9 Maternal Nutrient Restriction and Skeletal Muscle Development: Consequences for Postnatal Health

Camila Sandoval, Guoyao Wu, Stephen B. Smith, Kathrin A. Dunlap, and M. Carey Satterfield

Abstract

Severe undernutrition and famine continue to be a worldwide concern, as cases have been increasing in the past 5 years, particularly in developing countries. The occurrence of nutrient restriction (NR) during pregnancy affects fetal growth, leading to small for gestational age (SGA) or intrauterine growth restricted (IUGR) offspring. During adulthood, SGA and IUGR offspring are at a higher risk for the development of metabolic syndrome. Skeletal muscle is particularly sensitive to prenatal NR. This tissue plays an essential role in oxidation and glucose metabolism because roughly 80% of insulin-mediated glucose uptake occurs in muscle, and it represents around 40% of body weight. Alterations in myofiber number, hypertrophy and myofiber type composition, decreased protein synthesis, lower mitochondrial content and activity of oxidative enzymes, and increased accumulation of intramuscular triglycerides are among the described programming effects of maternal NR on skeletal muscle. Together, these features would add to a phenotype that is prone to insulin resistance, type 2 diabetes, obesity, and metabolic syndrome. Insights from diverse animal models (i.e. ovine, swine, and rodent) have provided valuable information regarding the molecular mechanisms behind those altered developmental pathways. Understanding those molecular signatures supports the development of efficient treatments to counteract the effects of maternal NR on skeletal muscle, and its negative implications for postnatal health.

Keywords

Maternal nutrient restriction · SGA · Skeletal muscle · Metabolic syndrome

9.1 Introduction

Long-term maternal nutrient restriction (NR) during pregnancy impairs fetal growth, leading to intrauterine growth restriction (IUGR) or small for gestational age (SGA) offspring. In human medicine, intrauterine growth restriction (IUGR) has been defined as the offspring placed below the tenth percentile of fetal weight distribution at birth, and is typically associated to asymmetric growth (Goldenberg and Cliver 1997). In livestock species, maternal nutrient restriction is also a prevalent cause for IUGR, which have been defined as an impairment in gestational develop-

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ment of a fetus or its parts (Wu et al. 2006). A similar concept is small for gestational age (SGA) offspring, which is a broader classification and refers to fetuses that are smaller than expected for the species at a given gestational age (Goldenberg and Cliver 1997). IUGR or SGA offspring present a higher perinatal mortality and increased risk of metabolic syndrome during postnatal life (Barker et al. 1989).

Skeletal muscle, which represents about 40–45% of body weight in the young and adult, respectively (Wu 2018), is among the most sensitive tissues to maternal NR (Desai et al. 1996), and it plays an essential role in metabolic dysregulation due to its prominence in glucose and oxidative metabolism (Brown 2014). In addition, skeletal muscle is the major site for initiating the catabolism of branched-chain amino acids to synthesize glutamate, alanine and glutamine in mammals (Hou and Wu 2018; Wu 2013). Both alanine and glutamine participate in the interorgan metabolism of nitrogen and carbons. Particularly, alanine is a major glucogenic precursor in the liver, whereas glutamine is used by the small intestine of many mammals (including sheep, swine and humans) to synthesize citrulline (Wu and Morris Jr. 1998). The latter is either converted locally into arginine in enterocytes or taken up by extra-intestinal tissues and cells (e.g., kidneys, endothelial cells, and macrophages) to generate arginine, the nitrogenous precursor of nitric oxide (a major vasodilator, a neurotransmitter, a signaling molecule, and a killer of pathogens), creatine (crucial for energy metabolism), and polyamines (essential for DNA and protein syntheses) in animals (Dai et al. 2013; Wang et al. 2014; Wu et al. 2016, 2018). Therefore, skeletal muscle plays an important role in both growth and health of individuals.

Using animal models to understand the effects of maternal undernutrition in skeletal muscle growth and metabolism provides valuable information for translational research as well as agricultural performance. This chapter will discuss insights from the sheep, pig, and rodent models regarding the effect of maternal nutrient restriction (NR) on fetal skeletal muscle and its potential implications for postnatal health.

9.2 Maternal Undernutrition and SGA Offspring

Worldwide estimations indicate that around 821 million people are undernourished. Famine and undernutrition cases have continuously increased since 2014 and are a public health concern primarily in developing and low-income countries (FAO 2017) with the majority of cases occurring in Africa and Asia, followed by Latin America and The Caribbean (FAO 2017). The consequences of undernutrition are ample and include a higher predisposition for disease, and in extreme situations, death. This scenario becomes particularly challenging during pregnancy, when the female experiences a physiological increase in nutrient requirements to support herself as well as the needs of her developing fetus and placenta. Maternal undernutrition during pregnancy results in SGA offspring, with more than 20 million cases reported annually (UNICEF 2004).

Individuals born as IUGR or SGA are more prone to suffer perinatal mortality and experience increased risk for hypertension (Gennser et al. 1988), obesity (Fernandez-Twinn and Ozanne 2006), type 2 diabetes (Rich-Edwards et al. 1999), heart disease (Barker et al. 1989) and metabolic syndrome (McMillen and Robinson 2005). Epidemiological studies in the field of fetal programming have suggested the thrifty phenotype hypothesis (Hales and Barker 1992), which suggests that early life nutrient deficiency leads to a programming effect that would support immediate survival. However, in a postnatal scenario of normal or excessive nutrient availability, these adaptations would lead to type 2 diabetes, obesity, and other dysregulations associated with metabolic syndrome (Gluckman et al. 2005; Symonds et al. 2009; Hyatt et al. 2011).

The use of animal models for the study of maternal NR on programming of fetal growth and metabolism has provided supporting evidence for the initial epidemiological studies. A decrease in fetal weight has been a seminal finding of these studies (Osgerby et al. 2002; Kwon et al. 2004; Gao et al. 2008; Lassala et al. 2010; Satterfield et al. 2010). Results from our group show that impairment of fetal growth is corre-

lated to reduced concentration of polyamines and amino acids in maternal and fetal plasma, as well as fetal allantoic and amniotic fluids (Kwon et al. 2004). Lower plasma levels of insulin like growth factor 1 (IGF1) and insulin have also been reported in fetal plasma as a consequence of maternal NR (Osgerby et al. 2002), and both factors play an essential role in stimulation of fetal growth (Fowden et al. 1989; Baker et al. 1993).

Growth and metabolism in several fetal organs are affected by maternal NR (Osgerby et al. 2002; Vonnahme et al. 2003; Zhu et al. 2004, 2006; Costello et al. 2008; George et al. 2012; Lloyd et al. 2012; Satterfield et al. 2013; Shukla et al. 2014). Among them, skeletal muscle is particularly susceptible to maternal NR during fetal development because of nutrient prioritization to vital organs such as the brain (Desai et al. 1996)

9.3 Overview of Fetal Skeletal Muscle Development

Skeletal muscle development and growth during the fetal stage are accomplished by both cellular hyperplasia and fusion to originate myofibers (myogenesis), and hypertrophy, which continues postnatally. Myogenesis can be divided into primary and secondary myogenesis. During primary myogenesis, myoblasts fuse to form a primary myotube which will become a primary myofiber. A small percentage of myofibers are formed in this process, which starts during the first third of pregnancy (Maltin 2008). Secondary myogenesis occurs during the second third of pregnancy and accounts for the majority of myofiber formation (Maltin 2008).

Once the majority of myofibers are formed, fetal muscle growth continues through hypertrophy which starts around the second half of pregnancy and remains as an active process postnatally. In the sheep, it has been shown that myofiber area begins to increase around gestational day (GD) 85 (term ~147 days), which was caused by the addition of myonuclei between GD 85 and 100, while myoblast proliferation was completed by GD 100, and was followed by an increase in myofiber size, likely due to intracellular protein deposition (Wei et al. 2014). Since hypertrophy continues during postnatal life, prenatal alterations in myofiber size due to maternal NR have the potential to be compensated postnatally. However, persistent reductions in muscle mass and a tendency to increased adipose tissue have been demonstrated in adult sheep after prenatal NR (Ford et al. 2007), and similarly, decreased muscle mass persists until adulthood in low-birth-weight humans (Kensara et al. 2005).

Protein deposition is essential for muscle growth and hypertrophy (Yao et al. 2008) and is dependent upon an increase in the net balance of protein synthesis and protein degradation (Brown 2014). A central regulator of protein deposition is mechanistic target of rapamycin (MTOR), particularly MTOR complex 1, which is associated with regulatory associated protein of MTOR complex 1 (RPTOR) (Kim et al. 2002) and is activated by phosphorylation of its serine 2448 residue. Insulin, IGF1, AKT1, and amino acids (e.g., leucine, arginine, glutamine and glycine) have a stimulatory effect on MTOR complex 1 activity (Sun et al. 2016; Yao et al. 2008; Yoon 2017). In contrast, the activity of MTOR complex 1 is inhibited by glucocorticoids (Shimizu et al. 2011), protein kinase AMP-activated catalytic subunit alpha 2AMP-dependent kinase (PRKAA2) (aka AMPK), and myostatin (Rodriguez et al. 2014) (Fig. 9.1). As activation of MTOR is nutrient-dependent, severe prenatal undernutrition has the potential to decrease protein deposition in the fetus, and produce a reduction in lean mass content in the body.

9.4 Maternal Nutrient Restriction and Developmental Programming of Skeletal Muscle

9.4.1 Role of Skeletal Muscle in Whole-Body Metabolism

Skeletal muscle plays an essential role in locomotion and structural support, but it is also

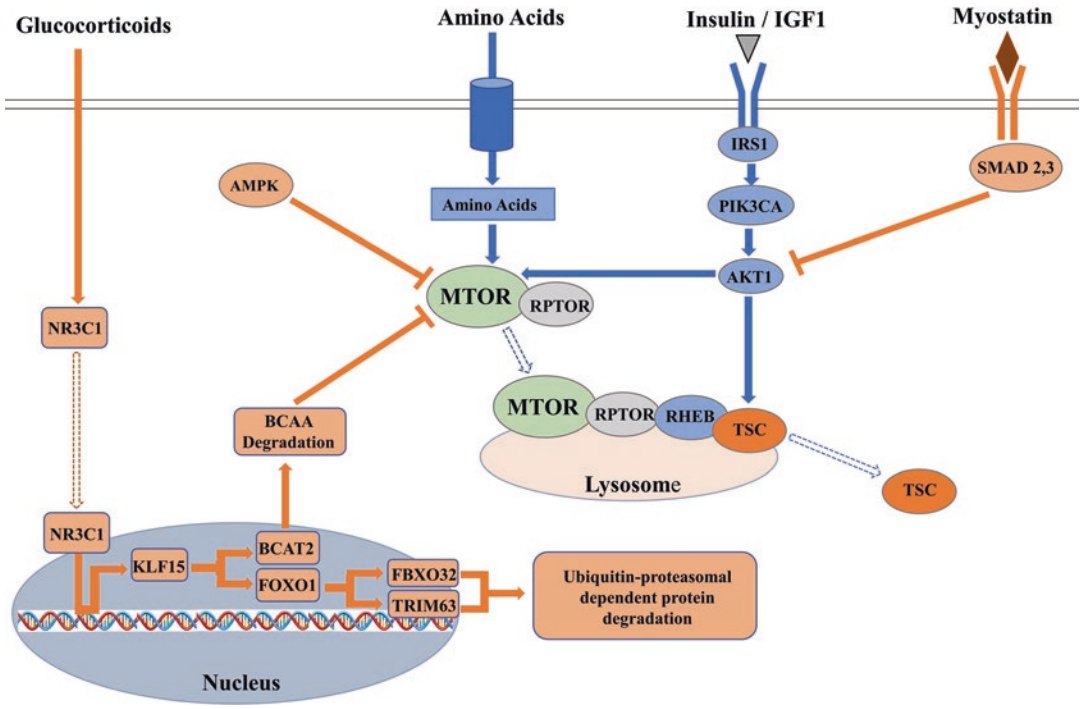

Fig. 9.1 Major regulatory pathways in skeletal muscle protein deposition. Protein deposition depends on the rate of protein synthesis and degradation. Pathways that stimulate protein synthesis in skeletal muscle are shown in blue. Amino acids (primarily the branched-chain amino acid leucine, and arginine) induce translocation of MTOR complex 1 to the lysosome, where the complex is activated by RHEB. TSC has inhibitory activity over RHEB. Insulin and IGF1 activate *AKT1* which activates RHEB by inducing its separation from the inhibitory factor TSC. Pathways that inhibit protein synthesis or stimulate protein degradation are shown in orange. Myostatin inhibits MTOR through inactivation of AKT1. Glucocorticoids bind to their receptor (NR3C1) to induce expression of KLF15. It is suggested that this decreases activation of MTOR through increased breakdown of branched-chain amino acids (BCAA) via BCAT2. KFL15 upregulation would also increase protein degradation through upregulation of the ubiquitin ligases FBXO32 and TRIM63. PRKAA2 (aka AMPK) also has an inhibitory effect on MTOR when AMP is increased in the cell (not shown) (Based on the data from Shimizu et al. 2011; Yoon 2017)

involved in several functions that regulate amino acid and energy metabolism. This tissue is highly abundant in free glutamine, glutamate, alanine, glycine, and taurine (Wu and Thompson 1990; Wu et al. 1991; Flynn and Wu 1996). Examples are, the capacity for oxidation of fatty acids, glucose, and some amino acids; storage of glycogen (Argilés et al. 2016), and support of gluconeogenesis in liver and kidney through the release of the amino acids, alanine and glutamine (Marliss et al. 1971; Garber and Missouri 1976). Skeletal muscle is essential in the regulation of glucose metabolism because about 80% of insulin-induced glucose uptake occurs in this tissue (Ferrannini et al. 1985; DeFronzo and Tripathy 2009). Skeletal muscle represents 45% of body mass in adult organisms (Janssen et al. 2000; Wu 2018), so any alteration in muscle mass or metabolism will significantly impact whole-body metabolism (Brown 2014). As example, it has been shown that insulin resistance at the skeletal muscle level is one of the primary metabolic alterations leading to type 2 diabetes in humans (DeFronzo and Tripathy 2009).

Solute carrier family 2 member 4 (SLC2A4) is the major glucose transporter in skeletal muscle, and its action is insulin-dependent. The abundance and activity of this transporter are essential for insulin-mediated glucose uptake (Scheepers et al. 2004). SLC2A4 proteins are stored in cytoplasmic vesicles and translocated to the plasma membrane by activation of the PI3K/AKT1 pathway after

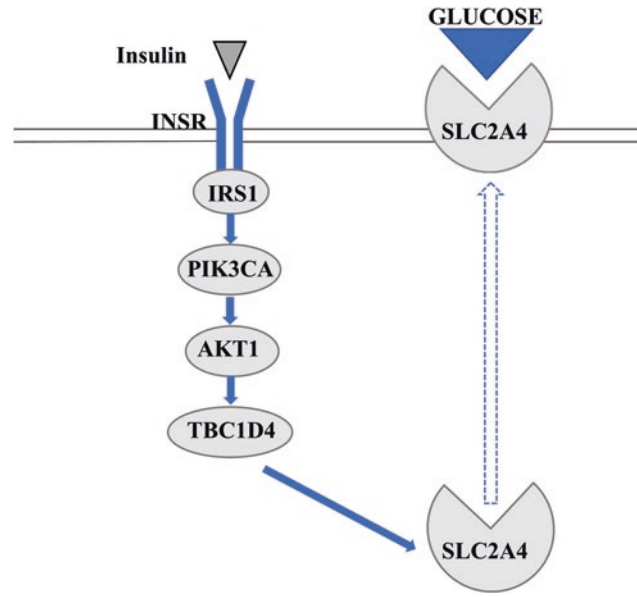

Fig. 9.2 Insulin-mediated SLC2A4 translocation. Around 80% of insulin-mediated glucose uptake occurs in skeletal muscle. Insulin binds to its receptor (INSR) to activate the downstream target *AKT1* which will activate TBC1D4 to induce SLC2A4 translocation from cytoplasmic vesicles to the sarcolemma. Because of a high level of homology, IGF1 can also activate this pathway through its receptor (IGF1R) or binding to INSR (not shown)

binding of insulin to insulin receptor (INSR) (Fig. 9.2) (Kohn et al. 1996; Taniguchi et al. 2006). IGF1 can also trigger the activation of this pathway by binding to its receptor or to INSR (Mora et al. 1995; Belfiore et al. 2009). Muscle contraction can also stimulate SLC2A4 translocation, which becomes relevant during postnatal life (Gao et al. 1994). Upregulation of SLC2A4 in skeletal muscle begins late in fetal life and continues postnatally when this glucose transporter reaches maximum functionality (Stuart et al. 2000).

Another factor that influences the metabolic characteristics of skeletal muscle is myofiber type composition, which impacts glucose metabolism and fatty acid oxidation (Mortensen et al. 2010). Type I myofibers are primarily oxidative and more sensitive to insulin than type II myofibers. Thus, its proportion shows a positive correlation with fatty acids and glucose oxidation, and with insulin-mediated glucose transport and whole-body insulin sensitivity (Lillioja et al. 1987; Fisher et al. 2017). Several studies have demonstrated that maternal NR impairs skeletal muscle growth, insulin sensitivity, and energetic metabolism (Table 9.1), which in addition to other systemic alterations, leads to a phenotype of increased risk for metabolic syndrome.

9.4.2 Prenatal Programming of Skeletal Muscle and Consequences for Postnatal Health

9.4.2.1 Ovine Model

Decreased number of secondary myofibers has been found in longissimus dorsi at GD 78 after 50% maternal NR between GD 28 and 78. Similarly, a peri-conception treatment of 50% NR applied from 18 days before ovulation to 6 days after ovulation found a tendency for decreased myofiber number in sheep semitendinosus muscle at GD 75 (Quigley et al. 2005). The study of Zhu et al. (2004) also found a decrease in myofiber area in longissimus dorsi of fetuses from NR dams which was associated with a reduction in MTOR and RPS6KB1 protein phosphorylation. Another model of 50% NR from GD 85 to 115 found a decrease in weight of longissimus dorsi in 14-day-old lambs (Fahey et al. 2005). Decreased muscle mass can be partially compensated postnatally as hypertrophy continues as an active process. However, having a lower number of myofibers limits a complete compensation because myofiber formation is not an active process under normal postnatal conditions.

Table 9.1 Summary of selected studies indicating the effect of maternal NR on fetal skeletal muscle features in different animal models

Model	Treatment	Gestational day	Effect	References
Ovine	50% NR	28 to 78	Reduced secondary myofiber number, smaller myofiber area, and downregulation in MTOR signaling at GD 78.	Zhu et al. (2004)
	50% NR	85 to 115	Reduced muscle mass in 14-day-old lambs.	Fahey et al. (2005)
		30 to 70	Increased type I myofiber content in 14-day-old- lambs	
	50% NR	28 to 78	Increased adipose tissue, tendency towards reduced muscle mass, hyperglycemia and reduced insulin secretion after GTT[a] in 280-day-old lambs.	Ford et al. (2007)
	50% NR	104 to 127	Upregulation of mRNA expression of *SLC2A4*, *INSR*, and *IGF1*, and reduced type I myofiber content at GD 127.	Costello et al. (2008)
	50% NR	28 to 78	Increased type IIb myofiber content, decreased activity of CPT1B, and increased IMTG[b] in 8-month-old lambs	Zhu et al. (2006)
Swine	6% crude protein	0 to Term	Decreased muscle mass, smaller myofiber area, upregulation in MSTN signaling, and downregulation in MTOR signaling in 35-day-old piglets.	Liu et al. (2015)
	Reduced digestible energy (11.24 MJ/kg)	0 to 90	Downregulation of mRNA expression of genes involved in mitochondrial signaling (*PPARGC1A*, *NRF1*, *TFAM*, *ATB5B*, *SIRT1*, and *CS*), and reduced mitochondrial DNA content at GD 90.	Zou et al. (2016)
	75% NR	0 to Term	Downregulation of mRNA expression of *SLC2A4,* and increased area under the curve in GTT in 6-week-old piglets.	Wang et al. (2016)
	Uterine crowding (naturally occurring NR)	0 to Term	Increased content of proteasome, a major system for protein degradation in skeletal muscle.	Wang et al. (2008)
Rat	50% protein-Isocaloric diet	0 to Term	Increased mRNA and protein levels of SLC2A4, and histone epigenetic modifications in SLC2A4 promotor zone in 38-day-old female offspring	Zheng et al. (2012)
	50% protein-Isocaloric diet	2 to Term	Upregulation in mRNA expression and protein content of C/EBPβ, and increase in histone acetylation at C/EBPβ promotor region in 38-day old female offspring	Zheng et al. (2011)
Mouse	50% NR	12.5 to 18.5	Reduced mitochondrial content, and resistance to weight loss in 14-week-old offspring.	Beauchamp et al. (2015)

[a]GTT = Glucose tolerance test
[b]IMTG = Intramuscular triglycerides

Impaired fetal growth after prenatal nutrient restriction is usually followed by compensatory growth during postnatal life (De Blasio et al. 2007). However, in the long term, this compensatory growth will favor adipose tissue deposition instead of muscle growth. For example, 280-day-old lambs born to dams that were subjected to 50% NR from GD 28 to 78 were heavier than controls, had increased renal and pelvic adipose tissue, and a tendency for decreased weight in longissimus dorsi and semitendinosus muscles. This study also found evidence of hyperglycemia and altered insulin secretion after a glucose tolerance test (Ford et al. 2007). Accordingly, 1-year-old offspring born to sheep under 50% NR from GD 110 to term, showed evidence of glucose intolerance as indicated by increased areas under the curve for glucose and insulin (Gardner et al. 2005).

Indicators of alterations in glucose and insulin metabolism have also been found in skeletal muscle at the fetal stage after maternal nutrient restriction. A sheep model of 50% NR from GD 104 to 127 produced upregulation of *SLC2A4*, *INSR*, and *IGF1* mRNA in fetal triceps brachii muscle at GD127 (Costello et al. 2008). These results suggest a metabolic programming effect that could be partly responsible for the compensatory growth that SGA animals experience early in postnatal life. The authors also suggested that an initial upregulation in insulin receptor may play a role in the development of metabolic diseases later in postnatal life (Costello et al. 2008).

Maternal nutrient restriction has also been shown to alter myofiber type composition in skeletal muscle. A 50% NR from GD 28 to GD 78 has been associated with increased content of type IIb myofibers in longissimus dorsi of 8-month-old lambs (Zhu et al. 2006). This study also found decreased activity of the enzyme carnitine palmitoyltransferase-1, which is involved in fatty acid oxidation, and accordingly, intramuscular triglyceride (IMTG) content was increased. These findings suggest a metabolic programming in skeletal muscle that would impair oxidative capacity and insulin sensitivity, as type II myofibers are primarily glycolytic and less insulin sensitive than type I myofibers (He et al. 2001). Accumulation of IMTG has also been recognized as a cause for disruption in insulin signaling, and insulin resistance in skeletal muscle (Corcoran et al. 2007).

Contradictory results have been found in the longissimus dorsi of 14-day-old lambs in which an increase in type I myofibers was found after 50% NR from GD 30 to 70 (Fahey et al. 2005). The difference in offspring age at which these two studies were conducted may be a cause for these conflicting results. However; the results of Zhu et al. (2006) are supported by the study of Costello et al. (2008), in which a sheep model of 50% NR from GD 104 to 127 was shown to reduce type I myofiber content in fetal triceps brachii muscle at GD127. Myofiber type composition conserves a certain level of plasticity during postnatal life in response to some stimuli such as exercise. Thus, more research is needed to confirm the long-lasting effect of myofiber type programming during fetal development (Brown 2014).

Findings from our group showed that administration of arginine to 50% NR ewes was successful in increasing fetal weight (Lassala et al. 2010). Similarly, administration of sildenafil citrate from GD 28 to 115 to ewes under 50% NR was effective in increasing fetal weight and total amino acids and polyamines in amniotic and allantoic fluids, and fetal serum (Satterfield et al. 2010). Amino acids are building blocks for protein synthesis (Wu 2013), and particularly leucine and arginine stimulate MTOR activity (Yao et al. 2008; Davis et al. 2010), enhancing protein deposition and skeletal muscle growth. Arginine also stimulates myoblast proliferation (Kalbe et al. 2013) and fusion (Long et al. 2006), likely supporting myofiber formation. These results represent potential treatments to mitigate the effects of maternal NR on skeletal muscle in the sheep model (Fig. 9.3).

9.4.2.2 Swine Model

A model of restricted protein (6% dietary crude protein) throughout pregnancy led to decreased muscle mass and myofiber area, upregulated MSTN signaling, and downregulated MTOR signaling in longissimus dorsi muscle of 35-day-old piglets (Liu et al. 2015). Moreover, a model of maternal low-energy diet (11.24 MJ/Kg of digestible energy) from mating to GD 90 was found to downregulate mRNA expression of *PPARGC1A*, *NRF1*, *TFAM*, *ATB5B*, *SIRT1,* and *CS*, which are regulators of mitochondrial biogenesis (Zou et al. 2016). Mitochondrial DNA content was also reduced, indicating a negative programming in oxidative capacity of skeletal muscle after prenatal NR (Zou et al. 2016). Decreased oxidative capacity in skeletal muscle may lead to IMTG accumulation, which is associated with the onset of insulin resistance (Corcoran et al. 2007). Accordingly, a model of 75% NR throughout pregnancy, followed by a postnatal cafeteria feeding up to 6 weeks, resulted in an impaired ability to clear blood glucose and was associated with a downregulation of *SLC2A4* mRNA in skeletal muscle (Wang et al. 2016).

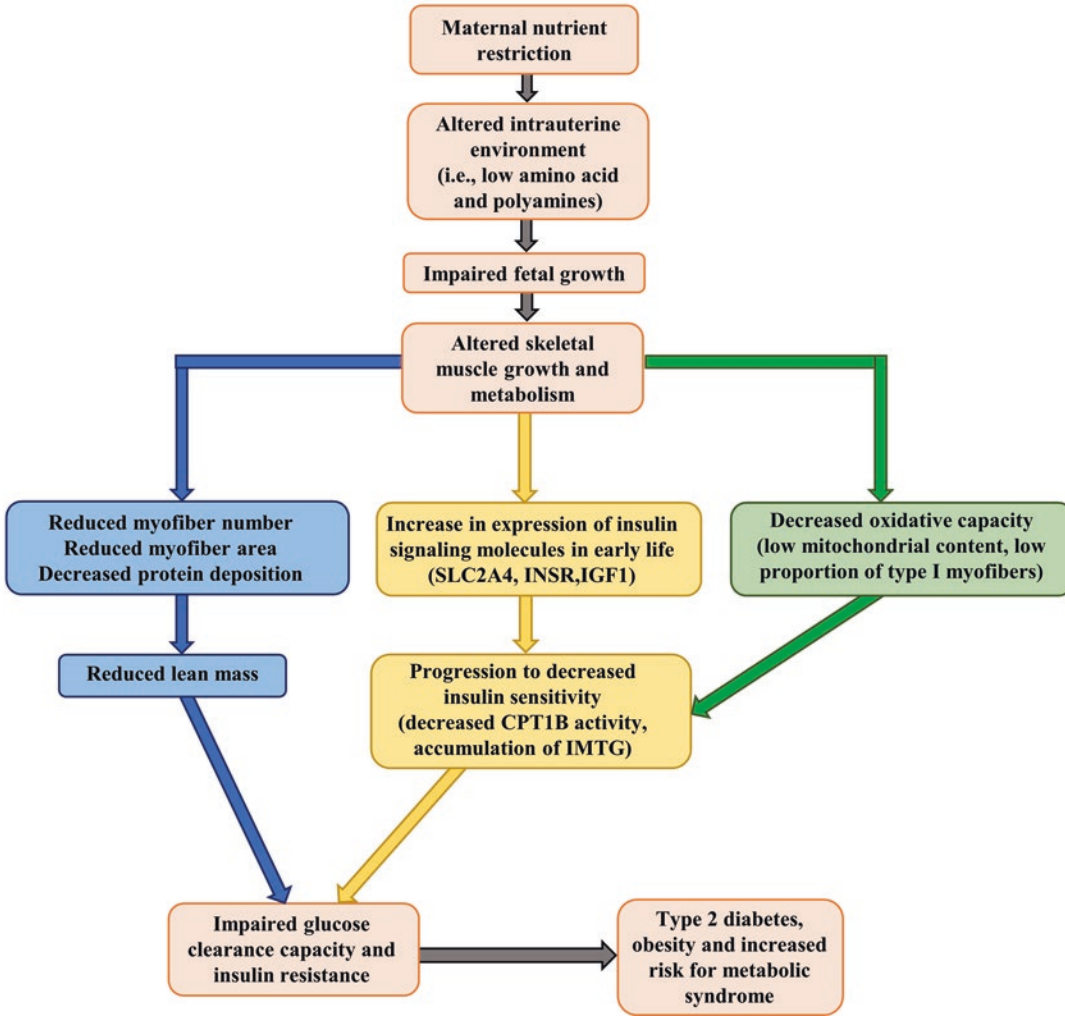

Fig. 9.3 Suggested model for the effects of maternal NR on fetal skeletal muscle growth and metabolism and consequences for postnatal health. Three major pathways of programming have been described in studies from ovine, swine, and rodent models. They are decreased muscle mass (blue), decreased oxidative capacity (green), and accumulation of IMTG and decreased insulin sensitivity (yellow). The additive effect of those programming trajectories would lead to impaired glucose clearance capacity, insulin resistance at the skeletal muscle level, and progression to type 2 diabetes, obesity, and metabolic syndrome

In addition to dietary NR, the pig model presents naturally occurring IUGR fetuses which suffer nutrient restriction because of uterine crowding (Wu et al. 2006). Using this model, the skeletal muscle proteome of IUGR piglets showed higher content of proteasome, a major system involved in protein degradation in skeletal muscle, indicating an upregulation of ubiquitin-dependent protein degradation in these animals (Wang et al. 2008). Enhanced protein degradation would lead to decreased muscle mass, which, in addition to impaired oxidative metabolism, may enhance the postnatal risk of metabolic syndrome. Through genetic and epigenetic changes, underdevelopment of fetal skeletal muscle has negative impacts on the postnatal growth and health of offspring (Ji et al. 2016, 2017).

Emerging evidence shows that glycine enhances MTOR activity and inhibits expression of genes involved in ubiquitin-dependent protein

degradation (*FBXO32* and *TRIM63*) in C2C12 myoblasts (Sun et al. 2016). Because the content of glycine is low in all plant-source foods (Hou et al. 2019), endogenous synthesis from amino acids or dietary provision of glycine plays an important role in stimulating muscle protein synthesis and animal growth (Li and Wu 2018, 2020; Wu et al. 2019). Leucine supplementation in neonatal pigs receiving a low-protein diet has been effective to enhance protein synthesis in longissimus dorsi muscle (Yin et al. 2010). Arginine supplementation in neonatal pigs was effective in increasing MTOR signaling and protein synthesis in skeletal muscle (Yao et al. 2008). Also, arginine supplementation in adult pigs had a beneficial effect on metabolic profiles in skeletal muscle and adipose tissue (Tan et al. 2011). These insights from the pig model are promising treatment alternatives to enhance muscle growth and metabolic profiles. However, their efficiency in a prenatal NR context remain to be determined.

9.4.2.3 Rodent Models

A rat model of 50% protein restriction and isocaloric diet throughout pregnancy showed increased mRNA and protein levels of SLC2A4 within gastrocnemius muscle in 38-day-old female offspring. Histone epigenetic modifications in the promoter region of *SLC2A4* were also found in female offspring from this study (Zheng et al. 2012). An early-life upregulation in insulin-responsive molecules has been suggested to happen before progression to metabolic diseases in postnatal life (Costello et al. 2008; Muhlhausler et al. 2009), and the discussed results indicate a potential sex-specific programming in glucose metabolism in skeletal muscle.

An upregulation in mRNA expression and protein content of *Cebpb* was found in gastrocnemius muscle of 38-day-old female offspring using a rat model of 50% protein restriction and isocaloric diet from GD 2 to term. An increase in histone acetylation was found at the promoter region of *Cebpb* in those females (Zheng et al. 2011). *Cebpb* is a transcription factor involved in the regulation of genes related to energy homeostasis, and one of its effects is the stimulation of adipogenesis by induction of fibroblast differentiation to adipocytes. These results support a programming effect towards increased intramuscular fat accumulation, which is correlated with insulin resistance and type 2 diabetes.

A mouse model of 50% NR from GD 12.5 to 18.5 reduced the mitochondrial content in tibialis anterior muscle and increased the levels of carcass adiposity in 14-week-old offspring (Beauchamp et al. 2015). This study also showed resistance to weight loss in offspring from NR dams, as these animals lost 50% of weight compared to control after a 40% caloric restriction from postnatal week 10−14. A decreased oxidative capacity and resistance to lose weight would further enhance the risk of metabolic disease. Interestingly, dietary supplementation with watermelon juice, which is a source of citrulline, increases arginine availability and reduced adipose tissue accretion, serum glucose concentrations and free fatty acids in a rat model of non-insulin dependent diabetes (Wu et al. 2007). Additionally, leucine supplementation to diet-induced obese mice was successful in activating genes involved in mitochondrial biogenesis and preventing mitochondrial dysfunction (Li et al. 2012). These results represent potential treatments to counteract the enhanced risk for metabolic disease once a stage of disease is already present. However, their effectiveness in individuals that have experienced maternal NR remains to be tested.

9.5 Concluding Remarks

Several studies have demonstrated that maternal nutrient restriction is a cause for SGA or IUGR offspring, which was epidemiologically correlated with increased risk of metabolic syndrome. Insights from diverse animal models have provided the molecular basis for the developmental trajectories that are induced by nutrient scarcity and lead to postnatal metabolic dysregulation. Seminal results collected from ovine, swine, and rodent models indicate that muscle mass, oxidative capacity, and insulin sensitivity are the major features affected by prenatal NR. These would

contribute to the onset of insulin resistance at the skeletal muscle level, with progression to a whole-body effect and type 2 diabetes, and obesity. Current data provide promising treatment alternatives to counteract these effects and minimize the negative consequences of prenatal NR in postnatal health. However, the specific windows for intervention, and conclusive results from NR models are still needed.

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References

Argilés JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Mañas L (2016) Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. J Am Med Dir Assoc 17:789–796

Baker J, Liu JP, Robertson EJ, Efstratiadis A (1993) Role of insulin-like growth factors in embryonic and postnatal growth. Cell 75:73–82

Barker DJP, Osmond C, Winter PD, Margetts B (1989) Weight in infancy and death from ischaemic heart disease. Lancet 2(8663):577–580

Beauchamp B, Ghosh S, Dysart MW et al (2015) Low birth weight is associated with adiposity, impaired skeletal muscle energetics and weight loss resistance in mice. Int J Obes 39:702–711

Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R (2009) Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev 30:586–623

Brown LD (2014) Endocrine regulation of fetal skeletal muscle growth: impact on future metabolic health. J Endocrinol 221:R13–R29

Corcoran MP, Lamon-Fava S, Fielding RA (2007) Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. Am J Clin Nutr 85:662–677

Costello PM, Rowlerson A, Astaman NA, Anthony FE, Sayer AA, Cooper C, Hanson M, Green L (2008) Periimplantation and late gestation maternal undernutrition differentially affect fetal sheep skeletal muscle development. J Physiol 586:2371–2379

Dai ZL, Wu ZL, Yang Y, Wang JJ, Satterfield MC, Meininger CJ, Bazer FW, Wu G (2013) Nitric oxide and energy metabolism in mammals. Biofactors 39:383–391

Davis TA, Suryawan A, Orellana RA, Fiorotto ML, Burrin DG (2010) Amino acids and insulin are regulators of muscle protein synthesis in neonatal pigs. Animal 4:1790–1796

De Blasio MJ, Gatford KL, Robinson JS, Owens JA (2007) Placental restriction of fetal growth reduces size at birth and alters postnatal growth, feeding activity, and adiposity in the young lamb. Am J Physiol Integr Comp Physiol 292:R875–R886

DeFronzo RA, Tripathy D (2009) Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 32(Suppl 2):S157–SS63

Desai M, Crowther NJ, Lucas A, Nicholas HC (1996) Organ-selective growth in the offspring of protein-restricted mothers. Br J Nutr 76:591–603

Fahey AJ, Brameld JM, Parr T, Buttery PJ (2005) The effect of maternal undernutrition before muscle differentiation on the muscle fiber development of the newborn lamb. J Anim Sci 83:2564–2571

FAO (2017) The state of food security and nutrition in the world 2017. Building resilience for peace and food security. Rome, FAO

Fernandez-Twinn DS, Ozanne SE (2006) Mechanisms by which poor early growth programs type-2 diabetes, obesity and the metabolic syndrome. Physiol Behav 88:234–243

Ferrannini E, Bjorkman O, Reichard GA, Pilo A, Olsson M, Wahren J, DeFronzo R (1985) The disposal of an oral glucose load in healthy subjects. A quantitative study. Diabetes 34:580–588

Fisher G, Windham ST, Griffin P, Warren J, Gower B, Hunter G (2017) Associations of human skeletal muscle fiber type and insulin sensitivity, blood lipids, and vascular hemodynamics in a cohort of premenopausal women. Eur J Appl Physiol 117:1413–1422

Flynn NE, Wu G (1996) An important role for endogenous synthesis of arginine in maintaining arginine homeostasis in neonatal pigs. Am J Physiol 271:R1149–R1155

Ford SP, Hess BW, Schwope MM, Nijland MJ, Gilbert JS, Vonnahme K, Means W, Han H, Nathanielsz PW (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

Fowden AL, Hughes P, Comline RS (1989) The effects of insulin on the growth rate of the sheep fetus during late gestation. Q J Exp Physiol 74:703–714

Gao J, Ren J, Gulve EA, Holloszy JO (1994) Additive effect of contractions and insulin on GLUT-4 translocation into the sarcolemma. J Appl Physiol 77:1597–1601

Gao F, Hou XZ, Liu YC, Wu SQ, Ao CJ (2008) Effect of maternal under-nutrition during late pregnancy on lamb birth weight. Asian-Australasian J Anim Sci 21:371–375

Garber J, Missouri L (1976) Alanine and glutamine synthesis and release from skeletal muscle. J Biol Chem 251:836–843

Gardner DS, Tingey K, Van Bon BWM, Ozanne SE, Wilson V, Dandrea J, Keisler DH, Stephenson T, Symonds ME (2005) Programming of glucose-insulin metabolism in adult sheep after maternal undernu-

trition. Am J Physiol Regul Integr Comp Physiol 289:947–954

Gennser G, Rymark P, Isberg PE (1988) Low birth weight and risk of high blood pressure in adulthood. Br Med J (Clin Res Ed) 296:1498–1500

George LA, Zhang L, Tuersunjiang N, Ma Y, Long NM, Uthlaut AB, Smith DT, Nathanielsz PW, Ford SP (2012) Early maternal undernutrition programs increased feed intake, altered glucose metabolism and insulin secretion, and liver function in aged female offspring. Am J Physiol Regul Integr Comp Physiol 302:R795–R804

Gluckman PD, Hanson MA, Spencer HG (2005) Predictive adaptive responses and human evolution. Trends Ecol Evol 20:527–533

Goldenberg RL, Cliver SP (1997) Small for gestational age and intrauterine growth restriction: definitions and standards. Clin Obstet Gynecol 40:704–714

Hales CN, Barker DJP (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35:595–601

He J, Watkins S, Kelley DE (2001) Skeletal muscle lipid content and oxidative enzyme activity in relation to muscle fiber type in type 2 diabetes and obesity. Diabetes 50:817–823

Hou YQ, Wu G (2018) L-Glutamate nutrition and metabolism in swine. Amino Acids 50:1497–1510

Hou YQ, He WL, Hu SD, Wu G (2019) Composition of polyamines and amino acids in plant-source foods for human consumption. Amino Acids 51:1153–1165

Hyatt MA, Gardner DS, Sebert S, Wilson V, Davidson N, Nigmatullina Y, Chan LLY, Budge H, Symonds ME (2011) Suboptimal maternal nutrition, during early fetal liver development, promotes lipid accumulation in the liver of obese offspring. Reproduction 141:119–126

Janssen I, Heymsfield SB, Wang Z, Ross R (2000) Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. J Appl Physiol 89:81–88

Ji Y, Wu ZL, Dai ZL, Sun KJ, Wang JJ, Wu G (2016) Nutritional epigenetics with a focus on amino acids: Implications for the development and treatment of metabolic syndrome. J Nutr Biochem 27:1–8

Ji Y, Wu ZL, Dai ZL, Wang XL, Li J, Wang BG, Wu G (2017) Fetal and neonatal programming of postnatal growth and feed efficiency in swine. J Anim Sci Biotechnol 8:42

Kalbe C, Bérard J, Porm M, Rehfeldt C, Bee G (2013) Maternal l-arginine supplementation during early gestation affects foetal skeletal myogenesis in pigs. Livest Sci 157:322–329

Kensara OA, Wootton SA, Phillips DI, Patel M, Jackson AA, Elia M (2005) Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. Am J Clin Nutr 82:980–987

Kim DH, Sarbassov DD, Ali SM, King JE, Latek RR, Erdjument-Bromage H, Tempst P, Sabatini DM (2002) mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 110:163–175

Kohn AD, Summers SA, Birnbaum MJ, Roth RA (1996) Expression of a constitutively active Akt Ser/Thr kinase in 3T3-L1 adipocytes stimulates glucose uptake and glucose transporter 4 translocation. J Biol Chem 271:31372–31378

Kwon H, Ford SP, Bazer FW, Spencer TE, Nathanielsz PW, Nijland MJ, Hess BW, Wu G (2004) Maternal nutrient restriction reduces concentrations of amino acids and polyamines in ovine maternal and Fetal plasma and Fetal Fluids1. Biol Reprod 71:901–908

Lassala A, Bazer FW, Cudd TA, Datta S, Keisler DH, Satterfield MC, Spencer TE, Wu G (2010) Parenteral administration of L-arginine prevents Fetal growth restriction in undernourished ewes. J Nutr 140:1242–1248

Li P, Wu G (2018) Roles of dietary glycine, proline and hydroxyproline in collagen synthesis and animal growth. Amino Acids 50:29–38

Li P, Wu G (2020) Composition of amino acids and related nitrogenous nutrients in feedstuffs for animal diets. Amino Acids 52:523–542

Li H, Xu M, Lee J, He C, Xie Z (2012) Leucine supplementation increases SIRT1 expression and prevents mitochondrial dysfunction and metabolic disorders in high-fat diet-induced obese mice. Am J Physiol Endocrinol Metab 303:1234–1244

Lillioja S, Young AA, Culter CL et al (1987) Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. J Clin Invest 80:415–424

Liu X, Pan S, Li X, Sun Q, Yang X, Zhao R (2015) Maternal low-protein diet affects myostatin signaling and protein synthesis in skeletal muscle of offspring piglets at weaning stage. Eur J Nutr 54:971–979

Lloyd LJ, Foster T, Rhodes P, Rhind SM, Gardner DS (2012) Protein-energy malnutrition during early gestation in sheep blunts fetal renal vascular and nephron development and compromises adult renal function. J Physiol 590:377–393

Long JHD, Lira VA, Soltow QA, Betters JL, Sellman JE, Criswell DS (2006) Arginine supplementation induces myoblast fusion via augmentation of nitric oxide production. J Muscle Res Cell Motil 27:577–584

Maltin CA (2008) Muscle development and obesity. Organogenesis 4:158–169

Marliss EB, Aoki TT, Pozefsky T, Most AS, Cahill GF (1971) Muscle and splanchnic glutmine and glutamate metabolism in postabsorptive and starved man. J Clin Invest 50:814–817

McMillen IC, Robinson JS (2005) Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev 85:571–633

Mora S, Kaliman P, Chillarón J, Testar X, Palacín M, Zorzano A (1995) Insulin and insulin-like growth factor I (IGF-I) stimulate GLUT4 glucose transporter translocation in Xenopus oocytes. Biochem J 311:59–65

Mortensen OH, Olsen HL, Frandsen L, Nielsen PE, Grunnet N, Quistorff B (2010) Gestational protein restriction in mice has pronounced effects on gene expression in newborn offspring's liver and skeletal muscle; protective effect of taurine. Pediatr Res 67:47–53

Muhlhausler BS, Duffield JA, Ozanne SE, Pilgrim C, Turner N, Morrison JL, McMillen IC (2009) The transition from fetal growth restriction to accelerated postnatal growth: a potential role for insulin signalling in skeletal muscle. J Physiol 587:4199–4211

Osgerby J, Wathes D, Howard D, Gadd T (2002) The effect of maternal undernutrition on ovine fetal growth. J Endocrinol 173:131–141

Quigley SP, Kleemann DO, Kakar MA, Owens JA, Nattrass GS, Maddocks S, Walker SK (2005) Myogenesis in sheep is altered by maternal feed intake during the periconception period. Anim Reprod Sci 87:241–251

Rich-Edwards JW, Colditz GA, Stampfer MJ, Willet CW, Gillman MW, Hennekens CH, Speizer FE, Manson JE (1999) Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med 130:278–284

Rodriguez J, Vernus B, Chelh I, Cassar-Malek I, Gabillard JC, Sassi AH, Seiliez I, Picard B, Bonnieu A (2014) Myostatin and the skeletal muscle atrophy and hypertrophy signaling pathways. Cell Mol Life Sci 71:4361–4371

Satterfield MC, Bazer FW, Spencer TE, Wu G (2010) Sildenafil citrate treatment enhances amino acid availability in the Conceptus and Fetal growth in an ovine model of intrauterine growth restriction. J Nutr 140:251–258

Satterfield MC, Dunlap KA, Keisler DH, Bazer FW, Wu G (2013) Arginine nutrition and fetal brown adipose tissue development in nutrient-restricted sheep. Amino Acids 45:489–499

Scheepers A, Joost HG, Schürmann A (2004) The glucose transporter families SGLT and GLUT: molecular basis of normal and aberrant function. J Parenter Enter Nutr 28:364–371

Shimizu N, Yoshikawa N, Ito N et al (2011) Crosstalk between glucocorticoid receptor and nutritional sensor mTOR in skeletal muscle. Cell Metab 13:170–182

Shukla P, Ghatta S, Dubey N et al (2014) Maternal nutrient restriction during pregnancy impairs an endothelium-derived hyperpolarizing factor-like pathway in sheep fetal coronary arteries. Am J Physiol Heart Circ Physiol 307:134–142

Stuart CA, Wen G, Gustafson WC, Thompson EA (2000) Comparison of GLUT1, GLUT3, and GLUT4 mRNA and the subcellular distribution of their proteins in normal human muscle. Metabolism 49:1604–1609

Sun K, Wu Z, Ji Y, Wu G (2016) Glycine regulates protein turnover by activating protein kinase B/mammalian target of rapamycin and by inhibiting MuRF1 and atrogin-1 gene expression in C2C12 myoblasts. J Nutr 146:2461–2467

Symonds ME, Sebert SP, Hyatt MA, Budge H (2009) Nutritional programming of the metabolic syndrome. Nat Rev Endocrinol 5:604–610

Tan B, Yin Y, Liu Z et al (2011) Dietary L-arginine supplementation differentially regulates expression of lipid-metabolic genes in porcine adipose tissue and skeletal muscle. J Nutr Biochem 22:441–445

Taniguchi CM, Emanuelli B, Kahn CR (2006) Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 7:85–96

UNICEF (2004) Low birtweight: country, regional and global estimates. UNICEF, New York

Vonnahme KA, Hess BW, Hansen TR et al (2003) Maternal undernutrition from early- to mid-gestation leads to growth retardation, cardiac ventricular hypertrophy, and increased liver weight in the fetal sheep. Biol Reprod 69:133–140

Wang J, Chen L, Li D, Yin Y, Wang X, Li P, Dangott LJ, Hu W, Wu G (2008) Intrauterine growth restriction affects the proteomes of the small intestine, liver, and skeletal muscle in newborn pigs. J Nutr 138:60–66

Wang XQ, Ying W, Dunlap KA, Lin G, Satterfield MC, Burghardt RC, Wu G, Bazer FW (2014) Arginine decarboxylase and agmatinase: an alternative pathway for de novo biosynthesis of polyamines for development of mammalian conceptuses. Biol Reprod 90:84

Wang J, Cao M, Zhuo Y, Che L, Fang Z, Xu S, Lin Y, Feng B, Wu D (2016) Catch-up growth following food restriction exacerbates adulthood glucose intolerance in pigs exposed to intrauterine undernutrition. Nutrition 32:1275–1284

Wei C, Li L, Su H, Xu L, Lu J, Zhang L, Liu W, Ren H, Du L (2014) Identification of the crucial molecular events during the large-scale myoblast fusion in sheep. Physiol Genomics 46:429–440

Wu G (2013) Amino acids: biochemistry and nutrition. CRC Press, Boca Raton

Wu G (2018) Principles of animal nutrition. CRC Press, Boca Raton

Wu G, Thompson JR (1990) The effect of glutamine on protein turnover in chick skeletal muscle in vitro. Biochem J 265:593–598

Wu G, Thompson JR, Baracos VE (1991) Glutamine metabolism in skeletal muscle from the broiler chick (Gallus domesticus) and the laboratory rat (Rattus norvegicus). Biochem J 274:769–774

Wu G, Morris SM Jr (1998) Arginine metabolism: nitric oxide and beyond. Biochem J 336:1–17

Wu G, Bazer FW, Wallace JM, Spencer TE (2006) Board-invited review: intrauterine growth retardation: implications for the animal sciences. J Anim Sci 84:2316–2337

Wu G, Collins JK, Perkins-Veazie P, Siddiq M, Dolan KD, Kelly KA, Heaps CL, Meininger CJ (2007) Dietary supplementation with watermelon pomace juice enhances arginine availability and ameliorates the metabolic syndrome in Zucker diabetic fatty rats. J Nutr 137:2680–2685

Wu ZL, Hou YQ, Hu SD, Bazer FW, Meininger CJ, McNeal CJ, Wu G (2016) Catabolism and safety of supplemental L-arginine in animals. Amino Acids 48:1541–1552

Wu G, Bazer FB, Johnson GA, Hou YQ (2018) Arginine nutrition and metabolism in growing, gestating and lactating swine. J Anim Sci 96:5035–5051

Wu ZL, Hou YQ, Dai ZL, Hu CA, Wu G (2019) Metabolism, nutrition and redox signaling of hydroxyproline. Antioxid Redox Signal 30:674–682

Yao K, Yin Y, Chu W et al (2008) Dietary arginine supplementation increases mTOR signaling activity in skeletal muscle of neonatal pigs. J Nutr 138:867–872

Yin Y, Yao K, Liu Z, Gong M, Ruan Z, Deng D, Tan B, Liu Z, Wu G (2010) Supplementing l-leucine to a low-protein diet increases tissue protein synthesis in weanling pigs. Amino Acids 39:1477–1486

Yoon MS (2017) mTOR as a key regulator in maintaining skeletal muscle mass. Front Physiol 8:1–9

Zheng S, Rollet M, Pan YX (2011) Maternal protein restriction during pregnancy induces CCAAT/enhancer-binding protein (C/EBPβ) expression through the regulation of histone modification at its promoter region in female offspring rat skeletal muscle. Epigenetics 6:161–170

Zheng S, Rollet M, Pan YX (2012) Protein restriction during gestation alters histone modifications at the glucose transporter 4 (GLUT4) promoter region and induces GLUT4 expression in skeletal muscle of female rat offspring. J Nutr Biochem 23:1064–1071

Zhu M-J, Ford SP, Nathanielsz PW, Du M (2004) Effect of maternal nutrient restriction in sheep on the development of fetal skeletal muscle1. Biol Reprod 71:1968–1973

Zhu MJ, Ford SP, Means WJ, Hess BW, Nathanielsz PW, Du M (2006) Maternal nutrient restriction affects properties of skeletal muscle in offspring. J Physiol 575:241–250

Zou T, Yu B, Yu J, Mao X, Zheng P, He J, Huang Z, Liu Y, Chen D (2016) Moderately decreased maternal dietary energy intake during pregnancy reduces fetal skeletal muscle mitochondrial biogenesis in the pigs. Genes Nutr 11:1–10