Review

Developmental Programming of Fetal Skeletal Muscle and Adipose Tissue Development

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Abstract

All important developmental milestones are accomplished during the fetal stage, and nutrient fluctuation during this stage produces lasting effects on offspring health, so called fetal programming or developmental programming. The fetal stage is critical for skeletal muscle development, as well as adipose and connective tissue development. Maternal under-nutrition at this stage affects the proliferation of myogenic precursor cells and reduces the number of muscle fibers formed. Maternal over-nutrition results in impaired myogenesis and elevated adipogenesis. Because myocytes, adipocytes and fibrocytes are all derived from mesenchymal stem cells, molecular events which regulate the commitment of stem cells to different lineages directly impact fetal muscle and adipose tissue development. Recent studies indicate that microRNA is intensively involved in myogenic and adipogenic differentiation from mesenchymal stem cells, and epigenetic changes such as DNA methylation are expected to alter cell lineage commitment during fetal muscle and adipose tissue development.

Key words: Maternal nutrition, fetal muscle development

Introduction

Obesity has become an epidemic. In the United States, more than one third of the population age 20 or older are obese (2007-2008) [1]. Data from Centers for Disease Control and Prevention shows that the overall obesity rate in 1989 was less than 15%, ten year later in 1999, the obesity rate was about 25%, and in 2009 it was 34%, showing that obesity is increasing rapidly in recent decades. Associated with the overall trend of increased obesity, obesity in non-pregnant women of child bearing age (between 20 to 39 yr old) is also becoming more and more prevalent, and has reached more than 30% [1]. Furthermore, nearly 17% of children and teenagers from 2-19 yr old were found to be obese [2]. Maternal obesity affects fetal development [3, 4], which is associated with obesity in offspring [5, 6].

In addition to maternal obesity, maternal nutrient deficiency results in insufficient nutrient supply to the fetus, negatively affecting fetal development [7]. Fetal nutrient deficiency results from many conditions in pregnancy, including maternal malnutrition, reduced placenta efficiency, adolescence pregnancy, and closely spaced pregnancy. Compared to brain and heart, skeletal muscle and fat have a lower priority for nutrition repartitioning, which makes the development of skeletal muscle and adipose tissue es-

pecially vulnerable to nutritional deficiency [8]. In this review, we focus our discussion on the effect of maternal nutrition on fetal skeletal muscle and adipose tissue development, and how fetal developmental programming might regulate the differentiation of myocytes, adipocytes and fibrocytes, as well as their impacts on postnatal body composition.

Skeletal Muscle, Adipose and Connective Tissue Development

Skeletal muscle development

Muscle fibers or myofibers are the structural units of skeletal muscle [9]. The formation of new muscle fibers is termed myogenesis, a differentiation process where multipotent stem cells are converted into committed muscle cells. In livestock, all muscle fibers are formed during the prenatal stage. Consequently, understanding the prenatal development of skeletal muscle is important, because events occurring at this stage have dramatic impact on postnatal development and growth (Dauncey and Harrison 1996).

Prenatal myogenesis can be divided into primary myogenesis and secondary myogenesis. Primary myogenesis mainly occurs during the embryonic stage, when primary muscle fibers arise; secondary myogenesis occurs during the fetal stage, and leads to the formation of secondary muscle fibers. Only a small number of primary muscle fibers develop during the embryonic period, which will serve as templates for the formation of secondary muscle fibers during the fetal stage. Both primary and secondary muscle fibers are derived from a pool of cells termed mesenchymal stem cells [10], which can be committed to a myogenic linage as well as other cell types such as adipocytes and chondrocytes. However, the committed cells, termed myogenic progenitor cells, are not yet muscle cells. Prenatal myogenesis is under the control of a panel of regulatory proteins, including Wingless and Int (Wnt), paired box gene (Pax) 3 and Pax 7 [11, 12]. Wnt signaling is very important for activating myogenesis [13]. The expression of Pax 3 and Pax 7 in mesechymal stem cells induces the expression of myogenic regulatory factors (MRFs) [10], which leads to myogenic differentiation [14]. Currently identified MRFs include myogenin, MRF-4, Myo-D and Myf-5 [15]. MRF-4 is mainly expressed at the very early stage of myogenesis, followed by the expression of MyoD and Myf-5, which converts precursor cells into myoblasts [15]. Myogenin is necessary for the fusion of myoblasts into myotubes [16] and is expressed later and maintained throughout the fetal stage. MRF-4 is also expressed later and becomes the dominant MRF in postnatal muscle. MyoD and

Myf-5 function compensatively to induce the differentiation of multipotent myogenic precursor cells into myoblasts [17].

Both myogenic precursor cells and myoblasts proliferate to increase their numbers. When there are pertinent environmental signals, myoblasts align with each other, fuse and differentiate into immature muscle fibers known as myotubes [18]. The exact process regulating myoblast fusion is not well understood. Because myogenic cells are derived from myogenic progenitor cells, increasing the proliferation of progenitor cells increases the number of myogenic cells which will form more primary myofibers. Due to the fact that only a very limited number of primary myofibers are formed during the embryonic stage, the impact of primary myogenesis on subsequent size and number of muscle fibers formed in the offspring is relatively minor [19].

Secondary myogenesis forms the majority of muscle fibers. Therefore, the fetal stage, when secondary myogenesis is ongoing, is critical for skeletal muscle development [18, 20]. Since the number of muscle fibers formed during the fetal stage is dependent on the number of available myogenic progenitor cells and their proliferation is highly sensitive to nutrients, maternal nutrition dramatically affects skeletal muscle development during this stage [7, 21-23].

The postnatal skeletal muscle development is mainly due to the increase in muscle fiber size, with no net formation of new muscle fibers [24]. New muscle fibers generated during the adult stage are only to replace injured muscle fibers [19].

The increase in muscle fiber size at the adult stage mainly relies on muscle satellite cells. Satellite cells are a population of postnatal myogenic stem cells located between the sarcolemma and basal lamina [25]. Satellite cells are dormant mononucleated cells, which are at the G0 phase of the cell cycle. Although the specific population dynamics of the cells are unknown, numerous subpopulations of these cells are found in skeletal muscle. After activation by various environmental stimuli related to growth, satellite cells undergo asymmetric proliferation with a portion of daughter cells replenishing the original pool and the remaining differentiating into myoblasts. These newly generated myoblasts fuse with existing muscle fibers to increase the muscle fiber size, as well as the number of nuclei in muscle fibers. Indeed, the majority of nuclei in an adult muscle fiber come from satellite cells [26]. However, recent studies indicate that a portion of satellite cells are also capable of differentiation into other cell types in addition to muscle cells, such as adipocytes and fibroblasts [27]. Physiological factors

and mechanisms controlling the differentiation of those multipotent cells are a current research focus.

Adipocyte and connective tissue development

In addition to energy storage, adipose tissue is a very important organ for secretion of many endocrine and paracrine factors [28-33]. Adipose tissue plays a critical role in the regulation of whole body metabolism and homeostasis [28, 34]. At the molecular level, the development of adipose tissue relies on preadipocyte hyperplasia, switching from proliferation to lipid assimilation, adipocyte hypertrophy and angiogenesis. Adipogenesis is the *de novo* development of adipocytes. Similar to myogenesis, however, adipogenesis can be briefly divided into two steps: determination and differentiation.

Key transcription factors regulating adipogenesis include the peroxisome proliferator-activated receptor (PPAR) γ and CCAAT/enhancer-binding proteins (C/EBPs) [31]. PPARγ is highly expressed and plays an indispensible role in the differentiation of adipocytes [35]. C/EBPβ/δ, which are induced in the early phases of adipogenesis, trigger the expression of PPARγ [36]. Bone morphogenetic proteins (BMPs), which belong to the transforming growth factors β (TGFβ) superfamily, exert important roles in the adipogenic determination from multipotent stem cells [37]. The Wnt signaling pathway inhibits adipogenesis [38].

Fibrogenesis refers to the formation of connective tissue. Fibrosis is characterized by the enhanced deposition of extracellular matrix (ECM) proteins in basement membrane and interstitial tissue of muscle [39]. A number of cytokines and growth factors are associated with the development of fibrosis, among which TGFβ has been recognized as the most powerful and widely expressed profibrogenic cytokine [39]. There are currently three TGFβ isoforms identified, including TGFβ1, TGFβ2 and TGFβ3; TGFβ1 is mainly expressed in endothelial cells, fibroblasts, hematopoietic cells and smooth muscle cells, TGFβ2 is primarily expressed in epithelial cells and neurons, and TGFβ3 is specifically expressed in mesenchymal cells [40]. However, the three isoforms of TGFβ transduce the signals through the same serine-threonine kinase cell surface receptors, including type I and type II receptors [41, 42]. Activation of TGFβ receptors induces the Smad signaling pathway [43] and the expression of target genes possessing Smad-specific elements in their promoters [44], leading to the synthesis of collagens [45, 46] and accumulation of extracellular matrix [47].

Myogenesis, adipogenesis and fibrogenesis are competitive processes

Fetal and neonatal skeletal muscle development occur in the same microenvironment and involve myogenesis, adipogenesis and fibrogenesis [19], all of which are derived mainly from mesenchymal stem cells. Therefore, the commitment of mesenchymal stem cells to myogenic, adipogenic or fibrogenic lineages can be considered a competitive process, and is "shaped" by numerous inductive regulators. Switching the commitment of stem cells from myogenesis to adipogenesis will increase intramuscular fat, an event associated with skeletal muscle insulin resistance due to the paracrine effect of intramuscular adipocytes [48-50], and switching to fibrogenesis leads to impairment of muscle function including oxidative capacity [51]. In addition, attenuation of myogenesis will reduce the muscle fiber density [22], exerting permanent negative effect on offspring muscle strength [52]. During aging, a progressive loss of muscle mass occurs accompanied by increased adiposity and fibrosis [51, 53], resulting in the decline in muscle structural integrity and functional capacity [54]. Thus, proper differentiation of mesenchymal stem cells during fetal development is crucial for the long-term health of offspring.

Maternal Nutrition and Fetal Programming

Fetal programming

Fetal programming, also known as developmental programming or the Barker hypothesis, pertains to the fetal origins of adult diseases. This hypothesis is based on epidemiological data that show that low birth weight due to maternal malnutrition has long-term effects on adult health [55]. The fetal programming hypothesis suggests that the alteration in the uterine environment as a result of nutritional stress at certain stages of conceptus growth and development might permanently change tissue structure and function [56]. The offspring of malnourished mothers have a higher chance of developing coronary heart diseases, stroke, diabetes and hypertension [57]. The prevalence of type-II diabetes (T2D) increases 3 fold for men who weighed 5.5 lb at birth when compared to those who had birth weight of 9.5 lb [58]. The correlation between human maternal nutrition and offspring birth weight and the subsequent development of hypertension, insulin resistance, T2D and cardiovascular diseases has been well studied by many researchers [8, 21, 23, 59-64].

Maternal undernutrition of skeletal muscle development

Maternal nutrition affects fetal development, especially fetal skeletal muscle development [7]. Maternal nutrition during the embryonic stage has relatively minor effects on skeletal muscle development, because only a very small number of myofibers are formed during this stage. Beef cattle receiving 30% nutrient restriction during 30 to 120 d of gestation had no effect on fetal body weight and carcass weight [65]. In a sheep study, 50% nutrient restriction from 18 days before until 6 d after conception decreased the number of muscle fibers, though fetal body weight at mid-gestation was not affected [66].

The critical stage for fetal skeletal muscle development is early to mid-gestation in the cattle and sheep, and mid to late gestation in pigs. A 50% decrease of nutrient availability in sheep from d 28 to 78 of gestation reduced the formation of secondary myofibers, and the ratio of secondary to primary myofibers [7]. It is also known that reducing skeletal muscle mass during fetal development have long-lasting, irreversible negative physiological consequences for offspring [67, 68]. So it is not surprising that the 8 m old offspring lambs born to nutrient-restricted mothers have fewer muscle fibers than control lambs [8]. Similar results were also observed in new born pigs [69], as well as in guinea pigs [70] with in-utero under-nutrition.

For the late gestation stage, maternal nutrient restriction does not have major impacts on the number of muscle fibers in cattle and sheep because skeletal muscle has matured [18]. Skeletal muscle matures in about d 105 of gestation in sheep (term about 150 d) and d 210 of gestation in cattle (term about 285 d) [18]. Maternal restriction at this time, however, does reduce muscle fiber size [71]. These results were also confirmed in a sheep study, when the growth of skeletal muscle was compared in single with twin pregnancies, only the hypertrophy but not the hyperplasia of skeletal muscle was affected [72]. In summary, maternal under-nutrition during early to mid-gestation reduces muscle fiber numbers and during late-gestation decreases muscle fiber sizes in sheep and cattle; in rodents and pigs, the mid to late gestation are important for muscle fiber formation.

Maternal over-nutrition and fetal skeletal muscle development

Besides maternal nutrient deficiency, maternal over-nutrition also affects fetal skeletal muscle development, mainly enhancing intramuscular adipogenesis and fibrogenesis. In ruminant animals and humans, adipogenesis begins around mid-gestation, which overlaps with myogenesis [18, 19, 30]. During fetal skeletal muscle development, a small portion of the progenitor cells differentiate into adipocytes, which form intramuscular fat and marbling in offspring [22]. Enhanced intramuscular fat accumulation is detrimental for health because increased intramuscular fat leads to skeletal muscle insulin resistance due to the paracrine effect of intramuscular adipocytes [48-50], pre-disposing to Type 2 diabetes. However, in animal production, enhancement of intramuscular fat accumulation or marbling improves meat quality; the amount of marbling is crucial for the flavor and juiciness of meat [73], and is determined by the number and size of intramuscular adipocytes [18]. Maternal over-nutrition elevates the expression of adipogenesis markers in skeletal muscle of mid-gestation fetuses [27]. A subsequent study also demonstrated that maternal over-nutrition resulted in increased number and size of adipocytes inside skeletal muscle of fetal sheep at late-gestation [23]. Postnatally, the increased adipocytes and total triglyceride content were also observed in offspring sheep of over-nourished mothers [4].

Besides myofibers and adipocytes, mesodermal progenitor cells can also differentiate into fibroblasts. These cells synthesize connective tissue which forms endomysium, perimysium and epimysium in fetal skeletal muscle during late gestation [19]. Maternal over-nutrition increases the collagen content and cross-linking of skeletal muscle, heart and large intestine of fetuses, suggesting an important role of maternal nutrition during pregnancy in fetal fibrogenesis [74-76]. Similar increase in collagen and cross-linking was also observed in skeletal muscle of offspring with maternal over-nutrition [4].

In summary, maternal over-nutrition enhances intramuscular adipogenesis and fibrogenesis, increasing intramuscular fat and connective tissue content in offspring muscle.

Mechanisms Associated with Fetal Programming of Skeletal Muscle and Adipose Tissue Development

MicroRNAs

MicroRNAs (miRNAs) introduction: MiRNAs are single-strand RNA molecules of 21-23 nucleotides in length [77], which play a crucial role in developmental processes by regulating the expression of target mRNA [78]. The target mRNA transcripts of miRNAs include genes which play important roles in proliferation and differentiation [79]. So far, thousands of miRNAs have been discovered; thus, miRNAs have become one of the most abundant categories of gene

regulatory molecules in multicellular organisms [80]. It is estimated that about 30% of all protein-coding genes are regulated by miRNAs [81].

MiRNA and skeletal muscle development: In 2006, miR-206 was the first miRNA shown to play an important role in skeletal muscle development by regulating the expression of connexin43, a gap junction protein required for skeletal myoblast fusion [82]. MiR-206, as well as miR-1 and miR-133, are muscle specific miRNAs [83-85]. MyoD induces the transcription of miR-206 [86], which promotes myogenic differentiation [87, 88]. BMP-2, which is known to inhibit myogenesis, represses the expression of miR-206 by inhibiting its maturation process [89]. Besides miR-206, miR-1 also promotes myogenic differentiation [90]. Overexpression of miR-1 increases the expression of α-actin, sarcomeric myosin and creatine kinase [90]. MicroR-181, a miRNA up-regulated during muscle differentiation, is likewise very important in muscle development [91]. MiR-133 induces myoblast proliferation [92]. MEF2 transcription factor, a critical regulator of myogenesis, induces the expression of miR-1 and miR-133 [93]. MiR-133 also regulates connective tissue growth factor, a key mediator of fibrosis [94]. MiR-1 and miR-133 in zebrafish control the expression of muscle genes and regulate sarcomeric actin organization [95]. The expression of miR-133 increases during myogenic differentiation of C2C12 cells, as visualized by a GFP-related retroviral vector system [96]. In addition, miR-181 promotes myogenesis by down-regulating the homeobox protein Hox-A11, an inhibitor of muscle differentiation [91]. MiR-27b regulates Pax3 protein level and ensures myogenic differentiation [97]. MiR-322/424 and miR-503 are induced during muscle differentiation and arrest the cell cycle by down-regulating Cdc25A [98]. MiR-486 has also been shown to induce myoblast differentiation by down-regulating Pax7 [99]. Repression of miR-214 expression inhibits proliferation and differentiation of C2C12 cells [100]. Fibroblast growth factors, which inhibit myogenic differentiation of C2C12 cells and interfere with the activity of MRFs, repress the expression of miR-206, miR-1 and miR-133 [101].

MiRNA and adipocyte differentiation: MiRNAs are involved in the regulation of adipogenesis. In 2004, miR-143 was determined to promote adipocyte differentiation [102]. Then, an *in vitro* study reported that 21 of the 100 miRNAs were differentially expressed before and after differentiation of 3T3-L1 preadipocytes [103]. Another study also demonstrated that miR-17-92 promotes adipogenic differentiation [104]. Moreover, miR-200 family promotes adipogenesis by inhibiting the Wnt signaling which is a negative reg-

ulator of adipogenesis [105]. Later studies also showed the role of miR-27 and let-7 in the regulation of adipogenesis [106, 107]. Over-expression of miR-27 prior to induction of adipogenesis inhibited adipogenesis by prevention of the expression of PPARγ and C/EBPα [106]. A recent study also demonstrated that miR-130 represses adipogenesis by inhibiting the expression of PPARγ [108].

MiRNA and stem cell proliferation and differentiation: MiRNAs are likely candidates for the maintenance of stem cell identity, which includes self-renewal and cell destiny decision, because miRNAs have the ability to control the expression of many targets simultaneously and provide a means for coordinated regulation of gene action [109]. The first study about miRNAs in stem cells reported several embryonic stem cell-specific miRNAs [110]. Subsequently, a number of studies indicated that miRNA are key regulators in stem cell functions [111].

MiRNAs are essential regulators of stem cell self-renewal and proliferation [109]. There are miRNAs only expressed in pluripotent embryonic stem (ES) cells but not in adult cells, which might play roles in stem cell self-renewal [112]. Stem cell division in *Drosophila* is regulated by a miRNA pathway, and germline stem cells with a mutation in *Dicer*1 are normal in identity but defective in cell cycle control [113]. Other studies have also shown that *Dicer*1 mutation leads to developmental arrest in zebrafish [114], embryonic lethality in mouse [115] and lower proliferation of ES cells [116]. The expression of miRNAs differs in undifferentiated and differentiated ES cells [117, 118], as well as in multipotent mesenchymal stromal cells [119, 120], indicating the involvement of miRNA in the regulation of stem cell phenotypes.

Epigenetics and its possible roles in fetal programming of skeletal muscle development

Epigenetics describes heritable changes in gene function without changes in gene sequence [121]. Epigenetic changes can pass from one cell generation to the next (mitotic inheritance), as well as from one generation of a species to the next (meiotic inheritance) [122]. Epigenetic modifications include DNA methylation, histone modification and microRNAs, which explain cell differentiation into different cell types with various phenotypes despite the same DNA sequence [122]. Interestingly, epigenetic status can be influenced by environmental factors [123], suggesting that pathogenic physiological conditions, such as low-grade inflammation associated with obesity, may induce epigenetic modifications and thus alter cell differentiation and lineage commitments.

DNA methylation: DNA methylation occurs on

cytosine residues of CG dinucleotides (also called CpG sites), which normally results in transcriptional silencing [124]. A typical example of DNA methylation could be the inactivation of one of the X chromosomes in female genome [125]. DNA methylation silences genes through several mechanisms: 1) recruitment of histone deacetylases, which removes histone acetylations inhibiting gene expression; 2) DNA methylation can interfere the binding of transcription factors; and 3) DNA methylation leads to formation of inactive chromatin structures [126].

DNA methylation is regulated by the DNA cytosine methyltransferases (DNMT), which include DNMT1, DNMT3a and DNMT3b in vertebrates [127]. DNMT1 is the maintenance DNA methytransferase, which functions on hemimethylated DNA during mitosis [128]. DNMT3 is also called the *de novo* methyltransferase, which works on unmodified DNA and has very important roles in cell differentiation and commitment during embryogenesis [129].

Histone modifications: In eukaryotic cells, genomic DNA binds with histones, together called chromatin. There are four core histones (H2A, H2B, H3, H4), usually densely packed, with their N-terminal tails unstructured and could be modified by enzymes, leading to acetylation, methylation, phosphorytion, sumoylation, ubiquitylation and other modifications [130]. DNA methylation could further recruit histone deacetyltransfereases (HDACs), which lead to histone deacetylation and chromatin condensation [131].

Polycomb group proteins (PcG) and trithorax (trxG) group proteins regulate histone methylation, which leads to other epigenetic modifications during cell differentiation [132]. PcG and trxG regulate the methylation of histone H3 through binding to PcG and trxG genomic response elements. PcG group proteins possesses H3K27-specific trimethylase activity which mediates gene expression repression, whereas trxG complexes have H3K4 trimethylase activity which mediates activation [133]. The PcG protein EZH2 (enhancer of Zeste homolog 2) serves as a recruitment platform for DNMTs, thus converting plastic histone modifications to stable DNA methylations [134]. Cell differentiation is associated with histone modifications and DNA methylations. Currently, there are no data available linking maternal nutrition to PcG and trxG protein functions during fetal muscle and adipose tissue development but inflammation, a condition associated with obesity, leads to alterations in PcG protein groups [135]. Because maternal obesity leads to inflammation in fetal muscle [23], this indirect evidence supports the role of epigenetic modification in developmental programming of skeletal muscle in offspring, which needs to be confirmed. Epigenetic

changes in fetal muscle and adipose tissue due to maternal nutrition and other physiological conditions should be the focus for future research.

Summary

The embryo-fetal stage is crucial for skeletal muscle development, as well as for adipose and connective tissue development. Maternal nutrition affects the proliferation of myogenic precursor cells and, thus, the subsequent number of muscle fibers formed. Alternatively, maternal over-nutrition during mid-gestation results in impaired myogenesis and elevated adipogenesis. The underlying mechanisms for the changes observed in fetal skeletal muscle in the setting of maternal obesity remain largely unknown. In addition to alteration of inductive regulators, it is likely that miRNA may be involved in the regulation of myogenesis and adipogenesis during fetal muscle development, which warrants further studies. In addition, epigenetic changes such as DNA methylation are expected to alter cell lineage commitment during fetal muscle and adipose tissue development, a question not yet examined in the framework of developmental programming of skeletal muscle.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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