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Minireview

Maternal Obesity, Inflammation, and Fetal Skeletal Muscle Development[1]

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ABSTRACT

Maternal obesity coupled with Western-style high-energy diets represents a special problem that can result in poor fetal development, leading to harmful, persistent effects on offspring, including predisposition to obesity and type 2 diabetes. Mechanisms linking maternal obesity to the increased incidence of obesity and other metabolic diseases in offspring remain poorly defined. Because skeletal muscle is the principal site for glucose and fatty acid utilization and composes 40%–50% of total body mass, changes in the properties of offspring skeletal muscle and its mass resulting from maternal obesity may be responsible for the increase in type 2 diabetes and obesity. Fetal stage is crucial for skeletal muscle development because there is no net increase in the muscle fiber number after birth. Fetal skeletal muscle development involves myogenesis, adipogenesis, and fibrogenesis, which are all derived from mesenchymal stem cells (MSCs). Shifting commitment of MSCs from myogenesis to adipogenesis and fibrogenesis will result in increased intramuscular fat and connective tissue, as well as reduced numbers of muscle fiber and/or diameter, all of which have lasting negative effects on offspring muscle function and properties. Maternal obesity leads to low-grade inflammation, which changes the commitment of MSCs in fetal muscle through several possible mechanisms: 1) inflammation downregulates wingless and int (WNT) signaling, which attenuates myogenesis; 2) inflammation inhibits AMP-activated protein kinase, which promotes adipogenesis; and 3) inflammation may induce epigenetic modification through polycomb group proteins. More studies are needed to further explore the underlying mechanisms associated with maternal obesity, inflammation, and the commitment of MSCs.

adipogenesis, fetus, inflammation, maternal obesity, mesenchymal stem cells, myogenesis, skeletal muscle

INTRODUCTION

Maternal Obesity and Offspring Health

Obesity is a growing, serious problem in developed and certain developing countries. According to the latest National Health and Nutrition Examination survey (1999–2002), 26% of nonpregnant women ages 20–39 yr are overweight, and 29% are obese [1]. More importantly, there is a shift toward higher gestational weight gain [2], which indicates excessive nutrient intake during gestation in affluent countries. In addition to maternal obesity (MO), an alarming trend in childhood obesity is also recorded. Epidemiological studies clearly establish a strong association between MO and obesity in offspring. Maternal obesity might adversely affect fetal development, producing lasting effects on offspring, including predisposition to obesity and diabetes [3–6]. Obesity and insulin resistance are closely linked. A growing body of evidence demonstrates that obesity and insulin resistance have a fetal origin in many patients. Insulin resistance indicated by slower glucose removal rates and higher insulin levels is observed in offspring of parents with type 2 diabetes [7–9].

Skeletal muscle and liver are the two key insulin-responsive organs [10]. Skeletal muscle composes 40%–50% of body mass, making it the most important tissue for glucose and fatty acid utilization. The fetal stage is crucial for skeletal muscle development because there is no increase in muscle fiber numbers after birth. Poor fetal skeletal muscle development impairs glucose and fatty acid metabolism by skeletal muscle in response to insulin stimulation, and thus predisposes offspring to diabetes and obesity later in life [11, 12]. Human infants who are small at birth are at greater risk for type 2 diabetes and obesity [13–15]; decreased muscle mass is a major factor in low birth weight [13, 16]. On the other hand, mice with enhanced fetal skeletal muscle growth due to a muscle-specific myostatin knockout have resistance to diabetes and obesity induced by high-glucose and high-fat diets [17, 18]. Skeletal muscle mass and oxidative capacity are positively related to the resting energy expenditure, and low resting energy expenditure is associated with increased incidence of obesity and diabetes [19, 20]. Therefore, changes in fetal skeletal muscle development are likely to provide a link between MO and progeny obesity.

In fetal muscle, a large number of mesenchymal stem cells (MSCs) exist. Although the vast majority of MSCs commit to myogenesis, MSCs are also capable of differentiating into other cell types, such as adipocytes or fibroblasts [21, 22]. A shift from myogenesis to adipogenesis or fibrogenesis will replace muscle fibers with adipocytes or fibrous tissues, impairing the physiological functions of skeletal muscle, such as reduction in

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muscle force [23] and oxidative capacity [24]. In addition, enhanced adipogenesis within muscle leads to skeletal muscle insulin resistance, which plays a key role in the pathogenesis of type 2 diabetes [21].

Low-grade inflammation accompanies obesity [25–27]. Maternal obesity induces fetal inflammation, which changes fetal skeletal muscle development by promoting adipogenesis [28, 29]. Because the effects of maternal obesity and overnutrition on inflammation and overall fetal developmental programming have been reviewed previously [30–32], this discussion will be limited to the impact on fetal skeletal muscle development of MO-induced fetal inflammatory response.

Fetal Skeletal Muscle Development

Skeletal muscle cells are derived from MSCs, a process controlled by a well-coordinated set of transcription factors, which include wingless and int (WNT), paired box gene 3 (PAX3) and PAX7, and myogenic regulatory factors (MRFs) [33, 34]. WNT signaling is crucial for mesoderm formation. Within the surrounding tissues, a portion of MSCs to become myogenic progenitor cells express PAX3 and PAX7, which then induce the expression of MRFs [35, 36]. Myogenic precursor cells further differentiate into myoblasts and then myotubes under the control of MRFs, which include MYOD, MYF5, MYOG (myogenin), and MYF6 (also known as MRF4) [37]. Skeletal muscle development can be roughly separated into three stages: embryonic, fetal, and postnatal. These stages correspond to primary, secondary, and postnatal myogenesis, respectively [38]. The secondary myogenesis during the fetal stage forms most muscle fibers [38, 39]. Because of the large number of muscle fibers needed to be formed, secondary myogenesis is susceptible to stresses, such as maternal undernutrition, which reduces fetal muscle fiber numbers [24, 40]. Skeletal muscle development has lower priority in nutrient partitioning than does the development of the neural system, internal organs, and bone, making it susceptible to nutrient fluctuation [24].

Formation of secondary myofibers and adipogenesis begins in mid gestation in humans and sheep and in late gestation in rodents [41–43]. There are a large number of MSCs in fetal muscle that can differentiate into adipogenic cells starting at mid gestation. Adipose tissue growth later in life is due to both hypertrophy and hyperplasia [41]. However, new adipocytes generated later in life are mostly located in visceral, retroperitoneal, and subcutaneous fat depots, with few located in intramuscular fat [44]. Thus, adipogenesis occurring inside muscle during the fetal stage has a dominant effect on the number of adipocytes existing inside the muscle, an event associated with skeletal muscle insulin resistance [21]. Enhanced adipogenesis in fetal muscle produces a large number of adipocytes in skeletal muscle, which predisposes the offspring muscle to accumulate intramuscular fat because of the hypertrophy of existing adipocytes [6]. Mechanisms controlling adipogenesis in fetal muscle in vivo are poorly defined, although there are numerous in vitro cell culture studies [45]. These studies identify several transcription factors regulating adipogenesis, which include CCAAT/enhancer-binding protein (CEBPA and CEBPB), peroxisome proliferator-activated receptor (PPARG), and sterol regulatory element-binding transcription factor 1 (SREBF1, also known as SREBP-1c) [46]. CEBPB is the first factor induced by adipogenic stimuli and is followed by an increase in PPARG and CEBPA expression. PPARG and CEBPA are essential transcription factors in adipogenesis that activate many downstream target genes specific to adipocytes [47–49].

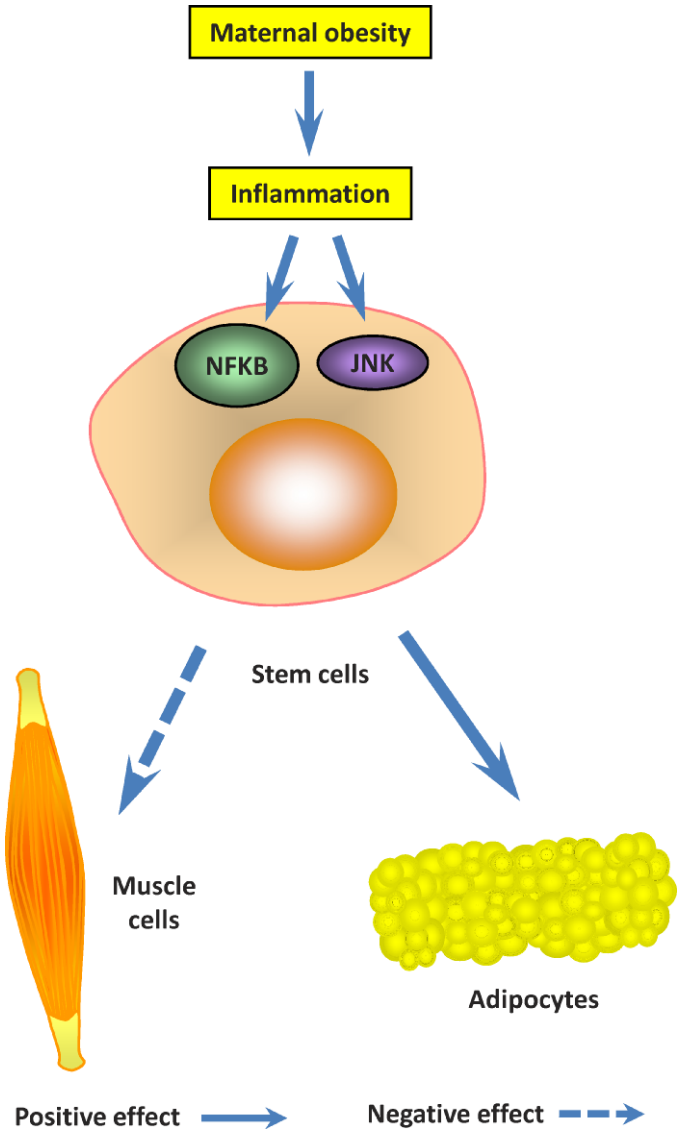

FIG. 1. Inflammation and fetal skeletal muscle development. Inflammation inhibits stem cell differentiation into myocytes but promotes differentiation into adipocytes.

Fetal stage is also associated with fibrogenesis. Fibroblasts developed during this stage synthesize connective tissue that forms perimysium and epimysium in fetal skeletal muscle during late gestation. Limited studies have also indicated that maternal nutrition affects the connective tissue content in skeletal muscle. In pigs, runts are smaller than their littermates and experienced maternal nutrient restriction during the fetal stage. When compared to their counterparts, grown runts have a higher concentration of collagen in their skeletal muscle [50]. Additional studies on the association between maternal nutrition, fibrogenesis, and collagen accumulation in offspring muscle are apparently needed.

OBESITY, INFLAMMATION, AND FETAL MUSCLE DEVELOPMENT

Inflammatory Signaling in Fetal Muscle of MO Mothers

Inflammation has received extensive attention recently because of its association with several diseases, including

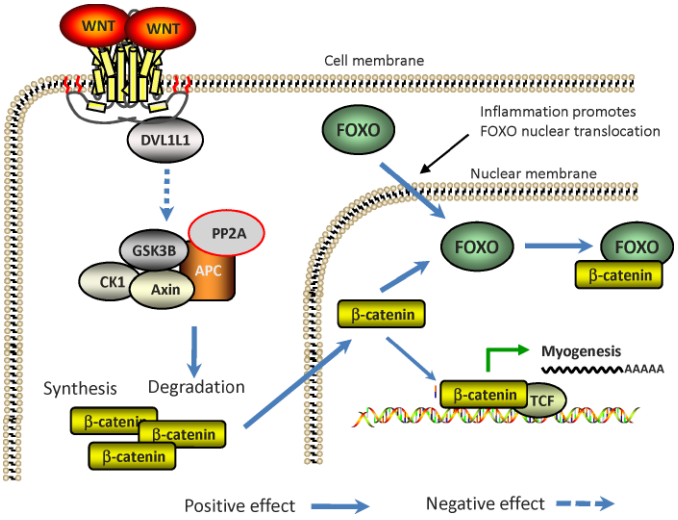

FIG. 2. WNT/β-catenin signaling, inflammation, and myogenesis. Wnt signaling enhances β-catenin nuclear translocation, but inflammation promotes the formation of β-catenin/FOXO complexes, which divert β-catenin from forming a complex with TCF to induce myogenesis. DVL1L1, disheveled, dsh homolog 1; GSK-3B, glycogen synthase kinase 3; PP2A, protein phosphatase 2A.

cancer, diabetes, and obesity. Obesity induces chronic low-grade inflammation that may be the primary cause of diseases associated with obesity [51]. Generally, inflammation is classified as acute or chronic [52]. Cellular and molecular mechanisms in acute inflammatory response are well studied. Events involved in chronic inflammation and their physiological consequences are beginning to be appreciated [53]. Interleukin 6 (IL6) and tumor necrosis factor α (TNF) are among the most studied inflammatory mediators associated with increased body fat [54–56].

Inflammatory signaling is primarily mediated by the nuclear factor-κB (NFKB) pathway (Fig. 1) [57]. Conserved helix-loop-helix ubiquitous kinase (CHUK, also known as IKKα) and IκB kinase β (IKBKB, also known as IKKβ) phosphorylate IκB, which results in its ubiquitination, and then degradation. This process releases NFKB from IκB and allows translocation of NFKB to the nucleus, where it activates the transcription of specific genes [58]. There are several NFKB target genes, such as IL6, TNF, and chemokine (C-C motif) ligand 2 (CCL2, also known as monocyte chemotactic protein-1 [MCP-1]), and their expression enhances inflammation [51].

The c-Jun N-terminal kinase (JNK) is another mediator of inflammation (Fig. 1) [59, 60]. Obesity activates the JNK signaling pathway [60]. JNK signaling activates JUN, which induces expression of inflammatory-related genes [61, 62].

Toll-like receptors (TLRs) function as pattern-recognition receptors in mammals and play an important role in the recognition of microbial components [63]. More than 10 members have been discovered in the TLR family [64]. Among these TLRs, TLR4 functions as a receptor of lipopolysaccharide (LPS) in Gram-negative bacterial cell walls [65]. When LPS binds to TLR4, the adaptor protein myeloid differentiation factor-88 (MYD88) is attracted to the TLR4 receptor. This leads to the autophosphorylation of IL1R-associated kinases (IRAKs). The phosphorylated IRAKs then bind to TNF-associated factor 6 (TRAF6), causing the activation of the NFKB [65] and JNK signaling pathways [66, 67]. Recent evidence indicates that fatty acids activate TLR4 signaling [68–70] and associate dietary fatty acids with inflammation.

Inflammatory Signaling, Myogenesis, and Adipogenesis

Inflammation changes fetal skeletal muscle development by downregulating myogenesis. Inactivation of NFKB restores myogenesis, which suggests a negative role for NFKB in myogenesis [71]. Ablation of NFKB is associated with induction of myogenic genes [72]. Mutant mice lacking RELA, a member of the NFKB family, exhibit enhanced myogenesis [73]. Furthermore, TNF, which activates NFKB signaling, inhibits myogenesis [74].

Inflammation promotes adipogenesis [28, 29]. NFKB is upregulated during fat cell differentiation [75]. Loss-of-function mutation in TLR4, a receptor known to induce the NFKB signaling pathway, prevents diet-induced obesity [60]. However, contradictory reports also exist in which NFKB signaling inhibited the expression of adipocyte-specific genes [76] through reducing PPARG expression in 3T3-L1 cells [77] and MSCs [78, 79]. The possible reason for such controversy might be due to the inflammatory drug doses used in cell culture studies. Acute inflammatory response is known to inhibit cell growth and induce apoptosis, not only to adipocytes but cells in general, which is quite different from obesity-induced inflammation, which is low grade and chronic. Indeed, in vivo studies support the role of NFKB in promoting adipogenesis [75, 79–81].

The possible role of inflammation in MSC differentiation was further evidenced by JNK signaling. JUN is activated by JNK [82]. c-Jun dimerizes with protein JDP2, which inhibits the transcriptional activity of JUN (also known as activator protein 1 [AP-1]), and thus myogenesis [83]. Less studied is the function of JNK in adipogenesis. The absence of JNK is reported to decrease adipogenesis [84]. JNK scaffold protein JNK-interacting protein 1, which binds to JNK signaling molecules, plays a critical role in JNK activation in adipocytes of obese mice [85]. In summary, accumulating data indicate that chronic inflammation downregulates myogenesis and enhances adipogenesis in fetal skeletal muscle [29].

INFLAMMATION, WNT SIGNALING, AND FETAL SKELETAL MUSCLE DEVELOPMENT

Introduction of WNT Signaling

The canonical WNT/β-catenin signaling pathway is well studied [86]. Binding of WNT to the Frizzled proteins activates Disheveled family proteins, which inhibit a destruction complex consisting of axin, glycogen synthase kinase GSK3B, and anaphase-promoting complex (APC), which degrades β-catenin [87]. As a result of inhibition, a pool of cytoplasmic β-catenin stabilizes, enters the nucleus, and interacts with members of the T-cell factor/Lymphoid enhancer factor (TCF/LEF) family of transcription factors to activate the transcription of specific target genes (Fig. 2) [88, 89].

WNT Signaling and Myogenesis

WNT signaling is required for early embryonic myogenesis [90]. Activation of the WNT signaling pathway leads to the transformation of nonmyogenic cells into the myogenic lineage [91, 92]. Myogenesis in the mesoderm and somites is inhibited by the WNT antagonist [93]. β-Catenin is a primary mediator of the canonical WNT/β-catenin signaling pathway [94, 95]. Activation of WNT/β-catenin signaling pathway leads to the stabilization of β-catenin, which enters the nucleus to activate target genes, including MYOD and MYF5 [29, 89]. Blocking the β-catenin pathway reduces the total number of myocytes

[96, 97]. Overexpression of β-catenin leads to increased myoblast proliferation and enhanced muscle repair following ischemia-induced muscle damage [92, 98]. β-Catenin is necessary for the growth response to mechanical overload in skeletal muscle [99]. β-Catenin regulates the expression of transcription factors PAX3 and GLI1 [100, 101]. PAX3 is essential for skeletal myogenesis and acts upstream of MYOD during skeletal muscle development, whereas GLI1 mediates MYF5 expression [102, 103]. In summary, β-catenin is sufficient to induce skeletal muscle development, which suggests that WNT signaling acts through the canonical pathway to promote myogenesis (Fig. 2) [104].

WNT Signaling and Adipogenesis

Adipocytes arise from MSCs during mid to late gestation [41, 45]. Many proadipogenic and antiadipogenic transcription factors function in a coordinated and sequential manner to control various steps in adipogenesis [105, 106]. Activation of WNT/β-catenin signaling suppresses MSC commitment to the adipogenic lineage and terminal differentiation [105]. The canonical WNT/β-catenin pathway suppresses both white and brown adipogenesis by blocking induction of PPARG and CEBPA. This pathway also blocks the thermogenic program through suppression of PPARG coactivator 1-α (PPARGC1A, also known as PGC1α). Several studies indicate that WNT10B activates antiadipogenic WNT signaling. The *WNT10B* gene is highly expressed in preadipocytes and declines rapidly during differentiation [107, 108]. Ectopic expression of WNT10B in 3T3-L1 preadipocytes stabilizes free cytosolic β-catenin and blocks adipogenesis. WNT10B antiserum added to 3T3-L1 media promotes adipocyte differentiation [105, 109]. Transgenic mice overexpressing *Wnt10b* showed a 50% decline in total body fat and were resistant to the high-fat diet-induced accumulation of white fat [110]. On the contrary, *Wnt10b* deficiency displayed increased adipogenic gene expression and contributed to increased lipogenic potential of myoblasts and excessive lipid accumulation in myofibers [111]. Activation of the WNT signaling pathway enhanced myogenesis and inhibited adipogenesis in cultured MSCs [112].

Inflammation, β-Catenin, and MSC Differentiation

Oxidative stress and inflammatory responses are inseparable [113], and both are associated with obesity [114]. Inflammatory responses attract monocytes that secrete reactive oxygen species and induce oxidative stress [115]. On the other hand, oxidative stress leads to inflammatory response [116–118]. In response to inflammation, β-catenin serves as a cofactor of forkhead transcription factors (FOXOs) [119]. β-Catenin binds directly to FOXO and enhances FOXO transcriptional activity in mammalian cells [120]. In OB6 cells, inflammation and oxidative stress cause a diversion of the limited pool of β-catenin from TCF-mediated transcription to FOXO-mediated transcription (Fig. 2) [121]. FOXO competes with TCF for interaction with β-catenin, thereby inhibiting TCF transcriptional activity and the expression of its targeted genes, like MYOD. Reduced binding between TCF and β-catenin is observed after FOXO overexpression and cellular oxidative stress [122]. Oxidative stress and inflammation decrease the amount of nuclear β-catenin and TCF/LEF-dependent transcription [123]. In an obese sheep model, an inflammatory response was observed in fetal skeletal muscle, which enhanced the formation of FOXO/β-catenin complex, downregulating myogenesis and upregulating adipogenesis [29].

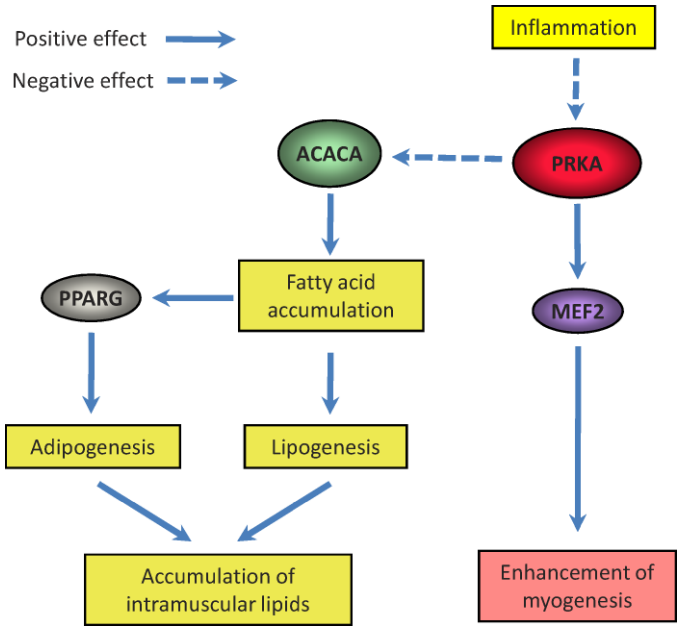

FIG. 3. PRKA myogenesis and adipogenesis. PRKA inhibition by inflammation downregulates myogenesis but enhances adipogenesis.

INFLAMMATION, AMP-ACTIVATED PROTEIN KINASE, AND MSC DIFFERENTIATION

PRKA Introduction

PRKA (also known as AMPK) is a serine-threonine kinase consisting of a catalytic subunit (α) and two regulatory subunits (β and γ). PRKA serves as the energy status guardian within cells. PRKA is activated after ATP depletion or, more accurately, a rise in the AMP:ATP ratio within the cell, and responds by adjusting the rates of ATP-consuming (anabolic) and ATP-generating (catabolic) pathways in an attempt to restore and maintain cellular energy levels [124]. Activated PRKA enhances fatty acid oxidation and inhibits de novo synthesis of fatty acids [125]. PRKA activation is associated with phosphorylation of the PRKAA subunit at Thr172 by LKB1 and calcium/calmodulin-dependent protein kinase kinases (CAMKKs) [126–130]. Protein phosphatase 2C (PP2C) dephosphorylates the Thr172 phosphorylation of PRKAA subunit, inactivating PRKA [131].

PRKA Activation Enhances Myogenesis but Inhibits Adipogenesis

Existing data suggest that PRKA mediates myogenesis. Activation of PRKA by AICAR increases the expression of myogenic enhancer factor 2 (MEF2), which enhances myogenesis [132]. In our previous studies in cattle, PRKA activity was positively associated with muscularity and negatively associated with the content of intramuscular adipocytes [133, 134], indicating that PRKA switches MSCs in skeletal muscle from adipogenesis to myogenesis (Fig. 3).

Studies also point to the important role of PRKA in regulating adipogenesis. Activation of PRKA inhibits the expression of PPARG and CEBPs in 3T3-L1 cells and also in obese mice [48, 135]. Genistein inhibits adipocyte differentiation through activation of PRKA [136]. Overnutrition in pregnant ewes inhibited PRKA activity in fetal skeletal muscle and enhanced expression of PPARG, a marker of adipogenesis. In addition, activation of PRKA by 5-aminoimidazole-4-

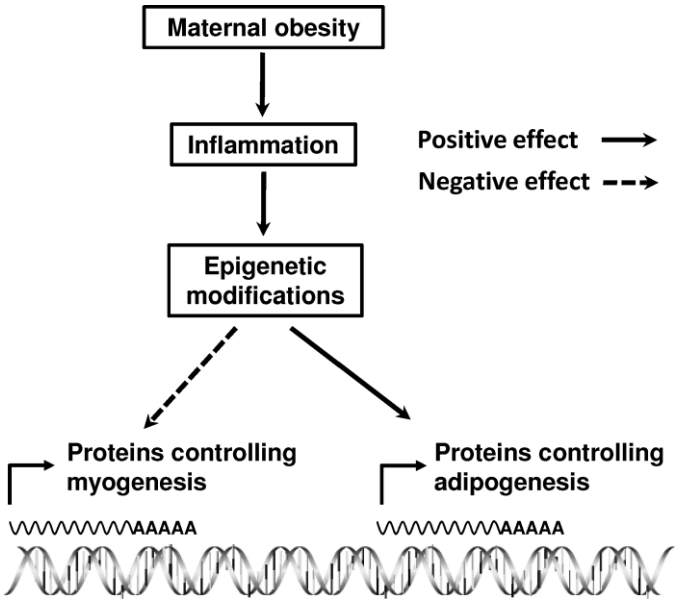

FIG. 4. Inflammation, epigenetic modification, myogenesis, and adipogenesis. Inflammation may induce epigenetic modifications that alter the expression of genes involved in myogenesis and adipogenesis in mesenchymal stem cells.

carboxamide-1-beta-D-ribofuranoside (ATIC, also known as AICAR), a specific activator of PRKA, inhibited adipogenesis in cultured 3T3-L1 cells [6, 137]. A plausible explanation for the inhibition of adipogenesis by PRKA is through regulation of PPARG activity. PRKA phosphorylates acetyl-coenzyme A-carboxylase (ACACA, also known as ACC) at Ser79, which inhibits the activity of ACACA and reduces malonyl-coenzyme A (malonyl-CoA) formation [138]. Accumulation of malonyl-CoA decreases fatty acid oxidation and increases lipogenesis [139], resulting in intracellular fatty acid accumulation. To be known ligands of PPARG, accumulated fatty acids promote adipogenesis (Fig. 3).

Tumor necrosis factor α reduces PRKA activity in skeletal muscle [140]. Increase in TNF production is a hallmark of the inflammatory response. Tumor necrosis factor α regulates PRKA activity by upregulation of PP2C, leading to PRKA dephosphorylation [140]. In MO sheep fetuses, circulating TNF was dramatically increased, which provides a primary reason for PRKA inhibition in the muscle of these fetuses [6]. Chronic oxidative stress in combination with low-grade inflammation associated with obesity leads to PRKA inhibition [6]. Ketone bodies that are enhanced under obesity and diabetic conditions inhibit the PRKA signaling pathway [141]. PRKA activity was also inhibited in obese rats [142]. In summary, an increasing body of evidence supports the notion that obesity inhibits PRKA, which provides another mechanism for the downregulation of myogenesis and enhancement of adipogenesis in fetal skeletal muscle due to MO (Fig. 3).

INFLAMMATION AND EPIGENETIC MODIFICATIONS

Because myogenesis, adipogenesis, and fibrogenesis from MSCs are controlled by the expression of one or more crucial genes, maternal nutrition might change fetal muscle development through epigenetic modifications. Depending on the nature of modifications, epigenetic modifications have different degrees of plasticity. Histone modification only passes through several cell generations [143], but histone modifications can guide DNA methylation, leading to stable alterations in gene expression [144, 145].

Polycomb group proteins (PcGs) and trithorax (trxG) group proteins regulate histone methylation, which leads to additional epigenetic modifications during cell differentiation [145]. Polycomb group proteins and trxGs regulate the methylation of histone H3 by binding to PcG and trxG response elements in the genome. Polycomb group proteins possess H3K27-specific trimethylase activity, which mediates gene expression repression, whereas trxG complexes have H3K4 trimethylase activity, which mediates activation of genes [146]. The crucial development is the demonstration that PcG-mediated gene repression leads to DNA methylation of the targeted genes [144]. The PcG protein enhancer of zeste homolog 2 (EZH2) interacts with DNA methyltransferases and serves as a recruitment platform for DNA methyltransferases, which convert plastic histone modifications to stable DNA methylation [144]. DNA methylation leads to the silence of genes by the following mechanisms: 1) recruitment of histone deacetylases, which remove histone acetylation. Deacetylation increases the affinity between histones and DNA and inhibits gene expression because acetylation of the lysine residues at the histone neutralizes its positive charges. 2) DNA methylation can interfere directly with the binding of transcription factors. 3) DNA methylation leads to the formation of inactive chromatin structure.

Currently, no studies are available linking maternal nutrition to epigenetic modifications in fetal muscle. However, indirect evidence does support epigenetic modification in key genes controlling fetal development. It is likely that maternal undernutrition permanently changes the insulin/insulinlike growth factor-1 signaling in fetal muscle [147], very likely through epigenetic modifications. Maternal diet alters the expression of PPARs in fetal muscle through DNA methylation [148]. Maternal cocaine administration caused epigenetic modification to a key protein kinase gene in rat heart [149]. Maternal obesity was recently shown to induce epigenetic changes in genes crucial for energy metabolism in primate liver [150]. NFKB p65 might inhibit myogenesis by stimulating expression of the PcG protein YY1 [72, 73], resulting in H3K27 trimethylation and inhibition of myogenic gene expression. This recent evidence points to the association between inflammation and epigenetic modification of key genes regulating myogenesis and adipogenesis, providing an additional mechanism for inflammation and altered fetal skeletal muscle development (Fig. 4).

OTHER POSSIBLE SIGNALING PATHWAYS LINKING INFLAMMATION AND FETAL SKELETAL MUSCLE DEVELOPMENT

There are other pathways likely involved in the differentiation of MSCs in fetal muscle resulting from MO. One important pathway is the transforming growth signaling pathway. Transforming growth factor β has immunosuppressive effects [151] and is involved in skeletal muscle development [152]. More importantly, TGFB1 contributes to the conversion of MSCs to fibroblasts [153]. In injured skeletal muscle, differentiation of MSCs into fibroblasts is enhanced through autocrine production of TGFB1 [154], enhancing fibrogenesis. However, until now, the role of TGFB1 signaling in fetal skeletal muscle development has not been studied, although a related growth factor, myostatin, has been extensively studied for its role as a negative regulator of fetal skeletal muscle development [155]. In addition, mitogen-activated protein kinase (MAPK) phosphatases (MKPs) are

negative regulators of MAPK, which is involved in immune suppression and negatively controls cell proliferation and growth [156]. Although there is no direct evidence linking MKPs to MSC differentiation in fetal skeletal muscle, further studies may establish such a relationship.

CONCLUSIONS AND FUTURE STUDIES

Proper fetal skeletal muscle development is crucial for offspring health. Maternal obesity changes fetal muscle development by shifting MSC differentiation from myogenesis toward adipogenesis. This shift is expected to have permanent effects on offspring skeletal muscle properties. Existing evidence points to the important role of inflammation in changes to fetal skeletal muscle development. Chronic inflammation associated with MO may alter fetal skeletal muscle development through three major mechanisms, which include: 1) downregulation of WNT signaling, 2) inhibition of PRKA activity, and 3) induction of epigenetic modifications. Additional pathways need to be further explored. Future studies should focus on mechanisms leading to fetal skeletal muscle inflammation due to MO and develop strategies to prevent such inflammation. Possible epigenetic modification of key genes regulating myogenesis and adipogenesis due to inflammation induced by MO is an exciting field to explore. It is possible that both WNT/β-catenin signaling and PRKA regulate MSC differentiation partially by inducing epigenetic modifications of these key genes, which awaits further exploration.

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