetal skeletal muscle development and adipogenesis in fetal skeletal muscle, thereby enhancing marbling in progeny. Wingless and *Int* signaling has a crucial role in regulating the differentiation of mesenchymal stem cells in fetal skeletal muscle into myocytes, adipocytes, and fibroblasts. Such differentiation involves a complex relationship with the level of maternal nutrition, which remains to be elucidated. Future studies should focus on identifying the underlying mechanisms associated with fetal programming of skeletal muscle development. For beef production, additional studies on maternal nutritional supplementation, especially gestation-stage-specific supplementation, on marbling and growth performance in offspring are likely to prove very beneficial in management to improve the growth efficiency of cattle and the eating quality of beef.

### LITERATURE CITED

Aguiari, P., S. Leo, B. Zavan, V. Vindigni, A. Rimessi, K. Bianchi, C. Franzin, R. Cortivo, M. Rossato, R. Vettor, G. Abatangelo, T. Pozzan, P. Pinton, and R. Rizzuto. 2008. High glucose induces adipogenic differentiation of muscle-derived stem cells. *Proc. Natl. Acad. Sci. USA* 105:1226–1231.

- Armstrong, D. D., and K. A. Esser. 2005. Wnt/ $\beta$ -catenin signaling activates growth-control genes during overload-induced skeletal muscle hypertrophy. *Am. J. Physiol. Cell Physiol.* 289:C853–C859.
- Barker, D. J., J. G. Eriksson, T. Forsen, and C. Osmond. 2002. Fetal origins of adult disease: Strength of effects and biological basis. *Int. J. Epidemiol.* 31:1235–1239.
- Bayol, S. A., B. H. Simbi, and N. C. Stickland. 2005. A maternal cafeteria diet during gestation and lactation promotes adiposity and impairs skeletal muscle development and metabolism in rat offspring at weaning. *J. Physiol.* 567:951–961.
- Bee, G. 2004. Effect of early gestation feeding, birth weight, and gender of progeny on muscle fiber characteristics of pigs at slaughter. *J. Anim. Sci.* 82:826–836.
- Biermann, D. H., R. G. Cassens, and G. J. Hausman. 1978. A second look at fiber type differentiation in porcine skeletal muscle. *J. Anim. Sci.* 46:125–132.
- Benyshek, D. C., C. S. Johnston, and J. F. Martin. 2004. Post-natal diet determines insulin resistance in fetally malnourished, low birthweight rats ( $F_1$ ) but diet does not modify the insulin resistance of their offspring ( $F_2$ ). *Life Sci.* 74:3033–3041.
- Bieswal, F., M. T. Ahn, B. Reusens, P. Holvoet, M. Raes, W. D. Rees, and C. Remacle. 2006. The importance of catch-up growth after early malnutrition for the programming of obesity in male rat. *Obesity (Silver Spring)* 14:1330–1343.
- Bispham, J., G. S. Gopalakrishnan, J. Dandrea, V. Wilson, H. Budge, D. H. Keisler, F. Broughton Pipkin, T. Stephenson, and M. E. Symonds. 2003. Maternal endocrine adaptation throughout pregnancy to nutritional manipulation: Consequences for maternal plasma leptin and cortisol and the programming of fetal adipose tissue development. *Endocrinology* 144:3575–3585.
- Borycki, A., A. M. Brown, and C. P. Emerson Jr. 2000. Shh and Wnt signaling pathways converge to control *Gli* gene activation in avian somites. *Development* 127:2075–2087.
- Buckingham, M. 2001. Skeletal muscle formation in vertebrates. *Curr. Opin. Genet. Dev.* 11:440–448.
- Capdevila, J., C. Tabin, and R. L. Johnson. 1998. Control of dorsoventral somite patterning by Wnt-1 and  $\beta$ -catenin. *Dev. Biol.* 193:182–194.
- Castillo, G., R. P. Brun, J. K. Rosenfield, S. Hauser, C. W. Park, A. E. Troy, M. E. Wright, and B. M. Spiegelman. 1999. An adipogenic cofactor bound by the differentiation domain of PPAR $\gamma$ . *EMBO J.* 18:3676–3687.
- Christodoulides, C., C. Lagathu, J. K. Sethi, and A. Vidal-Puig. 2009. Adipogenesis and Wnt signalling. *Trends Endocrinol. Metab.* 20:16–24.
- Clarke, S. L., C. E. Robinson, and J. M. Gimble. 1997. CAAT/enhancer binding proteins directly modulate transcription from the peroxisome proliferator-activated receptor  $\gamma$  2 promoter. *Biochem. Biophys. Res. Commun.* 240:99–103.
- Corah, L., and M. McCully. 2007. Declining quality grades: A review of factors reducing marbling deposition in beef cattle. *Certified Angus Beef News Releases-Research*. <http://www.cabpartners.com>



- com/news/research/declining\_quality\_grades.pdf Accessed Sep. 24, 2009.
- Cossu, G., and U. Borello. 1999. Wnt signaling and the activation of myogenesis in mammals. *EMBO J.* 18:6867–6872.
- Daniel, Z. C., J. M. Brameld, J. Craigon, N. D. Scollan, and P. J. Buttery. 2007. Effect of maternal dietary restriction during pregnancy on lamb carcass characteristics and muscle fiber composition. *J. Anim. Sci.* 85:1565–1576.
- Desai, M., D. Gayle, J. Babu, and M. G. Ross. 2005. Programmed obesity in intrauterine growth-restricted newborns: Modulation by newborn nutrition. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288:R91–R96.
- Dierick, H., and A. Bejsovec. 1999. Cellular mechanisms of Wingless/Wnt signal transduction. *Curr. Top. Dev. Biol.* 43:153–190.
- Du, M., X. Yan, J. F. Tong, J. Zhao, and M. J. Zhu. 2009. Maternal obesity, inflammation, and fetal skeletal muscle development. *Biol. Reprod.* In press.
- Dwyer, C. M., N. C. Stickland, and J. M. Fletcher. 1994. The influence of maternal nutrition on muscle fiber number development in the porcine fetus and on subsequent postnatal growth. *J. Anim. Sci.* 72:911–917.
- Enk, T. A., H. D. Picton, and J. S. Williams. 2001. Factors limiting a bighorn sheep population in Montana following a dieoff. *Northwest Sci.* 75:280–291.
- Fernandez-Twinn, D. S., S. Ekizoglou, A. Wayman, C. J. Petry, and S. E. Ozanne. 2006. Maternal low-protein diet programs cardiac  $\beta$ -adrenergic response and signaling in 3-mo-old male offspring. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 291:R429–R436.
- Fernandez-Twinn, D. S., A. Wayman, S. Ekizoglou, M. S. Martin, C. N. Hales, and S. E. Ozanne. 2005. Maternal protein restriction leads to hyperinsulinemia and reduced insulin-signaling protein expression in 21-mo-old female rat offspring. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288:R368–R373.
- Feve, B. 2005. Adipogenesis: Cellular and molecular aspects. *Best Pract. Res. Clin. Endocrinol. Metab.* 19:483–499.
- Ford, S. P., B. W. Hess, M. M. Schwoppe, M. J. Nijland, J. S. Gilbert, K. A. Vonnahme, W. J. Means, H. Han, and P. W. Nathanielsz. 2007. Maternal undernutrition during early to mid-gestation in the ewe results in altered growth, adiposity, and glucose tolerance in male offspring. *J. Anim. Sci.* 85:1285–1294.
- Freetly, H. C., C. L. Ferrell, and T. G. Jenkins. 2000. Timing of realimentation of mature cows that were feed-restricted during pregnancy influences calf birth weights and growth rates. *J. Anim. Sci.* 78:2790–2796.
- Frohnert, B. L., T. Y. Hui, and D. A. Bernlohr. 1999. Identification of a functional peroxisome proliferator-responsive element in the murine fatty acid transport protein gene. *J. Biol. Chem.* 274:3970–3977.
- Gnanalingham, M. G., A. Mostyn, M. E. Symonds, and T. Stephenson. 2005. Ontogeny and nutritional programming of adiposity in sheep: Potential role of glucocorticoid action and uncoupling protein-2. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 289:R1407–R1415.
- Greenwood, P. L., R. M. Slepatis, J. W. Hermanson, and A. W. Bell. 1999. Intrauterine growth retardation is associated with reduced cell cycle activity, but not myofibre number, in ovine fetal muscle. *Reprod. Fertil. Dev.* 11:281–291.
- Gustafsson, M. K., H. Pan, D. F. Pinney, Y. Liu, A. Lewandowski, D. J. Epstein, and C. P. Emerson Jr.. 2002. Myf5 is a direct target of long-range Shh signaling and Gli regulation for muscle specification. *Genes Dev.* 16:114–126.
- Hall, J. B. 1997. The cow-calf manager: Winter feeding and supplements, Virginia Polytechnic Inst. State Univ., Blacksburg.
- Hecht, A., and R. Kemler. 2000. Curbing the nuclear activities of  $\beta$ -catenin. Control over Wnt target gene expression. *EMBO Rep.* 1:24–28.
- Huelsken, J., and W. Birchmeier. 2001. New aspects of Wnt signaling pathways in higher vertebrates. *Curr. Opin. Genet. Dev.* 11:547–553.
- Hummasti, S., and P. Tontonoz. 2006. The peroxisome proliferator-activated receptor N-terminal domain controls isotype-selective gene expression and adipogenesis. *Mol. Endocrinol.* 20:1261–1275.
- Jensen, K. B., D. A. Johnson, K. H. Asay, and K. C. Olson. 2002. Seasonal-accumulated growth and forage quality of range grasses for fall and winter grazing. *Can. J. Plant Sci.* 82:329–336.
- Johnson, M. L., and N. Rajamannan. 2006. Diseases of Wnt signaling. *Rev. Endocr. Metab. Disord.* 7:41–49.
- Karunaratne, J. F., C. J. Ashton, and N. C. Stickland. 2005. Fetal programming of fat and collagen in porcine skeletal muscles. *J. Anat.* 207:763–768.
- Kassar-Duchossoy, L., E. Giacone, B. Gayraud-Morel, A. Jory, D. Gomes, and S. Tajbakhsh. 2005. Pax3/Pax7 mark a novel population of primitive myogenic cells during development. *Genes Dev.* 19:1426–1431.
- Katanaev, V. L., R. Ponzelli, M. Semeriva, and A. Tomlinson. 2005. Trimeric G protein-dependent frizzled signaling in drosophila. *Cell* 120:111–122.
- Keren, A., Y. Tamir, and E. Bengal. 2006. The p38 MAPK signaling pathway: A major regulator of skeletal muscle development. *Mol. Cell. Endocrinol.* 252:224–230.
- Kim, J. B., and B. M. Spiegelman. 1996. ADD1/SREBP1 promotes adipocyte differentiation and gene expression linked to fatty acid metabolism. *Genes Dev.* 10:1096–1107.
- King, J. C. 2006. Maternal obesity, metabolism, and pregnancy outcomes. *Annu. Rev. Nutr.* 26:271–291.
- Kliwer, S. A., J. M. Lenhard, T. M. Willson, I. Patel, D. C. Morris, and J. M. Lehmann. 1995. A prostaglandin J<sub>2</sub> metabolite binds peroxisome proliferator-activated receptor  $\gamma$  and promotes adipocyte differentiation. *Cell* 83:813–819.
- Kollias, H. D., and J. C. McDermott. 2008. Transforming growth factor- $\beta$  and myostatin signaling in skeletal muscle. *J. Appl. Physiol.* 104:579–587.
- Kuang, S., M. A. Gillespie, and M. A. Rudnicki. 2008. Niche regulation of muscle satellite cell self-renewal and differentiation. *Cell Stem Cell* 2:22–31.
- Kuang, S., K. Kuroda, F. Le Grand, and M. A. Rudnicki. 2007. Asymmetric self-renewal and commitment of satellite stem cells in muscle. *Cell* 129:999–1010.
- Liu, X., J. S. Rubin, and A. R. Kimmel. 2005. Rapid, Wnt-induced changes in GSK3 $\beta$  associations that regulate  $\beta$ -catenin stabilization are mediated by G $\alpha$  proteins. *Curr. Biol.* 15:1989–1997.
- Mandell, I. B., J. G. Buchanan-Smith, and C. P. Campbell. 1998. Effects of forage vs. grain feeding on carcass characteristics, fatty acid composition, and beef quality in Limousin-cross steers when time on feed is controlled. *J. Anim. Sci.* 76:2619–2630.
- Mann, N. J., E. N. Ponnampalam, Y. Yep, and A. J. Sinclair. 2003. Feeding regimens affect fatty acid composition in Australian beef cattle. *Asia Pac. J. Clin. Nutr.* 12(Suppl.):S38.
- McCoard, S. A., W. C. McNabb, S. W. Peterson, S. N. McCutcheon, and P. M. Harris. 2000. Muscle growth, cell number, type and morphometry in single and twin fetal lambs during mid to late gestation. *Reprod. Fertil. Dev.* 12:319–327.
- Mermelstein, C. S., D. M. Portilho, F. A. Mendes, M. L. Costa, and J. G. Abreu. 2007. Wnt/ $\beta$ -catenin pathway activation and myogenic differentiation are induced by cholesterol depletion. *Differentiation* 75:184–192.
- Moldes, M., Y. Zuo, R. F. Morrison, D. Silva, B. H. Park, J. Liu, and S. R. Farmer. 2003. Peroxisome-proliferator-activated receptor gamma suppresses Wnt/ $\beta$ -catenin signalling during adipogenesis. *Biochem. J.* 376:607–613.
- Muhlhauser, B. S., J. A. Duffield, and I. C. McMillen. 2007. Increased maternal nutrition stimulates peroxisome proliferator activated receptor- $\gamma$  (PPAR $\gamma$ ), adiponectin and leptin mRNA expression in adipose tissue before birth. *Endocrinology* 148:878–885.
- Munsterberg, A. E., J. Kitajewski, D. A. Bumcrot, A. P. McMahon, and A. B. Lassar. 1995. Combinatorial signaling by sonic hedge-

- hog and Wnt family members induces myogenic bHLH gene expression in the somite. *Genes Dev.* 9:2911–2922.
- Nagy, L., P. Tontonoz, J. G. Alvarez, H. Chen, and R. M. Evans. 1998. Oxidized LDL regulates macrophage gene expression through ligand activation of PPAR $\gamma$ . *Cell* 93:229–240.
- Nathanielsz, P. W., L. Poston, and P. D. Taylor. 2007. In utero exposure to maternal obesity and diabetes: Animal models that identify and characterize implications for future health. *Clin. Perinatol.* 34:515–526.
- National Weather Service. 1988–1989. National water summary—Floods and droughts: Wyoming. National Weather Service, Silver Spring, MD.
- Novakofski, J. 2004. Adipogenesis: Usefulness of in vitro and in vivo experimental models. *J. Anim. Sci.* 82:905–915.
- NRC. 1985. Nutrient Requirements of Sheep. 6th ed. Natl. Acad. Press, Washington, DC.
- NRC. 2000. Nutrient Requirements of Beef Cattle. 7th ed. Natl. Acad. Press, Washington, DC.
- Okamura, M., H. Kudo, K. Wakabayashi, T. Tanaka, A. Nonaka, A. Uchida, S. Tsutsumi, I. Sakakibara, M. Naito, T. F. Osborne, T. Hamakubo, S. Ito, H. Aburatani, M. Yanagisawa, T. Kodama, and J. Sakai. 2009. Coup-TFII acts downstream of Wnt/ $\beta$ -catenin signal to silence PPAR $\gamma$  gene expression and repress adipogenesis. *Proc. Natl. Acad. Sci. USA* 106:5819–5824.
- Pan, W., Y. Jia, J. Wang, D. Tao, X. Gan, L. Tsiokas, N. Jing, D. Wu, and L. Li. 2005. Beta-catenin regulates myogenesis by relieving I-mfa-mediated suppression of myogenic regulatory factors in P<sub>19</sub> cells. *Proc. Natl. Acad. Sci. USA* 102:17378–17383.
- Petropoulos, H., and I. S. Skerjanc. 2002.  $\beta$ -Catenin is essential and sufficient for skeletal myogenesis in P<sub>19</sub> cells. *J. Biol. Chem.* 277:15393–15399.
- Polesskaya, A., P. Seale, and M. A. Rudnicki. 2003. Wnt signaling induces the myogenic specification of resident CD45+ adult stem cells during muscle regeneration. *Cell* 113:841–852.
- Ponnampalam, E. N., N. J. Mann, and A. J. Sinclair. 2006. Effect of feeding systems on  $\omega$ -3 fatty acids, conjugated linoleic acid and trans fatty acids in Australian beef cuts: Potential impact on human health. *Asia Pac. J. Clin. Nutr.* 15:21–29.
- Puigserver, P., Z. Wu, C. W. Park, R. Graves, M. Wright, and B. M. Spiegelman. 1998. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* 92:829–839.
- Pyatt, N. A., L. L. Berger, D. B. Faulkner, P. M. Walker, and S. L. Rodriguez-Zas. 2005a. Factors affecting carcass value and profitability in early-weaned Simmental steers: I. Five-year average pricing. *J. Anim. Sci.* 83:2918–2925.
- Pyatt, N. A., L. L. Berger, D. B. Faulkner, P. M. Walker, and S. L. Rodriguez-Zas. 2005b. Factors affecting carcass value and profitability in early-weaned Simmental steers: II. Days on feed endpoints and sorting strategies. *J. Anim. Sci.* 83:2926–2937.
- Quigley, S. P., D. O. Kleemann, M. A. Kakar, J. A. Owens, G. S. Natrass, S. Maddocks, and S. K. Walker. 2005. Myogenesis in sheep is altered by maternal feed intake during the peri-conception period. *Anim. Reprod. Sci.* 87:241–251.
- Ridgeway, A. G., and I. S. Skerjanc. 2001. Pax3 is essential for skeletal myogenesis and the expression of Six1 and Eya2. *J. Biol. Chem.* 276:19033–19039.
- Rosen, E. D., C. H. Hsu, X. Wang, S. Sakai, M. W. Freeman, F. J. Gonzalez, and B. M. Spiegelman. 2002. C/EBP $\alpha$  induces adipogenesis through PPAR $\gamma$ : A unified pathway. *Genes Dev.* 16:22–26.
- Rosen, E. D., and O. A. MacDougald. 2006. Adipocyte differentiation from the inside out. *Nat. Rev. Mol. Cell Biol.* 7:885–896.
- Russell, R. G., and F. T. Oteruelo. 1981. An ultrastructural study of the differentiation of skeletal muscle in the bovine fetus. *Anat. Embryol. (Berl.)* 162:403–417.
- Schopfer, F. J., Y. Lin, P. R. Baker, T. Cui, M. Garcia-Barrio, J. Zhang, K. Chen, Y. E. Chen, and B. A. Freeman. 2005. Nitroli-noleic acid: An endogenous peroxisome proliferator-activated receptor  $\gamma$  ligand. *Proc. Natl. Acad. Sci. USA* 102:2340–2345.
- Shang, Y. C., C. Zhang, S. H. Wang, F. Xiong, C. P. Zhao, F. N. Peng, S. W. Feng, M. J. Yu, M. S. Li, and Y. N. Zhang. 2007. Activated  $\beta$ -catenin induces myogenesis and inhibits adipogenesis in BM-derived mesenchymal stromal cells. *Cytotherapy* 9:667–681.
- Sitz, B. M., C. R. Calkins, D. M. Feuz, W. J. Umberger, and K. M. Eskridge. 2005. Consumer sensory acceptance and value of domestic, Canadian, and Australian grass-fed beef steaks. *J. Anim. Sci.* 83:2863–2868.
- Spalding, K. L., E. Arner, P. O. Westermark, S. Bernard, B. A. Buchholz, O. Bergmann, L. Blomqvist, J. Hoffstedt, E. Naslund, T. Britton, H. Concha, M. Hassan, M. Ryden, J. Frisen, and P. Arner. 2008. Dynamics of fat cell turnover in humans. *Nature* 453:783–787.
- Stannard, S. R., and N. A. Johnson. 2004. Insulin resistance and elevated triglyceride in muscle: More important for survival than “thrifty” genes? *J. Physiol.* 554:595–607.
- Stern, H. M., A. M. Brown, and S. D. Hauschka. 1995. Myogenesis in paraxial mesoderm: Preferential induction by dorsal neural tube and by cells expressing Wnt-1. *Development* 121:3675–3686.
- Stickland, N. C. 1978. A quantitative study of muscle development in the bovine foetus (*Bos indicus*). *Anat. Histol. Embryol.* 7:193–205.
- Symonds, M. E., S. Pearce, J. Bispham, D. S. Gardner, and T. Stephenson. 2004. Timing of nutrient restriction and programming of fetal adipose tissue development. *Proc. Nutr. Soc.* 63:397–403.
- Therkildsen, M., and N. Oksbjerg. 2009. Muscle protein turnover. Page 115–128 in *Applied Muscle Biology and Meat Science*. M. Du, and R. J. McCormick, ed. CRC Press, Boca Raton, FL.
- Thomas, V. M., and R. W. Kott. 1995. A review of Montana winter range ewe nutrition research. *Sheep Goat Res. J.* 11:17–24.
- Tong, J., M. J. Zhu, K. R. Underwood, B. W. Hess, S. P. Ford, and M. Du. 2008. AMP-activated protein kinase and adipogenesis in sheep fetal skeletal muscle and 3T3-L1 cells. *J. Anim. Sci.* 86:1296–1305.
- Tong, J. F., X. Yan, M. J. Zhu, S. P. Ford, P. W. Nathanielsz, and M. Du. 2009. Maternal obesity downregulates myogenesis and  $\beta$ -catenin signaling in fetal skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.* 296:E917–E924.
- Underwood, K. R., J. M. Kimzey, J. Tong, P. L. Price, E. E. Grings, B. W. Hess, W. J. Means, and M. Du. 2008. Gestational nutrition affects growth and adipose tissue deposition in steers. *Proc. West. Sect. Am. Soc. Anim. Sci.* 59:29–32.
- United States Geological Survey. 2004. Climatic Fluctuations, Drought, and Flow in the Colorado River Basin. US Dept. Interior, Washington, DC.
- Ward, S. S., and N. C. Stickland. 1991. Why are slow and fast muscles differentially affected during prenatal undernutrition? *Muscle Nerve* 14:259–267.
- Wertz, A. E., L. L. Berger, P. M. Walker, D. B. Faulkner, F. K. McKeith, and S. Rodriguez-Zas. 2001. Early weaning and postweaning nutritional management affect feedlot performance of Angus  $\times$  Simmental heifers and the relationship of 12th rib fat and marbling score to feed efficiency. *J. Anim. Sci.* 79:1660–1669.
- Wertz, A. E., L. L. Berger, P. M. Walker, D. B. Faulkner, F. K. McKeith, and S. L. Rodriguez-Zas. 2002. Early-weaning and postweaning nutritional management affect feedlot performance, carcass merit, and the relationship of 12th-rib fat, marbling score, and feed efficiency among Angus and Wagyu heifers. *J. Anim. Sci.* 80:28–37.
- Wigmore, P. M., and N. C. Stickland. 1983. Muscle development in large and small pig fetuses. *J. Anat.* 137:235–245.
- Wu, Z., E. D. Rosen, R. Brun, S. Hauser, G. Adelmant, A. E. Troy, C. McKeon, G. J. Darlington, and B. M. Spiegelman. 1999. Cross-regulation of C/EBP $\alpha$  and PPAR $\gamma$  controls the

- transcriptional pathway of adipogenesis and insulin sensitivity. *Mol. Cell* 3:151–158.
- Yablonka-Reuveni, Z., K. Day, A. Vine, and G. Shefer. 2008. Defining the transcriptional signature of skeletal muscle stem cells. *J. Anim. Sci.* 86:E207–E216.
- Yamanouchi, K., T. Hosoyama, Y. Murakami, and M. Nishihara. 2007. Myogenic and adipogenic properties of goat skeletal muscle stem cells. *J. Reprod. Dev.* 53:51–58.
- Zambrano, E., C. J. Bautista, M. Deas, P. M. Martinez-Samayoa, M. Gonzalez-Zamorano, H. Ledesma, J. Morales, F. Larrea, and P. W. Nathanielsz. 2006. A low maternal protein diet during pregnancy and lactation has sex- and window of exposure-specific effects on offspring growth and food intake, glucose metabolism and serum leptin in the rat. *J. Physiol.* 571:221–230.
- Zambrano, E., P. M. Martinez-Samayoa, C. J. Bautista, M. Deas, L. Guillen, G. L. Rodriguez-Gonzalez, C. Guzman, F. Larrea, and P. W. Nathanielsz. 2005. Sex differences in transgenerational alterations of growth and metabolism in progeny ( $F_2$ ) of female offspring ( $F_1$ ) of rats fed a low protein diet during pregnancy and lactation. *J. Physiol.* 566:225–236.
- Zhu, M. J., S. P. Ford, W. J. Means, B. W. Hess, P. W. Nathanielsz, and M. Du. 2006. Maternal nutrient restriction affects properties of skeletal muscle in offspring. *J. Physiol.* 575:241–250.
- Zhu, M. J., S. P. Ford, P. W. Nathanielsz, and M. Du. 2004. Effect of maternal nutrient restriction in sheep on the development of fetal skeletal muscle. *Biol. Reprod.* 71:1968–1973.
- Zhu, M. J., B. Han, J. Tong, C. Ma, J. M. Kimzey, K. R. Underwood, Y. Xiao, B. W. Hess, S. P. Ford, P. W. Nathanielsz, and M. Du. 2008. AMP-activated protein kinase signalling pathways are down regulated and skeletal muscle development impaired in fetuses of obese, over-nourished sheep. *J. Physiol.* 586:2651–2664.

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