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Nutrigenomic regulation of adipose tissue development — role of retinoic acid: A review

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ABSTRACT

To improve the efficiency of animal production, livestock have been extensively selected or managed to reduce fat accumulation and increase lean growth, which reduces intramuscular or marbling fat content. To enhance marbling, a better understanding of the mechanisms regulating adipogenesis is needed. Vitamin A has recently been shown to have a profound impact on all stages of adipogenesis. Retinoic acid, an active metabolite of vitamin A, activates both retinoic acid receptors (RAR) and retinoid X receptors (RXR), inducing epigenetic changes in key regulatory genes governing adipogenesis. Additionally, Vitamin D and folates interact with the retinoic acid receptors to regulate adipogenesis. In this review, we discuss nutritional regulation of adipogenesis, focusing on retinoic acid and its impact on epigenetic modifications of key adipogenic genes.

1. Introduction

There are four adipose depots: visceral, subcutaneous, intermuscular and intramuscular. The visceral and subcutaneous fat depots develop and mature prior to the other fat depots (Cianzio, Topel, Whitehurst, Beitz, & Self, 1985), accounting for the vast majority of body fat. Due to the low value of visceral and subcutaneous fat, meat animals have been selected for generations for their high lean/fat ratio, resulting in lean animals. However, the selection for high lean growth is negatively associated with intramuscular fat accumulation, or marbling, which is critical for the palatability of meat (Du et al., 2013; Hausman, Basu, Du, Fernyhough-Culver, & Dodson, 2014; Kauffman, Carpenter, Bray, & Hoekstra, 1964). The use of implants and harvesting at increasingly younger ages are also contributing factors to the low marbling in beef cattle. As a result, marbling, together with tenderness, are consistently identified as the top issues related to beef quality (Garcia et al., 2008; McKenna et al., 2002), with only 2.1% of beef carcasses exhibiting the slightly abundant marbling necessary to grade as prime, the highest quality grade (Moore et al., 2012). While increasing the marbling present in beef would greatly enhance beef quality and consumer eating experiences, fat accumulation in the other fat depots is a waste. Thus, advanced strategies which can enhance marbling without increasing or even decreasing overall adiposity is needed.

Both adipocyte hyperplasia and hypertrophy contribute to adipose accumulation. Previous studies have focused on lipid metabolism, as lipid deposition accounts for adipose hypertrophy (Smith et al., 2009). On the other hand, adipogenesis, or the formation of new adipocytes, was less studied in livestock species. Adipogenesis can be separated into multiple stages, including adipogenic commitment, adipogenic differentiation and lipid accumulation. Vitamin A affects each stage of adipogenesis. Retinoic acid, an active metabolite of vitamin A, induces epigenetic changes in adipogenic genes, regulating their expression and adipocyte formation (Dani et al., 1997; Nebbioso et al., 2010; Wei, 2012). In addition, retinoic acid reduces lipid accumulation (Berry, DeSantis, Soltanian, Croniger, & Noy, 2012; Kawada, Kamei, & Sugimoto, 1996; Schwarz, Reginato, Shao, Krakow, & Lazar, 1997). Other nutrients, such as vitamin D, interacts with retinoic acid receptor signaling to alter adipogenic differentiation and development (Hida, Kawada, Kayahashi, Ishihara, & Fushiki, 1998). Altogether, nutrients have profound impacts on gene expression and cell differentiation. Research in this field is becoming increasingly active, which forms an exciting new field of research, termed nutrigenomics.

2. Adipose tissue development

The formation of discernible adipocytes/adipose tissue begins before mid-gestation in beef cattle (Bonnet, Cassar-Malek, Chilliard, & Picard, 2010). In perirenal fat, adipocytes were detected as early as 80 days of gestation while adipocytes in the intermuscular fat are detectable at 180 days of gestation (Taga et al., 2011, 2012). Most adipocytes are

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formed during the fetal and early postnatal stages, and adipocyte hyperplasia largely ceases in perirenal fat after birth (Bonnet et al., 2010). In humans, the total number of adipocytes is set when reaching adolescence (Goessling et al., 2009). Though new adipocytes can be generated lifelong, such capacity attenuates as animals become older due to the reduction in the density of adipogenic progenitors (Du, Yin, & Zhu, 2010). Therefore, nutritional and physiological conditions during the fetal, postnatal and early postweaning stages have greater impact on adipogenesis compared to the fattening stage.

Adipogenesis is used to describe the de novo generation of adipocytes, which is roughly separated into two stages: commitment and differentiation (MacDougald & Mandrup, 2002). During the differentiation stage, peroxisome proliferator-activated receptor γ (PPARγ) and CCAA T/enhancer-binding proteins (C/EBPs) have critical regulatory roles (Avram, Avram, & James, 2007). C/EBPβ/δ is expressed in the very early stage of adipogenesis and triggers the expression of PPARγ (Fajas, Debril, & Auwerx, 2001), an essential transcription factor for adipogenic differentiation (Rosen & MacDougald, 2006; Spiegelman & Flier, 1996). The mechanisms underlying adipogenic commitment are much less studied. Recently, based on studies in mice, Zinc-finger protein 423 (Zfp423) was identified as a transcriptional factor responsible for the adipogenic commitment of progenitor cells (Gupta et al., 2010). The expression of Zfp423 commits progenitor cells to the adipogenic lineage and differentiate into pre-adipocytes, further inducing PPARγ expression, which results in the terminal differentiation of adipocytes (Gupta et al., 2010, 2012). The importance of Zfp423 in bovine adipogenesis was further confirmed (Huang, Das, Yang, Zhu, & Du, 2012).

Sterol responsive element-binding protein-1c (SREBP-1c) is also an important regulator of adipogenesis, especially during terminal differentiation and lipid accumulation (Feve, 2005). It enhances adipose conversion by stimulating the generation of PPARγ ligands that in turn activate the transcriptional activity of PPARγ (Seo et al., 2004). Consistently, SREBP-1c induces the expression of adipocyte signature genes including fatty acid synthase and fatty acid binding protein (aP2). The expression of these genes leads to the rapid accumulation of lipids in adipocytes, allowing the adipocyte to expand in size. As a result of both the increased size of existing fat cells and the proliferation of preadipocyte cells, white adipose tissue deposition occurs rapidly after birth (Novakofski, 2004).

3. Epigenetic regulation of adipose development

3.1. Epigenetic modifications

Stem cells and progenitor cells maintain their pluri- or multipotency through reversible inhibition of lineage-specific genes while allowing genes for stem cell self-renewal to express. Conversely, lineage-specific genes are expressed while pluri-or multi-potency genes are inhibited during differentiation (Meissner et al., 2008; Mohn et al., 2008). Progenitor cell commitment to a specific lineage is often initiated by the expression of a key developmental gene, which induces the expression of a cascade of transcription factors and lineage specific genes (Reik, 2007). Key developmental genes possess CpG rich promoters, and their expression is primarily regulated by epigenetic modifications (Aloia, Di Stefano, & Di Croce, 2013), one of which is Zfp423 (Yang et al., 2013).

Epigenetic modifications refer to both histone modifications and DNA methylation. Polycomb repression complexes (PRCs) are mainly responsible for reversible inhibition of genes through catalyzing histone methylations. There are two well-characterized PRCs, namely PRC1 and PRC2. Enhancer of Zeste 2 (EZH2) is one of the core components of PRC2 (Margueron & Reinberg, 2011), which mediates histone 3 lysine 27 trimethylation (H3K27me3) (McCabe et al., 2012; Qi et al., 2012), a marker for gene silencing (Bernstein et al., 2006). A specific DNA binding element for PRC2 has not been previously identified, though PRC2 preferably binds to promoters with rich CpG sites, which subsequently attracts PRC1 binding (Mendenhall et al., 2010; Mohn et al., 2008). In the absence of stimulation to release PRCs, these promoters frequently become DNA methylated (Ko, Hsu, Shen, Chang, & Wang, 2008; Lorente et al., 2006; Mohn et al., 2008).

Trithorax group (trxG) catalyzes H3K4 trimethylation (H3K4me3), activating gene transcription. It appears that H3K4me3 is transient and only induced when gene expression is needed to counter the inhibitory effect of the Polycomb group (Eissenberg & Shilatifard, 2010; Schuettengruber, Martinez, Iovino, & Cavalli, 2011). Interestingly, H3K4me3 and H3K27me3 co-exist in key developmental genes which are highly enriched with CpG sites, forming a 'bivalent state' (Meissner et al., 2008; Mikkelsen et al., 2007), which positions genes for activation or inhibition. During differentiation, non-induced bivalent genes lost active H3K4me3 but kept repressive H3K27me3 mark (Schuettengruber & Cavalli, 2009), leading to generally permanent inhibition of gene expression by inducing DNA methylation (Mohn et al., 2008).

Recent studies also point to the importance of DNA demethylation in gene expression. Active DNA demethylation is mediated by ten–eleven translocation hydroxylases (TETs), including TET1, 2 and 3 (Ficz et al., 2011; Ito et al., 2010). In the reaction, TETs oxidize 5-methylcytosine (5mC) to form 5-hydromethylcytosine (5hmC) and further oxidation products. Oxidized cytosines are replaced by nucleotide or base excision repairs to achieve demethylation (Wu & Zhang, 2014), a process mediated by Growth arrest and DNA damage protein 45a (Gadd45a). It is a member of a stress response gene family which encodes 18-kDa acidic histone fold proteins (Zhan et al., 1994). Gadd45a mediates nucleotide exchange DNA repair and thus demethylation (Barreto et al., 2007; Ma, Guo, Ming, & Song, 2009; Niehrs & Schafer, 2012). However, Gadd45a protein lacks a DNA binding domain and depends on tumor suppressor inhibitor of growth protein 1 (ING1) to recruit to promoters enriched with H3K4me3, which then triggers locus specific DNA demethylation (Schafer, Karaulanov, Stapf, Doderlein, & Niehrs, 2013). In short, epigenetic modifications include histone methylations, DNA methylation and demethylation, which coordinate to regulate lineage-specific gene expression.

The dynamics of these epigenetic regulatory systems of key developmental genes are affected by both genetic and environmental factors. Gene polymorphisms in the promoters of key developmental genes affect the binding of complexes involved in epigenetic modifications, altering the lineage commitment of progenitor cells during development. Similarly, environmental factors and clues, including nutrients, alter cell signaling pathways or the recruitment of transcription factors which regulate epigenetic modifications to alter animal development, including adipogenesis (Fig. 1).

3.2. Zfp423 epigenetic modifications and adipogenic commitment

There are accumulating evidence supporting the role of epigenetic modifications in key genes regulating adipogenesis. In our previous studies in sheep, we observed that adipogenic differentiation was enhanced in the fetuses of dams fed with a high energy diet (Yan et al., 2010; Zhu et al., 2008). The high energy diet is correlated with increased intramuscular fat content in offspring (Yan et al., 2011), as well as overall adiposity (Samuelsson et al., 2008; Tong et al., 2011). We further found that Zfp423 expression was enhanced in fetal tissue of over-fed mothers (Yang et al., 2013). We then analyzed epigenetic modifications in the Zfp423 promoter and found that maternal high energy diet reduced DNA methylation in the Zfp423 promoter by about 50% (Yang et al., 2013). Our data has been independently confirmed by another study in rats (Borengasser et al., 2013).

The Zfp423 promoter has exceptionally rich CpG sites, positioning PRC2 as a key mediator of Zfp423 expression and adipogenic commitment (Bernstein et al., 2006). Our data show that the H3K27me3 and EZH2 levels in the Zfp423 promoter were lower in obese compared to