Endocrine regulation of fetal skeletal muscle growth: impact on future metabolic health

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Abstract

Establishing sufficient skeletal muscle mass is essential for lifelong metabolic health. The intrauterine environment is a major determinant of the muscle mass that is present during the life course of an individual, because muscle fiber number is set at the time of birth. Thus, a compromised intrauterine environment from maternal nutrient restriction or placental insufficiency that restricts muscle fiber number can have permanent effects on the amount of muscle an individual will live with. Reduced muscle mass due to fewer muscle fibers persists even after compensatory or 'catch-up' postnatal growth occurs. Furthermore, muscle hypertrophy can only partially compensate for this limitation in fiber number. Compelling associations link low birth weight and decreased muscle mass to future insulin resistance, which can drive the development of the metabolic syndrome and type 2 diabetes, and the risk of cardiovascular events later in life. There are gaps in knowledge about the origins of reduced muscle growth at the cellular level and how these patterns are set during fetal development. By understanding the nutrient and endocrine regulation of fetal skeletal muscle growth and development, we can direct research efforts toward improving muscle growth early in life to prevent the development of chronic metabolic diseases later in life.

Key Words
- muscle
- insulin
- IGF1
- amino acids
- protein synthesis
- neonatal

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Introduction

Epidemiological studies have demonstrated that lower birth weight for a given gestational age increases an individual's risk of developing obesity (Valdez *et al*. 1994, Ravelli *et al*. 1999), coronary heart disease (Barker *et al*. 1993, 2010), glucose intolerance (Hales *et al*. 1991, Phipps *et al*. 1993, McKeigue *et al*. 1998), and type 2 diabetes (Curhan *et al*. 1996, Rich-Edwards *et al*. 1999) later in life. Small for gestational age (SGA) status at the time of birth, defined arbitrarily as birth weight <10% on standard pediatric growth curves (Battaglia & Lubchenco 1967), can result from many causes, one of which is placental insufficiency (Platz & Newman 2008). Placental insufficiency is defined as a smaller-than-normal placenta, with or without specific transporter deficiencies, that restricts nutrient flow from the mother to the fetus and uniquely causes intrauterine growth restriction (IUGR; Molteni *et al*. 1978, Marconi *et al*. 2006, Marconi & Paolini 2008, Regnault *et al*. 2013). Fetal IUGR leads to increased perinatal and neonatal morbidity and mortality (Pollack & Divon 1992, Tuuli *et al*. 2011), as well as the later-life pathologies mentioned above. Although nearly every fetal organ system is affected in IUGR, skeletal muscle growth is particularly vulnerable because blood flow and nutrient supplies are preferentially shunted to vital organs in

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response to decreasing fetal oxygenation (Tchirikov *et al.* 1998, Yajnik 2004*a*). As a result, skeletal muscle growth is preferentially restricted (Yau & Chang 1993, Padoan *et al.* 2004, Larciprete *et al.* 2005, Beltrand *et al.* 2008).

Skeletal muscle serves several important metabolic functions. First, resting energy expenditure varies considerably based on the amount of lean mass that an individual possesses (Mifflin *et al.* 1990, Nelson *et al.* 1992, Taguchi *et al.* 2011). Based on estimates for the energy required to maintain the muscle fractional protein synthetic rate (Waterlow 1984, Tipton *et al.* 2003), it has been proposed that greater muscle mass and increased energy expenditure from muscle protein turnover may contribute to the prevention of obesity (Newsholme 1978, Wolfe 2006). Second, skeletal muscle accounts for 80% of whole-body insulin-stimulated glucose uptake; thus, muscle maintains whole-body insulin sensitivity (DeFronzo *et al.* 1981). Third, several muscle secretory products or 'myokines' improve insulin sensitivity (Basaria & Bhasin 2012) and stimulate energy consumption within adipose tissue (Bostrom *et al.* 2012). Finally, sarcopenia, or the degenerative loss of skeletal muscle mass and function, affects 30% of adults over the age of 65 years and is a large contributor to morbidity and mortality (Doherty 2003). Thus, low muscle mass affects adult health and has important implications for quality of life, excess weight gain, and risk of developing insulin resistance and type 2 diabetes.

Reduced fetal skeletal muscle growth is not fully compensated after birth, as individuals who are born with low birth weight have lower muscle mass in adulthood (Gale *et al.* 2001, Kensara *et al.* 2005, Yliharsila *et al.* 2007). As skeletal myofiber number is set at the time of birth (Rowe & Goldspink 1969, Wigmore & Stickland 1983), it is possible that disruptions in myofiber formation during fetal life may not be fully recovered (Widdowson *et al.* 1972). In sheep models of maternal undernutrition or placental insufficiency, skeletal muscle growth is preferentially sacrificed and skeletal muscle mass is reduced at birth (Du *et al.* 2010). Under such circumstances, compensatory or 'catch-up' postnatal growth favors fat deposition and not muscle development (Louey *et al.* 2005, De Blasio *et al.* 2007, Ford *et al.* 2007). In humans, compelling associations link low birth weight and decreased muscle mass to future insulin resistance (Srikanthan & Karlamangla 2011), development of the metabolic syndrome and type 2 diabetes (Barker *et al.* 2002, Whincup *et al.* 2008, Atlantis *et al.* 2009), and risk of cardiovascular events later in life (Basaria & Bhasin 2012). Thus, suppressed development of muscle in IUGR fetuses could be a major contributor to their increased risk of later-life sarcopenia, obesity, and diabetes.

An understanding of how fetal skeletal muscle growth adapts to nutrient availability is important for determining how deficits in muscle growth contribute to metabolic diseases in adulthood. Therefore, the objectives of this article are to i) review the fundamentals of fetal myogenesis; ii) review the experimental studies showing that fetal undernutrition from maternal dietary restriction or placental insufficiency influences skeletal muscle growth; iii) highlight the epidemiological studies showing that low birth weight is associated with reduced muscle mass in adulthood; and iv) discuss how insufficient muscle mass as a result of IUGR might influence long-term metabolic health. Finally, potential therapeutic approaches to improving muscle mass in IUGR fetuses and research needs in this area are addressed.

Skeletal muscle development

Proliferation and differentiation of myoblasts and myofibers

Myoblasts are mononuclear cells that have the capacity to proliferate and differentiate into skeletal myofibers (Gerrard & Grant 2003, Zammit *et al.* 2006). Myoblasts, as well as adipocytes and fibroblasts, differentiate from the multipotent mesenchymal stem cell (MSC) population in the developing human embryo (Pittenger *et al.* 1999). Because both myocytes and adipocytes share a common progenitor, the milieu of nutrients and growth factors in early embryonic and fetal life could affect MSC commitment to either a myogenic or an adipogenic lineage (Du *et al.* 2013). Indeed, exposure of C2C12 myoblasts to adipogenic inducers *in vitro* has been shown to convert the differentiation pathway of myoblasts into that of adipoblasts (Teboul *et al.* 1995).

Once differentiated, myoblasts are classified as embryonic, fetal, or adult (Gerrard & Grant 2003). Embryonic myoblasts fuse to form primary myofibers by 20% of the length of gestation in sheep (Russell & Oteruelo 1981). Primary myofibers provide the scaffolding for the proliferation and differentiation of fetal myoblasts into secondary myofibers (Beermann *et al.* 1978). Secondary myofibers comprise the majority of myofibers and are highly nutrient responsive (Ward & Stickland 1991, Dwyer *et al.* 1994, Zhu *et al.* 2004). Secondary myogenesis occurs between 20 and 70% of the length of gestation (Russell & Oteruelo 1981) and involves the proliferation of fetal myoblasts followed by the expression of muscle regulatory

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factors (MRFs) (Fig. 1a and b). MRFs are a set of helix–loop–helix transcription factors, including *MYF5*, *MYOD* (*MYOD1*), *MRF4* (*MYF6*), and myogenin, that are expressed in a sequential manner during the differentiation process (Berkes & Tapscott 2005, Braun & Gautel 2011). Targets of the MRFs include proteins that regulate the switch from proliferation to differentiation, including retinoblastoma protein (RB (RB1)), which is an inhibitor of cell-cycle progression. Cyclin D1 and cyclin-dependent kinase 4 (CDK4) phosphorylate and inhibit RB to induce proliferation (Weinberg 1995, Spiller *et al*. 2002). As differentiation occurs, *MYOD* binds to myostatin, which results in the withdrawal of myoblasts from the cell cycle (Spiller *et al*. 2002). In addition, P21 inhibits CDK4 so that RB remains dephosphorylated to reduce cell-cycle activity (Guo *et al*. 1995). Cell-cycle withdrawal is concomitant with the expression of *MYOD*, *MYF5*, and myogenin (Sabourin & Rudnicki 2000; Fig. 1c).

Myogenesis is nearly complete by the end of gestation, as a full complement of myofibers has been observed at the time of birth in both mice and piglets (Rowe & Goldspink 1969, Wigmore & Stickland 1983). Postnatal muscle growth occurs primarily by myofiber hypertrophy, as has been demonstrated in mice (White *et al*. 2010). Muscle satellite cells (or adult myoblasts) reside between the basal lamina and myofiber membrane (Yin *et al*. 2013). During late fetal and early postnatal life, myofiber growth is accompanied by the proliferation and fusion of satellite cells with existing myofibers (Moss & Leblond 1971, White *et al*. 2010). During later stages of postnatal life and into adult life, increases in myofiber cross-sectional area occur without significant changes in myonuclear number (White *et al*. 2010). In response to extreme mechanical loading, injury, inflammation, and/or anabolic hormone stimulation, satellite cells serve as bona fide stem cells that can proliferate and differentiate to create new muscle (Ten Broek *et al*. 2010, Yin *et al*. 2013). Thus, satellite cells retain plasticity and regenerative capacity during postnatal life. However, the postnatal satellite cell population is vulnerable to fetal undernutrition. When pregnant mice were undernourished during the last week of gestation, pups at 7 weeks of postnatal age had reduced muscle mass, a 33% decrease in skeletal muscle precursor cells, and reduced regenerative capacity in response to muscle injury *in vivo*

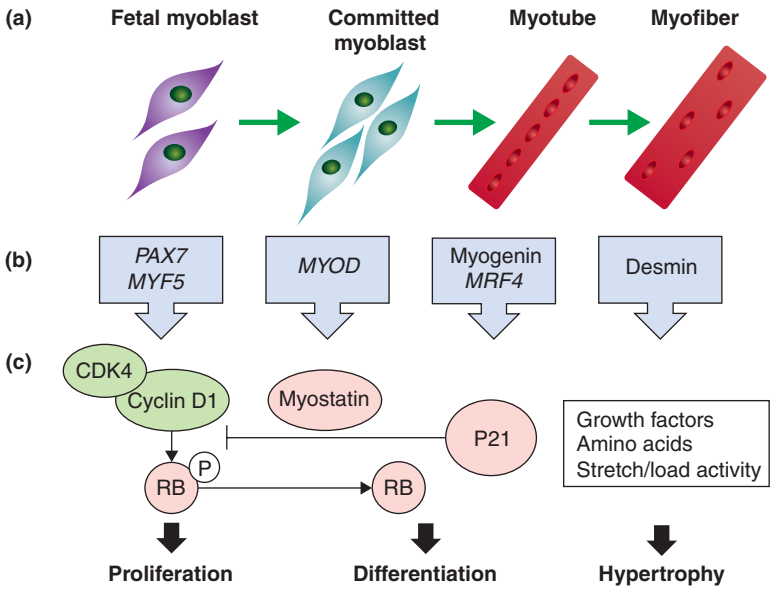

Figure 1
Key regulatory genes and proteins involved in fetal myogenesis. (a) Schematic diagram showing the differentiation of proliferating myoblasts into multinucleated myotubes and maturation into myofibers during fetal life. (b) Expression of muscle regulatory factors (MRFs) during myogenesis: *PAX7* and *MYF5* are expressed in the myoblast. The progression of differentiation is marked by the temporal expression of *MYOD*, *MRF4*, and myogenin. Desmin is the major intermediate filament expressed in mature muscle and its expression increases during gestation. (c) Targets of MRFs regulate the switch from proliferation to differentiation: expression of cyclin D1 and CDK4 induces myoblast proliferation by maintaining the inhibitor retinoblastoma protein (RB) in its phosphorylated and inactive state. As differentiation is activated, MYOD binds to myostatin and myoblasts withdraw from the cell cycle. In addition, P21 inhibits CDK4, which results in the dephosphorylation of RB to reduce cell cycle activity. This process results in the withdrawal of myoblasts from the cell cycle and subsequent fusion into myotubes. Myotube maturation and hypertrophy are stimulated by growth factors, amino acids, and stretch/load activity (Molkentin & Olson 1996, Yang & Makita 1996, Gaster *et al*. 2001, Zammit *et al*. 2006).

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(Woo *et al*. 2011). Whether the satellite cell population is permanently compromised during pregnancies complicated by IUGR in humans is an important question when considering the long-term effects of the compromised intrauterine environment.

Myofiber hypertrophy

Myofiber hypertrophy, or an increase in fiber diameter and length with or without satellite cell fusion, occurs as a net increase in balance between protein synthesis and degradation. When the rate of protein synthesis exceeds that of protein breakdown, the end result is net protein accretion and myofiber hypertrophy. Nutrients and growth factors are primary regulators of net protein balance and myofiber hypertrophy. However, stretching and loading of muscle also regulate muscle mass and protein synthesis, even during fetal life (Racca *et al*. 2013).

Nutrients and growth factors coordinate net protein accretion in skeletal muscle through the mammalian target of rapamycin (mTOR). Two multiunit complexes constitute mTOR: mTORC1 and mTORC2. The mTORC1 complex senses both intracellular and extracellular cues, such as growth factors, amino acids, energy status, and oxygen availability to either stimulate or inhibit cell growth. Comprehensive reviews of mTOR signaling and its coordination with cell growth in skeletal muscle are available (Goodman *et al*. 2011, Dodd & Tee 2012, Laplante & Sabatini 2012, Weigl 2012).

Under conditions of nutrient sufficiency (Fig. 2), growth factors such as insulin and insulin-like growth factor 1 (IGF1) bind to their respective tyrosine kinase receptors, which phosphorylate insulin receptor substrate 1 (IRS1). IRS1 activates phosphoinositide 3-kinase and protein kinase B (AKT) to stimulate mTORC1 (Takahashi *et al*. 2002). Amino acids such as leucine can stimulate mTORC1 independently of insulin or IGF1 by binding to leucyl-tRNA synthetase and activating RAG GTPase proteins, thus bringing Ras homolog enriched in brain (RHEB) to the surface of the lysosome (Han *et al*. 2012). Based on these positive inputs, mTORC1 then activates two major downstream effectors, ribosomal protein S6 kinase and 4E-binding protein 1 (4EBP1). mTORC1 phosphorylates the translation initiation repressor 4EBP1, which then releases eukaryotic initiation factor 4E and enables it to form the translation initiation complex.

Under conditions of nutrient and energy restriction (Fig. 2), rates of protein synthesis are decreased by the activation of the tuberous sclerosis complex (TSC) and suppression of mTORC1 activity. Limited oxygen and energy availability to the cell are sensed by three key proteins, all of which can activate TSC: hypoxia-inducible factor (HIF), regulated in development and DNA damage responses 1 (REDD1 (DDIT4)), and 5′-AMP-activated protein kinase (AMPK) (Hardie *et al*. 2012, Liu *et al*. 2012). AMPK, which is activated by an increased AMP:ATP ratio, also inhibits eukaryotic elongation factor 2 and peptide chain elongation (Leprivier *et al*. 2013). When amino acids are not available, uncharged tRNAs activate the protein general control nonrepressed 2 to phosphorylate eIF2A and suppress mRNA translation (Dong *et al*. 2000, Saad *et al*. 2013).

In catabolic states such as starvation, cancer, and burn injury, proteolytic pathways are activated in skeletal muscle for the purpose of supplying amino acids to organs such as the heart, liver, and brain (Biolo *et al*. 1995, Kadar *et al*. 2000, Biolo *et al*. 2002). Two proteolytic systems are active within skeletal muscle: ubiquitin–proteasome pathway (mediated by ubiquitin ligases atrogin 1 and muscle RING-finger protein 1 (*MURF1* (*TRIM63*))) and the autophagy–lysosome pathway. These pathways can modulate one another and are under coordinated control with protein synthetic pathways to maintain proper cell size (Bonaldo & Sandri 2013). AKT and forkhead box transcription factors (*FOXO*) play a crucial role in the regulation of this process (Fig. 2). The translocation of *FOXO* into the nucleus in its dephosphorylated state is required for the upregulation of atrogin 1 and *MURF1*, as well as for the transcription of autophagy-related genes, including *LC3* (*MAP1LC3A*) and *BNIP3* (Mammucari *et al*. 2007, Zhao *et al*. 2007). With growth factor stimulation, AKT phosphorylates *FOXO*, promoting its export from the nucleus, which thereby suppresses proteolysis when conditions favor protein synthesis. A recent report has also shown that autophagy in skeletal muscle of starved rats is regulated by insulin via mTORC1-mediated inhibition of UNC 51 like kinase (ULK1; Naito *et al*. 2013).

Our laboratory and others have shown that the AKT–mTORC1 signaling pathway is active in the skeletal muscle of fetal sheep in response to a variety of anabolic stimuli such as amino acids, insulin, and IGF1 (Shen *et al*. 2002, Anderson *et al*. 2005, Brown *et al*. 2009). However, it is not known whether the human IUGR fetus slows protein synthetic rates in muscle via adaptation to reduced levels of nutrients and growth factors or whether it activates protein breakdown as a result of cellular stress. Probably, these processes are not mutually exclusive; the fetus might develop a slower growth rate in response to decreased nutrient supply early in the course of placental

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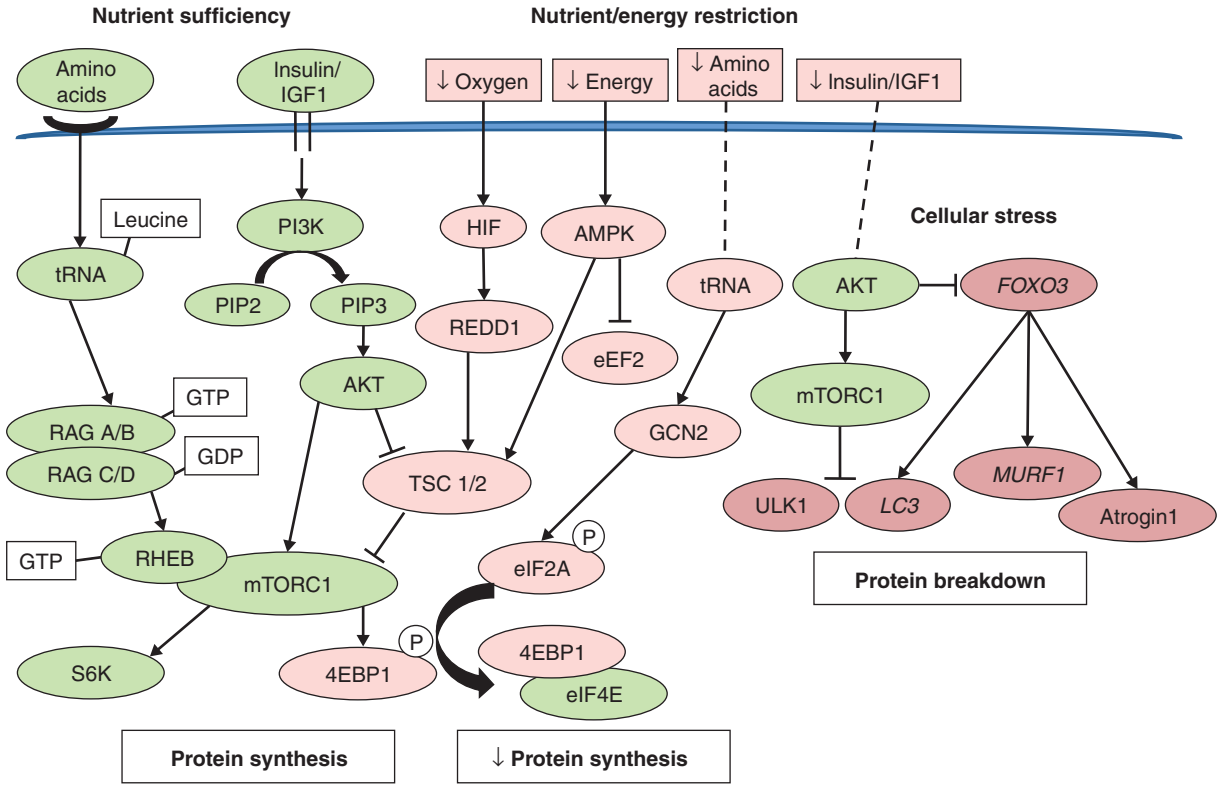

Figure 2

Major signaling pathways that regulate myofiber growth. Under conditions of nutrient sufficiency (depicted in green), nutrients (leucine), and growth factors (insulin and IGF1) coordinate net protein accretion in skeletal muscle through the mammalian target of rapamycin complex 1 (mTORC1). Leucine binds to its respective leucyl-tRNA synthetase and activates RAG GTPase proteins, thus bringing Ras homolog enriched in brain (RHEB) to the surface of the lysosome. Insulin and IGF1 bind to their respective tyrosine kinase receptors, which phosphorylate insulin receptor substrate 1 (IRS1). IRS1 activates phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) to stimulate mTORC1. mTORC1 activates ribosomal protein S6 kinase (S6K) and phosphorylates the translation initiation repressor 4EBP1, which then releases eukaryotic initiation factor 4E (eIF4E) and enables it to form the translation initiation complex. Under conditions of oxygen and energy restriction (depicted in pink), hypoxia-inducible factor (HIF), regulated in development and DNA damage responses 1 (REDD1), and 5′-AMP-activated protein kinase (AMPK) decrease the rates of protein synthesis by activating tuberous sclerosis complex (TSC) to suppress mTORC1 activity. When amino acids are not available, uncharged tRNAs activate the protein general control nonrepressed 2 (GCN2) to phosphorylate eIF2A and suppress mRNA translation. Under conditions of cellular stress (depicted in red), forkhead box transcription factor 3 (*FOXO3*) in its dephosphorylated state is translocated into the nucleus to upregulate ubiquitin-mediated proteolysis markers atrogin 1 and *MURF1*, as well as the autophagy marker *LC3*. Dashed lines represent lack of signal.

insufficiency, but then might activate catabolic pathways in the setting of worsening hypoxia and increased catecholamine and cortisol production as nutrient restriction progresses. This is a fundamental area of future investigation, as treatments to improve muscle growth will vary based on whether growth is slowed because of decreased anabolism or increased catabolism.

Nutrient and growth factor regulation of fetal skeletal muscle growth

Growth factors

Skeletal muscle growth is regulated by several growth factors, including IGF1, insulin, basic fibroblast growth factor (bFGF), and transforming growth factor-β (TGFB) (Allen & Rankin 1990, Frost & Lang 2012).

Several studies in humans, transgenic animals, and cell lines have demonstrated that IGF1 regulates both myoblast proliferation and myofiber hypertrophy. *Igf1* heterozygous knockouts in mice have reduced muscle mass (Powell-Braxton *et al.* 1993), whereas homozygous knockouts have severe muscle hypoplasia due to both decreased myocyte number and myofiber cross-sectional area (Liu *et al.* 1993, Mavalli *et al.* 2010). Similarly, mutations in the *IGF1* and *IGF1R* genes in humans cause both IUGR and postnatal growth restriction (Woods *et al.* 1996, Abuzzahab *et al.* 2003). Conversely, excessive IGF1 results in increased muscle mass and hypertrophy in postnatal life, as demonstrated by

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overexpressing *Igf1* in a transgenic mouse or by direct i.v. infusion into rats (Coleman *et al*. 1995, Adams & McCue 1998). In subconfluent myoblasts *in vitro*, IGF1 acts initially to promote proliferation (Rosenthal & Cheng 1995). In differentiated myotubes, IGFI promotes protein synthesis (Harper *et al*. 1987, Coleman *et al*. 1995).

Insulin also functions as a potent fetal skeletal muscle growth factor. Pancreatectomy in fetal sheep results in growth-restricted fetuses with decreased upper and lower extremity limb length (Fowden *et al*. 1989). These experiments confirm lack of insulin as the cause of growth restriction in cases of pancreatic agenesis in humans (Lemons *et al*. 1979). Conversely, studies in catheterized fetal sheep have shown that both insulin and IGF1 infusions promote whole-body and muscle-specific protein synthesis (Milley 1994, Boyle *et al*. 1998, Shen *et al*. 2003). Furthermore, insulin infusion into neonatal piglets stimulates skeletal muscle protein synthesis (Davis *et al*. 2002). High doses of insulin (at least 0.1 μM) increase protein synthesis and suppress protein breakdown in both primary cultured and immortalized myotubes *in vitro* (Gulve & Dice 1989, Cassar-Malek *et al*. 1999, Shen *et al*. 2005), including myotubes harvested and cultured directly from fetal sheep (Harper *et al*. 1987).

Other growth factors, including bFGF and TGFB, upregulate cyclin D1 levels in myoblasts, which then stimulate proliferation and myogenesis (Rao & Kohtz 1995). Myostatin is a member of the TGFB family of regulators and a potent inhibitor of myogenesis. Double-muscled cattle carry an inactivating mutation in the myostatin gene and have 20% more muscle than normal-muscled cattle (Grobet *et al*. 1997). Myostatin-null mice have two to three times greater muscle mass than WTs (McPherron *et al*. 1997). These animals also exhibit less insulin resistance and fat deposition, demonstrating the important role of muscle in the regulation of adipose tissue balance and insulin sensitivity (Guo *et al*. 2012). Follistatin is an inhibitor of myostatin and works through the activation of the IGF1R. Mice overexpressing follistatin have a threefold greater increase in myofiber diameter than those over-expressing follistatin with a nonfunctional IGF1R (Kalista *et al*. 2012).

Amino acids

Amino acids are essential for muscle protein synthesis. In addition to forming the building blocks of proteins, amino acids have important regulatory effects on mTORC1 activation and muscle protein synthesis. Amino acids increase skeletal muscle protein synthesis in adults, both under normal postprandial conditions and during catabolic states such as after trauma and sepsis (Wolfe 2005, Drummond & Rasmussen 2008). Increasing amino acid delivery positively affects net protein balance in infants born preterm or at term (Poindexter *et al*. 1997, Thureen *et al*. 2003, Reynolds *et al*. 2008). In neonatal piglets, mixed amino acid or leucine supplementation increases muscle protein synthesis through mTORC1-dependent pathways (O'Connor *et al*. 2003*a*,*b*, Suryawan *et al*. 2008, 2012).

Studies that address the effects of amino acids on skeletal muscle growth during fetal life are more limited. One study carried out by de Boo *et al*. (2005) showed that a mixed amino acid infusion administered for 4 h increased whole fetal protein accretion in fetal sheep studied during late gestation. Our laboratory showed that a mixed amino acid infusion activated signaling through mTORC1 within the skeletal muscle of fetal sheep, but only when there was a concurrent rise in insulin concentrations (Brown *et al*. 2009). Further studies to determine the interactive roles of amino acids and growth factors in the regulation of fetal skeletal muscle development are needed.

Reduced fetal skeletal muscle growth: insights from models of fetal undernutrition

Effects of fetal undernutrition on myoblast proliferation and myofiber number

Studies in mice and pigs have shown that myofiber number is set around the time of birth (Rowe & Goldspink 1969, White *et al*. 2010). Similar growth patterns have been observed in humans, as DNA content in the gastrocnemius muscle increases exponentially between weeks 15 and 25 of gestation and plateaus by term (Widdowson *et al*. 1972). Thus, conditions that deprive the fetus of nutrients and growth factors during myofiber formation can have a lasting impact on myofiber number.

Studies of maternal nutrient restriction during pregnancy in a variety of animal models have shown dramatic effects of reduced nutrient supply on the establishment of fetal myofiber number, with secondary myofibers being more vulnerable to restricted fetal nutrient supply than primary myofibers in sheep and pigs (Ward & Stickland 1991, Dwyer *et al*. 1994, Zhu *et al*. 2004). In rats fed 30% of an *ad libitum* diet during gestation, secondary myofiber number within the fetal soleus and lumbrical muscles was decreased by 30% (Wilson *et al*. 1988). When pregnant

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sheep were diet restricted by 50% during early gestation and mid-gestation, which are coincident with the maximal period of myoblast proliferation (Fahey *et al.* 2005*a*), fetal myofiber number was decreased at mid-gestation and this effect persisted when tested at 8 months of age (Zhu *et al.* 2004, 2006). Guinea piglets born to mothers who had a 40% reduction in feed intake during the entirety of gestation had 25% less myofibers within glycolytic muscle types (Dwyer & Stickland 1992*a*). Similar reductions in myofiber number were observed when the duration of maternal dietary restriction in guinea pigs was shortened, but still overlapped with the peak period of secondary myofiber formation (Dwyer *et al.* 1995). Runted piglets, or those piglets that weigh 60% of the mean litter weight, have persistent deficits in myofiber number and muscle mass as adults (Powell & Aberle 1980). They also become fatter and less insulin sensitive (Poore & Fowden 2004). Myofiber number in pigs positively correlated with average daily weight into early adulthood (70–130 days of postnatal age), providing evidence that myofiber number influences postnatal muscle growth trajectory (Dwyer *et al.* 1993).

The mechanisms for restriction of muscle fiber number from fetal undernutrition are not understood, though there is evidence for the suppression of fetal myoblast cell-cycle activity. In a model of placental insufficiency resulting from sheep bred to produce litters of multiple lambs of variable birth weight (from 2 to 5 kg), low-birth-weight lambs had less muscle DNA and decreased percentage of nuclei entering the S-phase of the cell cycle, indicative of fewer myonuclei per myofiber and decreased cell-cycle activity compared with larger lambs (Greenwood *et al.* 1999, 2000). This is not unexpected, given that maternal nutrient restriction results in reductions in circulating fetal plasma IGF1 concentrations in rats (Straus *et al.* 1991), guinea pigs (Dwyer & Stickland 1992*b*), and sheep (Lee *et al.* 1997, Osgerby *et al.* 2002, Costello *et al.* 2008, Ward *et al.* 2008). However, it should be noted that total myofiber number was not different between small and large lambs in this study (Greenwood *et al.* 1999). There remain many unanswered questions about the interaction between the effects of chronic nutrient restriction and subsequent decreases in fetal growth factor concentrations on myoblast proliferation and the capacity for compensatory muscle growth.

Effects of fetal undernutrition on myofiber hypertrophy

Studies that extend maternal dietary restriction into late gestation to evaluate the effects on fetal myofiber hypertrophy are more limited. When pregnant sheep were fed 70% of a control diet beginning at day 26 of gestation, the fetal semitendinosus muscle weight was decreased by 20% on day 135 of gestation (Osgerby *et al.* 2002). When pregnant sheep were diet restricted by 50% during mid-gestation to late gestation (days 85–115 of a 145-day gestation period), individual muscle weights of offspring at 2 weeks of life were decreased by 15–20% compared with controls (Fahey *et al.* 2005*b*). A shorter but more severe dietary restriction allowing 30% of *ad libitum* intakes for 7 days during late gestation in sheep resulted in decreased muscle weights compared with controls (Greenwood *et al.* 1999). In a model of placental insufficiency in sheep bred to produce multiple lambs per litter, the trajectory of muscle growth was decreased in small, runted lambs compared with large lambs, as measured by weight over time between 85 and 130 days of gestation. The muscle protein:DNA ratio on day 130 of gestation in small lambs was also decreased (Greenwood *et al.* 1999).

Normalizing dietary intake after early maternal nutrient restriction (days 30–70) in pregnant sheep, however, resulted in compensatory myofiber hypertrophy as evidenced by fewer myofibers but larger fiber cross-sectional area compared with controls (Fahey *et al.* 2005*b*, Zhu *et al.* 2006). The phenomenon of postnatal catch-up growth after fetal growth restriction has been well described in a variety of species, including in humans (Jimenez-Chillaron & Patti 2007, Tudehope *et al.* 2013). However, the extent to which muscle growth is able to fully compensate during postnatal life after nutrient restriction *in utero* is not entirely clear. Longer-term follow-up of sheep into adolescence and adulthood after mid-gestation nutrient restriction has shown accelerated fat deposition at the expense of lean mass growth (Louey *et al.* 2005, De Blasio *et al.* 2007, Ford *et al.* 2007). In undernourished fetal rats, compensatory myofiber hypertrophy in the diaphragm occurs through postnatal day 21, though adult myofiber cross-sectional area is ultimately smaller (Prakash *et al.* 1993). These results, taken together, indicate decreased protein accretion and fetal myofiber hypertrophy as a result of fetal undernutrition, with partial, but not complete capacity for compensatory muscle growth during postnatal life.

Effects of fetal undernutrition on myofiber maturation

A complex schema exists for defining muscle fiber types in mammals based on a variety of features, including the predominant type of myosin heavy chain (MHC)

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expressed (type I, type IIa, type IIx, and type IIb), contractile machinery and speed of contraction, distribution of oxidative and glycolytic enzymes, and mitochondrial density (Pette & Staron 2001, Schiaffino & Reggiani 2011). Fiber type composition of skeletal muscle can undergo changes based on environmental influences (Simoneau & Bouchard 1995), as myofibers can be affected by neuromuscular activity, exercise training, mechanical loading, and aging (Pette & Staron 2001). Additionally, maternal dietary restriction results in fiber type transitions in offspring, generally favoring increased type I fiber expression. For example, studies that have evaluated fiber type shifts in the late fetal or early neonatal period after maternal dietary restriction in both sheep and rats found either a relative increase in type I oxidative fibers or a relative decrease in glycolytic type II fibers (Fahey *et al.* 2005*b*, Prakash *et al.* 1993, Costello *et al.* 2008). Runted piglets have more type I fibers than their appropriately grown littermates (Wank *et al.* 2000, Bauer *et al.* 2006). These findings are not uniformly consistent, as pups of undernourished pregnant mice exhibited a shift from type I to type IIa and IIb fibers at 7 weeks of age (Woo *et al.* 2011). However, any adaptation in MHC expression that develops in response to fetal undernutrition does not appear to persist and, in fact, may shift during the lifespan. For example, when fiber type assessments were extended into the adolescent period in offspring of nutrient-restricted sheep, glycolytic type II fibers predominated (Zhu *et al.* 2006, Daniel *et al.* 2007). Low-birth-weight humans evaluated at 19 years of age had a decreased proportion of type IIa fibers compared with a control group with normal birth weights (Jensen *et al.* 2007). Further work in this area is required to determine the long-term significance of fiber type shifts as a result of fetal undernutrition.

Skeletal muscle growth is particularly vulnerable in the fetus exposed to fetal undernutrition from placental insufficiency

Placental insufficiency is a condition whereby a poorly functioning placenta restricts nutrient supply to the fetus, preventing normal fetal growth (Figueras & Gardosi 2011). If placental insufficiency begins early in pregnancy, the entire process of myogenesis is at a high risk of getting attenuated and/or disrupted. Deficient skeletal muscle mass is a characteristic of the human fetus affected by IUGR (Yau & Chang 1993, Padoan *et al.* 2004, Larciprete *et al.* 2005, Beltrand *et al.* 2008). Placental insufficiency commonly begins early in pregnancy so that nutrient restriction to the fetus is chronic, progressive, and severe, often leading to preterm delivery when fetal well-being is severely compromised (De Jesus *et al.* 2013). Fetal skeletal muscle growth is particularly vulnerable during placental insufficiency, because blood, oxygen, and nutrients are preferentially shunted to vital organs (Tchirikov *et al.* 1998, Yajnik 2004*a*). Consequently, at least in animal models of placental insufficiency, skeletal muscle weight is disproportionately reduced compared with body weight (Desai *et al.* 1996, Greenwood *et al.* 2000, Bauer *et al.* 2003).

Placental size and function, fetal growth, and fetal nutrient and growth factor availability have been well characterized in a sheep model of chronic and progressive placental insufficiency, which was developed to mimic a natural condition of placental and fetal growth restriction that occurs in sheep that carry their pregnancies in the hot summer months (PI-IUGR; Bell *et al.* 1987; Fig. 3). The PI-IUGR model accurately reflects the characteristics that occur during human pregnancies affected by conditions that cause placental insufficiency and IUGR (Barry *et al.* 2008). Similar to maternal dietary restriction during pregnancy, fetal plasma insulin and IGF1 concentrations in PI-IUGR fetuses are 50% of the normal values as early as 70% of the total length of pregnancy (Fig. 3; de Vrijer *et al.* 2006, Thorn *et al.* 2009, Macko *et al.* 2013). Other sheep models of chronic placental insufficiency caused by pre-pregnancy reduction of placental attachment sites or uteroplacental embolization also demonstrate decreased fetal insulin and IGF1 concentrations (Owens *et al.* 1994, Eremia *et al.* 2007), as do human IUGR fetuses (Nicolini *et al.* 1990, Lassarre *et al.* 1991, Leger *et al.* 1996, Iniguez *et al.* 2006). Leucine flux from the mother to the fetus is decreased by 90% of the length of gestation in PI-IUGR sheep (Fig. 3; Brown *et al.* 2012, Regnault *et al.* 2013). Similarly, amino acid transport across the placenta is impaired in the third trimester of human IUGR pregnancies (Cetin *et al.* 1992, Paolini *et al.* 2001).

Two of the distinguishing features that separate models of placental insufficiency from maternal dietary restriction are fetal hypoxemia and increased production of counter-regulatory hormones. In the PI-IUGR sheep model, norepinephrine and cortisol concentrations are increased (Leos *et al.* 2010), and fetuses are severely hypoxemic (Regnault *et al.* 2007, Leos *et al.* 2010), consistent with evidence from severe IUGR in human pregnancies (Pardi *et al.* 1993). Oxygen sensors such as HIF (HIF1A) and AMPK (PRKAA1) might play a role in the regulation of fetal muscle growth under conditions of placental insufficiency, as has been shown in placentas

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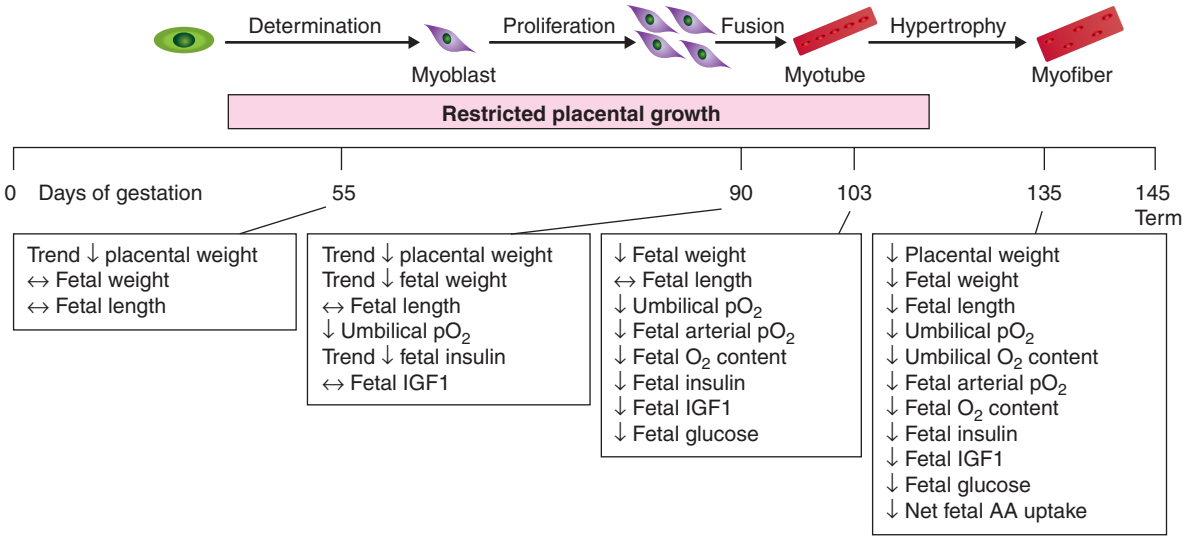

Figure 3

Progressive physiological changes in a model of placental insufficiency-induced IUGR (PI-IUGR) in relation to fetal myogenesis. Pregnant sheep were housed in an environmental chamber with elevated ambient temperatures to restrict placental growth (PI-IUGR) beginning on day 40 for a maximum of 80 days during their 145-day gestation period. Placental weights, fetal weights, and fetal lengths were compared between PI-IUGR sheep and sheep housed in thermo-neutral conditions (controls) during early gestation (day 55), mid-gestation (days 90 and 103), and late gestation (day 135). At mid- and late-gestation time points, surgery was performed in PI-IUGR and control sheep for the placement of fetal umbilical and arterial sampling catheters to compare umbilical and fetal oxygenation, circulating fetal growth factor concentrations, and fetal glucose and amino acid (AA) concentrations. Arrows (↓) represent changes in parameters in PI-IUGR animals compared with controls; ↔, no change in PI-IUGR animals and controls. A schematic showing the progression of fetal myogenesis during ovine gestation is shown at the top of the figure (Fahey *et al*. 2005*a*, Regnault *et al*. 1999, 2002, 2007, Limesand *et al*. 2006, de Vrijer *et al*. 2006, Ziebell *et al*. 2007, Arroyo *et al*. 2008, 2009, Thorn *et al*. 2009, Brown *et al*. 2012, Macko *et al*. 2013).

collected from human IUGR pregnancies (Cindrova-Davies *et al*. 2013).

Relationships between low birth weight and skeletal muscle mass in humans

Epidemiological evidence supports that reduced muscle mass in adulthood is, in part, due to environmental influences from placental insufficiency during fetal life. Such evidence has been generated by studies carried out in infants with a birth weight <2500 g at term gestation or who were documented as SGA. Two important studies using epidemiological data from the third National Health and Nutrition Examination Survey (NHANES) cohort have identified low birth weight as an early predictor of reduced muscle growth in childhood. Hediger *et al*. (1998) first demonstrated an overall deficit in the amount of muscularity estimated by anthropometric measurements of upper-arm circumference in SGA infants compared with appropriately sized for gestational age (AGA) infants up to 3 years of age. Baker *et al*. (2010) further showed that while head circumference growth is maintained between 2 months and 8 years of age in SGA children compared with AGA children, muscle growth remains stunted. When body composition was measured by dual-energy X-ray absorptiometry (DXA) in adolescents, low birth weight was found to be associated with decreased lean body mass independent of age, sex, pubertal stage, physical activity, and height (Singhal *et al*. 2003). Even as early as the immediate neonatal period, lean body mass was found to increase between 36 and 41 weeks in AGA neonates, but not in SGA neonates (Lapillonne *et al*. 1997).

The association between birth weight and muscle mass extends into adulthood. Several large population-based studies have found that low birth weight predicts lower adult muscle mass (measured by DXA) in men and women during young adulthood (Kahn *et al*. 2000), middle-ages (Sayer *et al*. 2004, Kensara *et al*. 2005, Yliharsila *et al*. 2007), and late adulthood (Gale *et al*. 2001). Monozygotic twin studies in both men and women have found that the lower-birth-weight twin had less lean body mass and more subcutaneous fat than the heavier twin, supporting the consistent observation that the intrauterine environment, independent of genetic influences, predicts lean mass in adulthood (Loos *et al*. 2001, 2002). Even as late as the seventh decade of life, 25% of the

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variation in lean body mass was explained by birth weight (Gale *et al.* 2001). As obesity is generally associated with excess lean as well as fat mass, obesity found following low birth weight presents a unique mechanism that may not necessarily be due to increased energy intake that characterizes most cases of adult obesity.

Effects of IUGR on skeletal muscle growth and function and long-term metabolic health

Populations around the world are faced with epidemic increases in the incidence of obesity and diabetes. In the USA, more than one-third of adults and 17% of children and adolescents are obese (Ogden *et al.* 2012). Projections show that one in three Americans will develop diabetes by 2050 (Boyle *et al.* 2010). Compelling associations link low birth weight and decreased muscle mass to the development of the metabolic syndrome and type 2 diabetes (Whincup *et al.* 2008, Atlantis *et al.* 2009) and an increased risk of cardiovascular events later in life (Basaria & Bhasin 2012). Thus, it is imperative that all major factors that contribute to diabetes and obesity risk be investigated, including the role of disproportionately reduced muscle mass.

The amount of muscle mass has major impact on fat deposition, insulin sensitivity, strength, and locomotion. Interactions between muscle mass, fat mass, and fat distribution (visceral vs subcutaneous) have been demonstrated, supporting the concept that reduced capacity for muscle growth favors and accelerates visceral fat deposition and obesity (Yajnik 2004*b*, Kensara *et al.* 2005). For example, intrauterine growth patterns contribute to the 'thin-fat' phenotype of Indian diabetic patients. This phenotype is characterized by less muscle mass but greater body fat and central obesity (Yajnik 2004*b*). Infants born in India compared with infants born in the UK are lighter, shorter, and thinner, but have similar subscapular skin fold thicknesses, indicating smaller muscle mass but preserved fat mass (Yajnik *et al.* 2003). There are also direct links between low birth weight and insulin resistance, with evidence that insulin signaling pathways within human skeletal muscle are disrupted as a result of an IUGR pregnancy (Ozanne *et al.* 2005, Jensen *et al.* 2008). The effects of low birth weight have also been shown to affect muscle strength. Grip strength is a measure of muscle strength and predictor of quality of life, morbidity, and mortality (Rantanen *et al.* 2000). Epidemiological studies have shown a positive correlation between birth weight and grip strength in adulthood (Inskip *et al.* 2007), primarily through the association of lean mass composition (Yliharsila *et al.* 2007, Ortega *et al.* 2009). One study comprehensively evaluated grip strength, maximal isometric voluntary contraction (MVC) of the quadriceps femoris, and muscle fatigue before and after an 8-week training program in women who had a ponderal index (PI, a marker of thinness) recorded at the time of birth. Results showed that women born with a PI $<10\%$, reflecting IUGR during the pregnancy, had 11% lower grip strength, 9–24% lower MVC, and a higher rate of muscle fatigue both before and after training compared with women who had a normal PI at the time of birth (Brutsaert *et al.* 2011). In summary, these findings implicate structural and functional deficits in muscle as major contributors to an increased risk of later-life development of metabolic and cardiovascular diseases in those born with a low birth weight due to IUGR (Barker *et al.* 2005, Barker 2006, Warner & Ozanne 2010).

Potential for improving fetal muscle growth in IUGR: future research directions

Clinical attempts at increasing maternal nutrition during human pregnancy to improve fetal growth have been largely

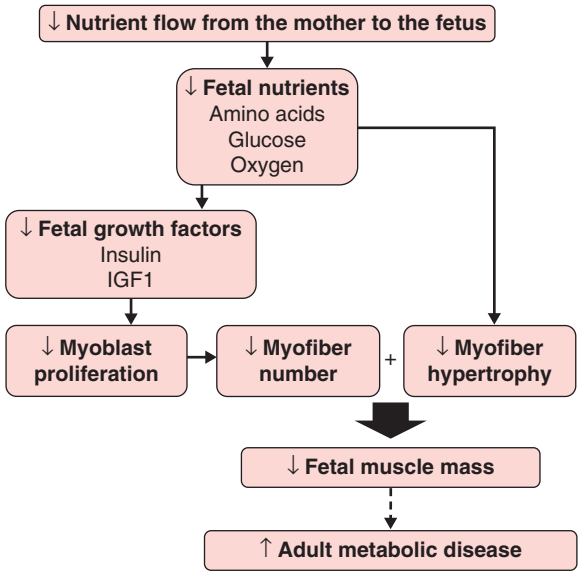

Figure 4
Proposed mechanisms for reduced skeletal muscle growth during conditions of fetal undernutrition. During conditions of fetal undernutrition (from either maternal dietary restriction or placental insufficiency), nutrient delivery to the fetus (amino acids, glucose, and oxygen) and circulating fetal growth factors (insulin and IGF1) are restricted. The combination of decreased supply of growth factors and nutrients leads to reduced rates of myoblast proliferation and myofiber hypertrophy, ultimately leading to reductions in fetal skeletal muscle mass. The dashed line indicates pathways yet to be determined for how decreased fetal muscle mass contributes to an increased risk of adult metabolic diseases such as obesity, coronary heart disease, and type 2 diabetes.

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unsuccessful. Nutritional supplements with balanced energy and proteins given to pregnant mothers at a high risk of having an IUGR fetus increased birth weight, though whether this promoted fat deposition vs lean mass was not determined (Rush *et al.* 1980). Current postnatal nutritional interventions for IUGR neonates designed to increase body weight favor fat deposition over muscle growth. The problem is magnified when preterm birth is considered. Almost all extremely low-birth-weight preterm infants experience postnatal growth restriction in the neonatal intensive care unit, even when they are born AGA (Dusick *et al.* 2003, Ehrenkranz *et al.* 2006). Preterm birth alone can disrupt normal skeletal muscle development, as preterm infants who are not IUGR have decreased lean mass and increased fat mass at the time of discharge compared with normal full-term infants (Johnson *et al.* 2012).

Promisingly, however, specific nutrient and growth factor supplementation studies in sheep models of placental insufficiency have yielded encouraging results. Chronic, low-dose IGF1 infusions into IUGR sheep fetuses, either by direct fetal i.v. infusion or by intra-amniotic supplements, improved fetal organ growth (Eremia *et al.* 2007). Additionally, short-term amino acid infusion given directly to PI-IUGR sheep fetuses increased protein accretion rates by suppressing protein breakdown rates, although whether this affected skeletal muscle growth specifically is yet to be determined (Brown *et al.* 2012). The use of large animal models of chronic placental insufficiency, such as the PI-IUGR model, allows for the manipulation of fetal substrate and hormone concentrations during critical windows in muscle development. This strategy will provide critical information about the optimal timing and type of supplementation to improve muscle growth in IUGR fetuses, as well as determine cellular deficits that might explain how myoblast proliferation and myofiber hypertrophy become permanently impaired (Fig. 4). Targeting strategies to promote fetal muscle development could improve the potential for postnatal muscle growth, thereby minimizing the risk of developing long-term insulin resistance and chronic metabolic diseases in IUGR individuals.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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