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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.

Keywords

Adipogenesis; Vitamin A; Retinoic acid; Marbling; Meat; Progenitor cells

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., 2013a; 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

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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, 1997b). 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 discernable 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; Taga et al., 2012). Most adipocytes are 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 CCAAT/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; Gupta et al., 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 multi-potency 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 encode 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 control fetal tissue, consistent with the lower DNA methylation and the high expression of Zfp423. Furthermore, the level of H3K4me3 in the Zfp423 promoter was slightly higher in OB fetal tissue, which indicates that trxG was also involved in the control of Zfp423 expression due to maternal high energy diet (Yang et al., 2013). Overall, maternal high energy diet regulates Zfp423 expression and adipogenesis during fetal adipose tissue development through inducing epigenetic modifications.

In a related study, we analyzed the role of Zfp423 in intramuscular adipogenesis and marbling in beef cattle. We sampled beef muscle for separation of stromal vascular cells. These cells were immortalized with pCI neo-hEST2 and individual clones were selected by G418. Three clones with high and low adipogenic potential respectively were selected for further analyses. The expression of Zfp423 was much higher in high adipogenic cells, which was correlated with lower DNA methylation in the Zfp423 promoter (Huang et al., 2012). In conclusion, the data suggest that Zfp423 is a critical regulator of adipogenesis in bovine stromal vascular cells and its expression is regulated epigenetically.

Besides Zfp423, epigenetic regulation of PPARγ and C/EBPα during adipogenesis was also observed (Ngo et al., 2014). The PPARγ2 promoter DNA demethylation was detected during 3T3-L1 adipogenesis (Kamstra et al., 2014). Histone H3K9 methylation suppresses PPARγ expression (Wang et al., 2013). Changes in histone acetylation in C/EBPα promoter was also observed during the adipogenic differentiation of bone marrow stromal cells (Zhao et al., 2013). Up to now, in livestock cells, epigenetic changes in these genes during adipogenic differentiation have not been examined and warrant further studies.

4. Nutrients and adipose development

4.1. Vitamin A, retinoic acid receptors, and adipogenesis

Nuclear receptors are intracellular receptors activated by lipid signaling molecules, including steroid hormones, thyroid hormones, retinoids, Vitamin D metabolites and several others. They are also ligand-activated transcription factors, which activate target gene expression through binding to their cognate DNA elements. In the following discussion, we summarize the effect of retinoids and Vitamin D metabolites on adipogenesis.

Dietary vitamin A is absorbed and converted into all-trans retinoic acid. Retinoic acid serves as a ligand for retinoic acid receptors (RARα, RARβ, and RARγ). They partner with retinoid X receptors (RXRα, RXRβ, and RXRγ) (Chawla, Repa, Evans, & Mangelsdorf, 2001) to bind to retinoic acid response elements (RAREs) on target gene loci (de The, Vivanco-Ruiz, Tiollais, Stunnenberg, & Dejean, 1990). Retinoic acid also activates orphan receptor PPARβ/δ, stimulating cell proliferation (Shaw, Elholm, & Noy, 2003) and lipid oxidation (Ravnskjaer et al., 2010). Thus, the partitioning of retinoic acid between RAR and PPARβ/δ determines the biological effects of retinoic acid. It appears that two cellular retinoic acid binding proteins regulate retinoic acid partitioning, with cellular retinoic acid binding protein II (CRABP-II) delivers retinoic acid to RAR, and fatty acid binding protein

type 5 (FABP5) to PPARβ/δ. Adipogenic progenitor cells express a high ratio of CRABP-II/FABP5, resulting in the domination of RAR signaling (Noy, 2013). During adipogenic differentiation, however, CRABP-II and RAR down-regulate while FABP5 and PPARβ/δ up-regulate, which activate PPARβ/δ signaling in mature adipocytes (Berry, Soltanian, & Noy, 2010). Thus, retinoic acid affects progenitor cells and mature adipocytes differently due to the stage-specific expression of related transcription factors (Fig. 2a).

As a metabolite of vitamin A, retinoic acid plays major roles in both preadipocyte commitment and terminal maturation of adipocytes. Decades ago, in an *in vitro* adipogenesis model using embryonic stem cells, retinoic acid was found to promote adipogenic commitment of embryonic stem cells (Dani et al., 1997). Consistently, retinoic acid treatment on stem cells derived from embryoid bodies leads to prolonged activation of the extracellular signal-regulated kinase-1 (ERK) pathway, required for adipogenic commitment (Bost et al., 2002). Retinoic acid is required for Zfp423 expression in adipocytes. In the mice lacking aldehyde dehydrogenase-1a1 (Aldh1a1), which catalyzes retinoic acid production from retinaldehyde, the expression of Zfp423, PPARg and Fabp4 were reduced by 70% (Reichert et al., 2011). Thus, retinoic acid promotes the adipogenic commitment. On the other hand, retinoic acid hampers terminal differentiation of adipocytes. In both 3T3-L1 and C3H10T1/2 cell lines, retinoic acid blocks terminal adipocyte maturation by enhancing preadipocyte gene expression (Berry et al., 2012) as well as inhibiting C/EBPβ mediated transcription (Schwarz, Reginato, Shao, Krakow, & Lazar, 1997a).

The promotion of retinoic acid on adipogenic commitment involves epigenetic modifications. Depending on the availability of RA, RAR/RXR heterodimers interact with nuclear co-repressor proteins including silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) and nuclear receptor corepressor (NCoR), or with coactivators such as (SRC)/p160 family and p300/CREB-binding protein (CBP) (Kashyap & Gudas, 2010). Nuclear co-repressor proteins elicit locus-specific changes in the chromatin structure which inhibits gene expression, while coactivators facilitate gene expression through recruiting ATP-dependent chromatin remodeling complex to loosen the structure, allowing RNA polymerase II to initiate gene expression. In the presence of retinoic acid, the PRC proteins rapidly dissociate from RAR target genes, forming permissive condition for gene expression (Kashyap & Gudas, 2010), which in turn, reduces DNA methylation in the corresponding promoters. This could explain the promotion effect of retinoic acid on preadipocyte gene expression (Berry et al., 2012).

4. 2. Synergism of Vitamin D metabolites with retinoic acid receptor signaling to regulate adipogenesis

Beyond the traditional role in calcium homoeostasis and bone metabolism, Vitamin D is now recognized as a regulator of adipogenesis. Obesity, a metabolic disorder associated with excessive accumulation of adipocytes, is frequently associated with Vitamin D deficiency (Yao et al., 2015). Polymorphisms in genes involved in Vitamin D metabolism and signaling increase the susceptibility to obesity and diabetes (Jiang et al., 2007; Ye et al., 2001). Vitamin D consistently demonstrates inhibitory effects on adipogenesis in both *in vivo* and *in vitro* studies. The active metabolite of Vitamin D, 1,25-dihydroxyvitamin D, inhibits 3T3-

L1 preadipcyte differentiation in a dose dependent manner (Ishida, Taniguchi, & Baba, 1988), which reduces the expression of adipogenic genes (Hida et al., 1998; Kong & Li, 2006). It has been further demonstrated that 1,25-dihydroxyvitamin D regulates adipogenesis by activating the vitamin D receptor (VDR). In the presence of 1,25-dihydroxyvitamin D, VDR blocks adipogenesis by down-regulating C/EBPβ expression (Blumberg et al., 2006).

The exact reasons for the inhibitory effect of VDR on adipogenesis remain to be clarified. Because RXR is a heterodimeric partner for both VDR and PPARγ, it is possible that VDR competes with PPARγ for RXR, which reduces adipogenesis. Supportively, in 3T3-L1 cells, VDR expression reduced PPARγ expression while simultaneous RXR ectopic expression abolishes this inhibition, confirming the competitive relationship between VDR and PPARγ for RXR (Kong & Li, 2006). This also raises the possibility that activated VDR depletes RXR needed for the formation of RXR/RAR complex, thus inhibiting adipogenic commitment (Fig. 2b). These notions were confirmed by a recent study in the inhibitory effect of vitamin D on adipogenesis (Ji, Doumit, & Hill, 2015).

4.3. Methyl donors and B vitamins

Epigenetic modifications include both histone and DNA methylations. For methylation to occur, the presence of methyl donors is indispensable. DNA methyltransferases catalyze the transfer of a methyl group to DNA using S-adenosyl methionine (SAM) as the methyl donor. SAM is converted to S-adenosylhomocysteine (SAH) after the methyl group is transferred to DNA or histone. In this process, dietary nutrients including folic acid, vitamin B12, choline and betaine are involved. Dietary methyl supplementation of folic acid, vitamin B12, choline and betaine consistently increases DNA and histone methylations of genes by contributing to SAM synthesis (Waterland & Jirtle, 2003).

There is accumulating evidence supporting the inhibitory roles of methyl donor supplementation in suppressing adipogenesis both *in vivo* and *in vitro*. Folate increases overall CpG methylation in C/EBPa promoter, and inhibits its expression and adipogenesis in chicken preadipocytes (Yu et al., 2014). In 3T3-L1 cells, treatment of folic acid and vitamin B12 attenuates adipogenic differentiation by upregulating Wingless and Int (Wnt)10b (Bellner et al., 2015). Eight months of methyl donor (choline, betamine, vitamin B12 and folic acid) supplementation reverts DNA hypomethylation in the fatty acid synthase promoter induced by a high fat diet, suppressing weight gain (Cordero, Gomez-Uriz, Campion, Milagro, & Martinez, 2013). On the contrary, maternal dietary folate and vitamin B12 restrictions increases visceral adiposity in rat offspring (Kumar et al., 2013). These data show that methyl donors affect adipogenesis through altering epigenetic changes in genes associated with adipogenesis.

5. Retinoic acid and lipid accumulation in mature adipocytes

While retinoic acid promotes adipogenic commitment, in mature adipocytes, vitamin A reduces lipid accumulation. Because vitamin A metabolite, retinoic acid, activates PPARα and PPARβ/δ in mature adipocytes, which induces fatty acid oxidation and lipid catabolism (Berry & Noy, 2009; Berry et al., 2010; Noy, 2013), it is not surprising that vitamin A

reduces both lipid accumulation and adipocyte hypertrophy (Amengual, Petrov, Bonet, Ribot, & Palou, 2012; Amengual, Ribot, Bonet, & Palou, 2008; Cook, Yeldandi, Rao, Hashimoto, & Reddy, 2000). In addition, retinoic acid may also affect PPARγ transcription activity via enhancing the partnership of RAR with RXR, depriving RAR/PPARγ required for late stage adipogenesis (Dawson & Xia, 2012; Ziouzenkova & Plutzky, 2008). Retinoic acid blocks late-stage adipogenesis by inhibiting C/EBPβ-mediated transcription (Schwarz et al., 1997b) and PPARγ transcriptional activity (Berry et al., 2012; Kawada et al., 1996), and thus terminal differentiation of adipocytes. Therefore, reducing vitamin A intake has been used to enhance intramuscular lipid accumulation and marbling in finishing beef cattle (Arnett et al., 2009; Gorocica-Buenfil, Fluharty, Bohn, Schwartz, & Loerch, 2007; Pickworth, Loerch, & Fluharty, 2012a, 2012b; Smith et al., 2009; Ward, McKinnon, Hendrick, & Buchanan, 2012). However, there are also reports showing that vitamin A deficiency has no effect on lipid metabolism and marbling (Bryant et al., 2010; Gorocica-Buenfil, Fluharty, Bohn, et al., 2007; Gorocica-Buenfil, Fluharty, & Loerch, 2008; Gorocica-Buenfil, Fluharty, Reynolds, & Loerch, 2007; Pickworth et al., 2012a, 2012b). Such discrepancy could be due to the difference in the degree of deficiency, time and duration of deficiency, as well as cattle nutrition and genetics.

6. Complications and Conclusions

Available studies suggest that nutrients such as vitamin A promote early adipogenic commitment, which may promote later formation of adipocytes during the fattening stage, likely enhancing marbling. Vitamin D metabolites by depriving RXR needed for adipogenesis, reduce adipocyte formation during early adipose development. Methyl donors also affects adipogenesis by regulating epigenetic modifications during early adipose development. On the other hand, vitamin A supplementation to feedlot beef cattle promotes lipid oxidation and thus reduces adipocyte hypertrophy and marbling.

The remaining question is how to specifically promote intramuscular adipogenesis without increase in adipogenesis in the visceral and subcutaneous fat. This problem can be partially addressed by targeting a period critical for intramuscular adipocyte formation. The four adipose depots of cattle do not develop at the same time; the formation of visceral fat occurs earliest in beef cattle, the formation of subcutaneous adipocytes occurs slightly later and prolongs to the early weaning stage in cattle, while the formation of intramuscular adipocytes is estimated to occur mainly during the late fetal/neonatal stage to about 250 days of age in beef cattle (Du et al., 2013b); the dwindling presence of progenitor cells as animals age is the major reason for the declining ability to generate new adipocytes (Du et al., 2010). Due to the sequential formation of adipocytes in different tissues, nutrient supplementation such as vitamin A during the neonatal to pre-weaning stages may specifically enhance intramuscular adipocyte formation, leading to more intramuscular preadipocytes that will provide sites for lipid accumulation (hypertrophy) during the ‘fattening’ stage, enhancing marbling without overall increase in carcass fatness (Fig. 3).

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Highlights

1. Nutrigenomics is a new direction in adipogenic research.
2. Retinoic acid enhances adipogenic commitment through altering epigenetic modifications in the promoters of key adipogenic genes.
3. Retinoic acid alters the partnership of retinoid X receptors with other nuclear receptors to regulate adipogenesis.
4. Methyl donors inhibit adipogenesis through promoting histone and DNA methylation.

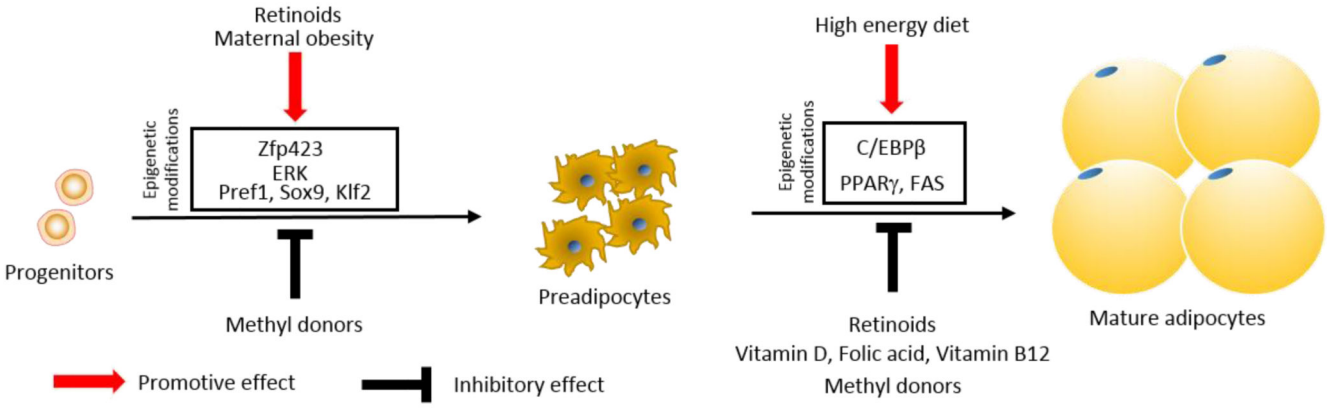

Fig. 1.

Genetic and environmental factors converge on the epigenome of progenitor cells to regulate adipogenesis during the early stage of animal development

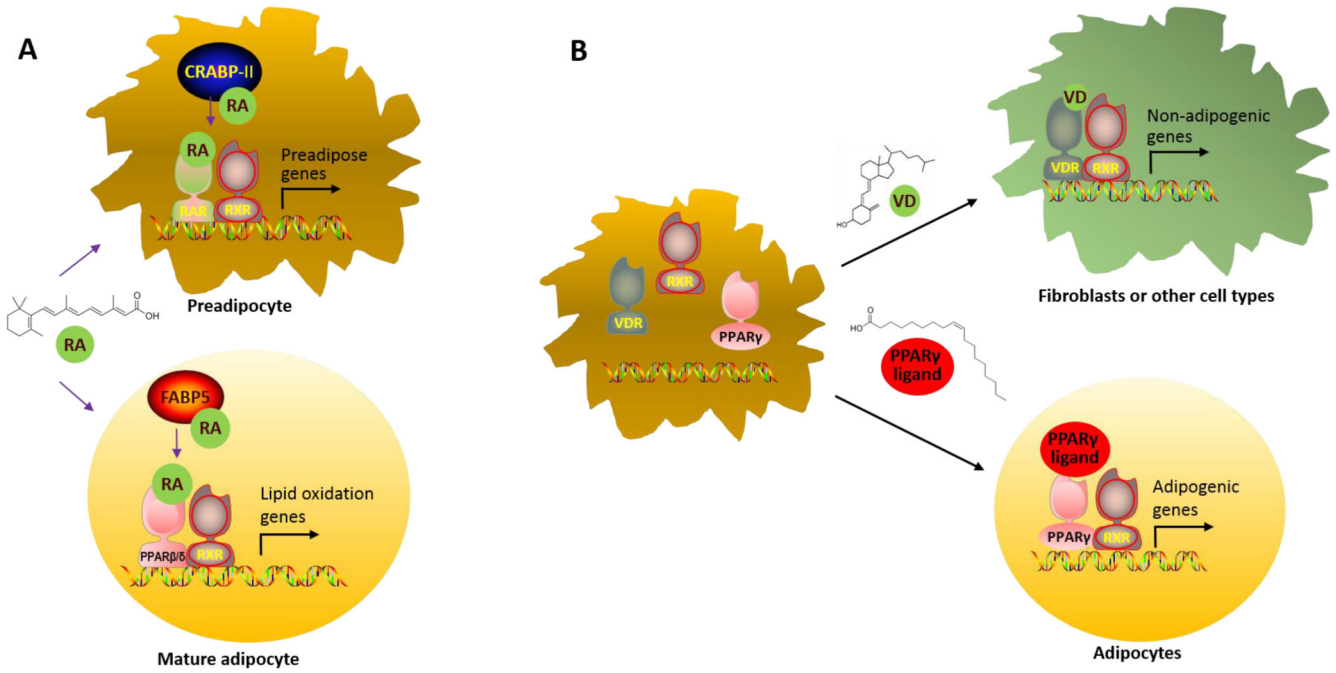

Fig. 2.

Choice of partnership determines fates. A. Delivery of retinoic acid to either retinoic acid receptor (RAR) or peroxisome proliferator-activated receptor β/δ (PPARβ/δ) determines its biological effects on adipose development; B. RAR and Vitamin D receptor (VDR) compete for retinoid X receptor (RXR) needed for partnering with PPARγ to initiate adipogenic differentiation.

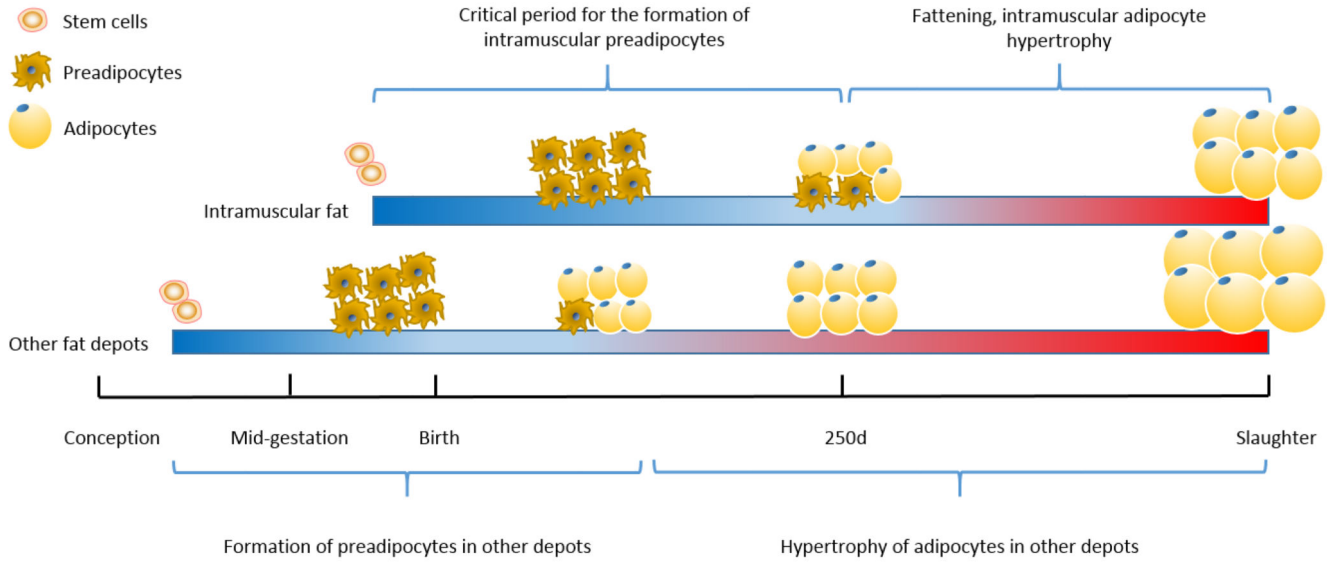

Fig. 3.

Approximate timelines for adipose tissue development of beef cattle. Nutrient supplementation during a period critical for intramuscular adipocyte formation enhances preadipocyte formation and adipocyte hyperplasia, which provide sites for later lipid accumulation to enhance marbling, without significantly increase fat mass in other fat depots (Du, Wang, Fu, Yang, & Zhu, 2015).