Regulatory Effects and Mechanisms of Vitamin A on Animal Lipid Metabolism: Postprint

Authors: Wang Xue, Yan Sumei

Date: 2017-10-23T00:00:00+00:00

Abstract

Vitamin A is a key factor influencing lipid metabolism in animal tissues. This review summarizes the effects of vitamin A on animal lipid metabolism and elucidates its potential mechanisms of action from the perspectives of expression of lipid metabolism-related genes and their signaling pathways, adipocyte number, adipocytokine secretion, and participation in epigenetic modifications, thereby providing a theoretical foundation for further investigation into the mechanisms by which vitamin A influences animal lipid metabolism and for the regulation of animal fat metabolism through vitamin A.

Full Text

Regulatory Effects of Vitamin A on Lipid Metabolism in Animals and the Underlying Mechanisms

WANG Xue, YAN Sumei*
(College of Animal Science, Inner Mongolia Agricultural University, Hohhot 010018, China)

Abstract: Vitamin A is a key regulator influencing lipid metabolism in animal tissues. This review synthesizes current knowledge on the effects of vitamin A on animal lipid metabolism and explores the underlying mechanisms from multiple perspectives: regulation of lipid metabolism-related gene expression and signaling pathways, control of adipocyte number, modulation of adipocytokine secretion, and involvement in epigenetic modifications. This comprehensive overview provides a theoretical foundation for further investigation into vitamin A' s regulatory mechanisms and for developing strategies to modulate animal lipid metabolism through vitamin A supplementation.

Keywords: Vitamin A; animals; lipid metabolism; regulatory mechanism

1. Effects of Vitamin A on Fat Synthesis in Animals

Recent studies have demonstrated that vitamin A generally inhibits fat synthesis in animals, suggesting that obesity resulting from excessive fat accumulation may be physiologically linked to vitamin A nutritional status. Ayuso et al. [1] found that vitamin A restriction increased monounsaturated fatty acid content in porcine backfat, leg fat, and intramuscular fat while decreasing saturated fatty acids and n-6/n-3 polyunsaturated fatty acid (PUFA) ratios. Pigs subjected to long-term vitamin A restriction showed higher intramuscular fat content in the semimembranosus muscle compared to control groups and those with late-finishing vitamin A restriction. In adult mice, supplementation with all-trans retinoic acid (ATRA) at various doses and through different administration methods reduced body weight and fat synthesis while improving glucose tolerance and insulin sensitivity [2]. *In vivo* experiments revealed that mice lacking retinaldehyde dehydrogenase 1 were resistant to diet-induced obesity, and treatment with retinaldehyde or retinaldehyde dehydrogenase inhibitors reduced fat mass while increasing insulin sensitivity in ob/ob mice, indicating that retinaldehyde, a precursor of retinoic acid, also possesses anti-adipogenic properties [3]. Notably, ATRA-induced weight loss and fat reduction occurred despite unchanged or even increased energy intake, accompanied by elevated body temperature and increased circulating glycerol concentrations, while free fatty acid levels remained constant [4]. These findings suggest that ATRA's anti-obesity effects stem from enhanced fat mobilization and efficient oxidation of lipolysis-derived fatty acids, thereby increasing energy expenditure. The impact of dietary vitamin A on fat synthesis also appears stage-dependent: long-term oral β-carotene supplementation in young ferrets increased body weight and subcutaneous fat mass [5], whereas short-term ATRA treatment in adulthood showed a tendency to reduce obesity [6].

However, contradictory findings have also been reported. Yehya et al. [7] observed that excessive vitamin A intake in humans caused hypertriglyceridemia and elevated serum low-density lipoprotein levels. Studies in rodents demonstrated that high doses of retinol or vitamin A palmitate induced hepatic accumulation of fatty acids and triglycerides while enhancing hepatic fatty acid oxidation, whereas vitamin A deficiency reduced serum triglycerides, high-density lipoprotein, and body fat content [8]. Some reports suggest that vitamin A promotes fat synthesis more strongly than fat oxidation, leading to hepatic fat accumulation [9].

2.1. Effects on Hepatic Lipid Metabolism

The liver plays a crucial role in maintaining lipid metabolism homeostasis as a primary site for de novo fatty acid synthesis, converting excess dietary carbohydrates into fatty acids. Research indicates that vitamin A and retinoids can promote fatty acid oxidation or inhibit fat synthesis in the liver. Vitamin A supplementation enhances expression of genes encoding enzymes involved in mitochondrial and peroxisomal β-oxidation, thereby increasing hepatic fatty acid

oxidation [10]. Conversely, other studies report that vitamin A deficiency in rats reduces fat synthesis due to decreased activity and gene expression of acetyl-CoA carboxylase (ACC), the rate-limiting enzyme in fatty acid synthesis. Since ACC inhibits carnitine palmitoyltransferase-1 (CPT-1), vitamin A deficiency increases hepatic mitochondrial CPT-1 activity and gene expression, enhancing fatty acid oxidation by 30% [11]. Some studies attribute retinoid-induced hypertriglyceridemia to increased hepatic triglyceride synthesis and secretion rather than enhanced fat mobilization [12].

2.2. Effects on Lipid Metabolism in Adipose Tissue

Mammalian adipose tissue comprises two distinct types: white adipose tissue (WAT) with low oxidative capacity that primarily stores energy, and brown adipose tissue (BAT) with high oxidative capacity that generates ATP through fatty acid oxidation. Uncoupling protein 1 (UCP1) serves as the molecular effector of BAT thermogenesis. Both *in vitro* brown adipocyte cultures and *in vivo* rodent studies demonstrate that vitamin A promotes UCP1 expression, reducing both lipid content and brown adipocyte mass [13]. Rodent feeding trials confirm that vitamin A regulates BAT thermogenesis, as vitamin A-deficient diets decrease thermogenic capacity while vitamin A supplementation increases heat production [14].

In vivo studies in mice show that ATRA reduces body fat by promoting fatty acid oxidation and energy expenditure while inhibiting fat synthesis in WAT. Brown adipocytes exhibit three characteristic features: high oxidative capacity, efficient UCP1 expression, and multilocular lipid distribution. ATRA treatment induces morphological changes in WAT adipocytes, including reduced cell size and increased multilocular adipocyte numbers, suggesting ATRA can promote "browning" of white fat. *In vitro* treatment of differentiated mature adipocytes (3T3-L1 or 3T3-F442A) with ATRA enhances lipolysis and fatty acid oxidation while reducing triglyceride concentrations [4].

2.3. Effects on Lipid Metabolism in Skeletal Muscle

Skeletal muscle possesses high oxidative capacity and represents a major organ for fatty acid metabolism. Muscle cells can store intramuscular fat, synthesize triglycerides, and perform de novo fatty acid synthesis. Accumulation of intramuscular fat, particularly bioactive lipid intermediates such as long-chain acyl-CoA, diacylglycerol, and ceramide, impairs skeletal muscle oxidative capacity and insulin sensitivity, contributing to type II diabetes in mammals. Studies show that ATRA treatment in mice enhances fatty acid oxidation, respiration, and thermogenesis in skeletal muscle, inducing expression of numerous genes related to oxidative metabolism and reducing intracellular fat content [14].

3.1. Regulation of Lipid Metabolism-Related Gene Expression via Transcription Factors

In the liver, liver X receptor (LXR) α, a transcription factor regulating fat synthesis, exerts dual promotional effects on lipogenic genes such as fatty acid synthase (FAS) because the FAS promoter contains binding sites for both LXR and sterol regulatory element-binding protein-1c (SREBP-1c), which is itself induced by LXRα [15]. Peroxisome proliferator-activated receptors (PPARs) are lipid-activated transcription factors belonging to the nuclear receptor superfamily, with three isoforms (α, β, γ). PPARγ specifically induces adipocyte differentiation and plays a crucial role in adipogenesis, while PPARα is the primary transcription factor regulating hepatic fatty acid catabolism, controlling expression of genes encoding proteins involved in fatty acid oxidation in peroxisomes, mitochondria, and microsomes. Vitamin A deficiency reduces PPARα transcription, decreasing expression of genes for acyl-CoA ligase, CPT-1, medium-chain acyl-CoA dehydrogenase, 3-ketoacyl-CoA thiolase, citrate synthase, acyl-CoA oxidase 1, and peroxisomal thiolase, while increasing hepatic triglyceride synthesis and fat accumulation. Concurrently, reduced β-oxidation in vitamin A-deficient rat livers leads to increased polyunsaturated fatty acids including linoleic acid, linolenic acid, arachidonic acid, and docosahexaenoic acid [16], indicating that vitamin A regulates fatty acid composition. PPARα activation can downregulate lipogenic gene expression by inhibiting the LXR-SREBP-1c pathway, while LXR activation suppresses PPARα-induced fatty acid oxidation [17]. PPARβ/δ plays similar roles in skeletal muscle as PPARα, and ATRA exhibits high affinity for PPARβ/δ, enhancing its transcriptional activity [18]. PPARβ/δ activation promotes fat breakdown in skeletal muscle, slows obesity development in WAT, and improves insulin sensitivity in obesity-prone mice [19].

The CCAAT/enhancer-binding protein (C/EBP) family was the first transcription factor family demonstrated to play important roles in adipocyte differentiation, expressed temporally during adipogenesis. Growth-arrested preadipocytes 3T3-L1, when induced by adipogenic hormones (such as cAMP inducers and glucocorticoids), cease proliferation and initiate differentiation. During this process, C/EBPβ expression transiently increases in early differentiation, followed by transcriptional activation of C/EBPα and PPARγ accompanied by expression of adipocyte-specific genes such as 422/aP2 and phosphoenolpyruvate carboxykinase (PEPCK) [20]. Studies show that ATRA inhibits adipogenesis by reducing C/EBP transcription factor activity, and interfering with C/EBPs is a prerequisite for ATRA' s anti-adipogenic effects [21].

3.2. Regulation of Lipid Metabolism-Related Gene Expression via Signaling Pathways

Vitamin A also influences fat metabolism through multiple signaling pathways. Retinoic acid receptors (RARs) bind ATRA and 9-cis-retinoic acid with high affinity *in vitro*, while retinoid X receptors (RXRs) specifically bind 9-cis-retinoic

acid. RAR:RXR heterodimers regulate transcription of retinoic acid target genes by binding to specific retinoic acid response elements in their promoters. RAR-dependent signaling pathways may transcriptionally regulate protein-coding genes involved in lipid metabolism, including PEPCK [22], stearoyl-CoA desaturase (SCD) [23], UCP1 [13], and medium-chain acyl-CoA dehydrogenase [24]. Both *in vivo* and cellular studies demonstrate upregulation of these genes by retinoids. ATRA, RAR agonists, and PPARβ/α-specific agonists can induce expression of hormone-sensitive lipase (HSL), the rate-limiting enzyme in lipolysis, suggesting HSL may be a RAR target. The intracellular distribution of ATRA between RARs and PPARβ/δ depends on relative expression levels of cellular retinoic acid-binding protein II (CRABP-II) and fatty acid-binding protein 5 (FABP5), which deliver ATRA to RARs and PPARβ/δ respectively, thereby determining ATRA' s biological effects. RXR target gene apolipoprotein C-III (Apo C-III) is crucial for plasma triglyceride metabolism. ATRA promotes Apo C-III expression through RXR pathways, which inhibits lipoprotein lipase gene expression [25] and causes weight gain and increased plasma triglyceride concentrations. Taniguchi et al. [26] reported that vitamin A reduces transcription of genes related to intramuscular fat formation in bovine preadipocytes through RAR and RXR pathways. The net effect of vitamin A on fat metabolism likely depends on the balance of activation among PPAR:RXR, RAR:RXR, and LXR:RXR heterodimers.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is an important intracellular signaling cascade that transduces lipid metabolism-related signals to maintain homeostasis. STATs, including STAT 1-4, 5A, 5B, and 6, are the primary transcription factors in the JAK-STAT pathway and exhibit cell- and tissue-specific functions. Vitamin A, when bound to retinol-binding protein 4 (RBP4), can activate membrane protein STRA6, subsequently activating the JAK2-STAT5 signaling pathway and promoting expression of STAT5 target genes including suppressor of cytokine signaling 3 (SOCS3) and PPARγ. Since SOCS3 inhibits insulin receptors, this pathway suppresses insulin signaling and promotes fat synthesis [27]. Kang et al. [28] demonstrated that increased plasma RBP4 concentrations reduce insulin sensitivity in mice, while RBP4 knockout improves insulin sensitivity, both effects related to JAK2-STAT5 pathway activation.

The p38 mitogen-activated protein kinase (p38 MAPK) is a member of the MAPK signaling family. ATRA can rapidly activate p38 MAPK in various cell types. p38 MAPK inhibits hepatic fat synthesis by downregulating transcription of SREBP-1c and its coactivator PGC-1β [29], and promotes fatty acid β-oxidation and energy metabolism by catalyzing phosphorylation and activation of PPARα and PGC-1α [30]. AMP-activated protein kinase (AMPK) acts as an energy sensor regulating lipid metabolism. ATRA treatment induces phosphorylation of acetyl-CoA carboxylase (ACC), an AMPK target, in skeletal muscle cells, downregulating ACC expression and reducing malonyl-CoA concentrations, thereby stimulating fatty acid breakdown and inhibiting synthesis. Thus, retinoic acid, particularly ATRA, may influence fat metabolism

in skeletal muscle and other tissues including liver through activation of the AMPK-p38 MAPK pathway, though the precise regulatory mechanisms remain unclear and require further investigation.

3.3. Regulation of Adipocyte Number

Adipocyte number is a primary determinant of total body fat, and retinoids regulate fat synthesis by controlling adipocyte number through effects on adipogenesis and preadipocyte proliferation. The Wnt/β-catenin signaling pathway maintains preadipocytes in an undifferentiated state and inhibits adipogenesis. Recent studies show that treating 3T3-L1 cells with 1 mol/L ATRA for 1-2 days did not significantly alter β-catenin mRNA levels by semi-quantitative PCR, indicating ATRA does not directly upregulate β-catenin at the transcriptional level. However, Western blot analysis revealed that while ATRA did not markedly change expression of the Wnt/β-catenin negative regulator glycogen synthase kinase 3β (GSK3β), it could phosphorylate GSK3β by activating the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, thereby preventing β-catenin degradation and ultimately activating Wnt/β-catenin signaling to affect fat synthesis [31]. Kim et al. [32] demonstrated that ATRA inhibits 3T3-L1 preadipocyte differentiation through β-catenin transcriptional activation, thereby affecting fat synthesis. Other studies indicate that Wnt5α inhibits adipocyte differentiation and suppresses PPARγ function by regulating histone methyltransferases [33]. However, some results show that retinoic acid signaling can inhibit Wnt/β-catenin activity or have no significant effect [34]; these inconsistencies may be attributed to differences in retinoic acid dosage, cell type, and differentiation stage.

Bone morphogenetic proteins (BMPs) can induce stem cells or preadipocytes to differentiate into osteoblasts or mature adipocytes. Retinoic acid promotes osteogenic differentiation through the BMP2-Smad-Runx2/Msx2 pathway while inhibiting BMP2-induced adipocyte differentiation by suppressing expression of the key adipogenic transcription factors PPARγ, C/EBPα, and C/EBPδ, thereby reducing adipocyte number [35]. Liu [31] reported that ATRA enhances BMP9' s osteogenic activity while inhibiting its adipogenic differentiation in preadipocytes, decreasing adipocyte number. Retinoic acid-dependent pathways also induce Smad3 expression and nuclear accumulation, which physically interacts with C/EBPβ to impair its binding to downstream target gene promoters and inhibit fat synthesis [36].

3.4. Regulation of Adipocytokine Secretion via Signaling Pathways

White adipose tissue secretes signaling factors that regulate energy balance, insulin sensitivity, and other physiological functions, produced by adipocytes themselves or stromal vascular cells. Vitamin A supplementation reduces body weight and fat synthesis in animals, likely by affecting adipocyte secretory function. Resistin and leptin exert paracrine effects in WAT, resisting insulin signals and promoting fat synthesis within adipose tissue [37]. ATRA treatment *in vivo*

or in adipocyte models inhibits secretion of leptin and resistin [2,38], possibly because retinoic acid suppresses C/EBP activity while activating PPARγ:RXR heterodimers, and leptin and resistin gene expression are positively regulated by C/EBPα and negatively regulated by PPARγ [39].

3.5. Involvement in Epigenetic Modification of Adipogenesis

Some studies suggest vitamin A promotes fat synthesis through epigenetic modifications, which include DNA methylation, histone acetylation and methylation, and RNA-associated silencing. Zinc finger protein 423 (Zfp423) is a key transcription factor in progenitor cells that promotes adipogenesis by inducing PPARγ expression and driving differentiation into adipocytes. Huang et al. [40] demonstrated Zfp423' s important role in bovine fat synthesis. Polycomb repression complexes (PRCs) primarily suppress target gene expression through histone methylation. PRC2 can bind to CpG sites in the Zfp423 gene promoter, causing histone methylation within the promoter region. In the presence of vitamin A, PRC2 rapidly dissociates from the Zfp423 promoter, leading to histone demethylation and Zfp423 expression, thereby promoting fat synthesis [41].

4. Summary and Future Perspectives

In summary, vitamin A generally inhibits fat synthesis while promoting fat mobilization and oxidation of lipolysis-derived fatty acids in animals. Current research has analyzed vitamin A' s regulatory mechanisms primarily through transcription factors and signaling pathways controlling fat synthesis and oxidation, adipocyte number, adipocytokine secretion, and epigenetic modifications. However, the effects of vitamin A on animal lipid metabolism remain inconsistent, the mechanisms are highly complex, and tissue-specific differences exist. Therefore, further in-depth research should focus on elucidating vitamin A' s mechanisms of action in different tissues to better understand its role in animal lipid metabolism.

References:

[1] AYUSO M,FERNÁNDEZ A,ISABEL B,et al.Long term vitamin a restriction improves meat quality parameters and modifies gene expression in Iberian pigs[J].Journal of Animal Science,2015,93(6):2730-2744.
[2] FELIPE F,BONET M L,RIBOT J,et al.Modulation of resistin expression by retinoic acid and vitamin A status[J].Diabetes,2004,53(4):882-889.
[3] JEYAKUMAR S M,SHERIL A,VAJRESWARI A.Chronic vitamin A-enriched diet feeding induces body weight gain and adiposity in lean and glucose-intolerant obese rats of WNIN/GR-Ob strain[J].Experimental Physiology,2015,100(11):1352-1361.
[4] BERRY D C,NOY N.All-trans-retinoic acid represses obesity and insulin resistance by activating both peroxisome proliferation-activated receptor β/δ retinoic receptor[J].Molecular and Cellular Biology,2009,29(12):3286-3296.

[5] MURANO I,MORRONI M,ZINGARETTI MC,et al.Morphology of ferret subcutaneous adipose tissue after 6-month daily supplementation with oral beta-carotene[J].Biochimica et Biophysica Acta (BBA): Molecular Basis of Disease,2015,1740(2):305-312.
[6] SÁNCHEZ J,FUSTER A,OLIVER P,et al.Effects of β-carotene supplementation on adipose tissue thermogenic capacity ferrets (Mustela putorius furo)[J].British Journal of Nutrition,2009,102(11):1686-1694.
[7] YEHYA A,BAER J T,SMILEY W,et al.Hypervitaminosis A altering the lipid profile in a hypercholesterolemic patient[J].Journal of Clinical Lipidology,2009,3(3):205-207.
[8] KHANNA A,REDDY T S.Effect of undernutrition and vitamin A deficiency on the phospholipid composition of tissues at 21 days of age- .Liver,spleen and kidney[J].International Journal for Vitamin and Nutrition Research,1983,53(1):3-8.
[9] CHEN W,CHEN G X.The roles of vitamin A in the regulation of carbohydrate,lipid,and protein metabolism[J].Journal of Clinical Medicine,2014,3(2):453-479.
[10] TRIPATHY S,CHAPMAN J D,HAN C Y,et al.All-trans-retinoic acid enhances mitochondrial function in models of Human Liver[J].Molecular Pharmacology,2016,89(5):560-574.
[11] OLIVEROS L B,DOMENICONI M A,VEGA V A,et al.Vitamin A deficiency modifies lipid metabolism in rat liver[J].British Journal of Nutrition,2007,97(2):263-272.
[12] SOLOMON L W,ERDMAN J W Jr.Vitamin A induced hypertriglyceridemia in cholesterol-fed rats[J].Lipids,1980,15(3):157-162.
[13] PUIGSERVER P,VÁZQUEZ F,BONET M L,et al.In vitro and in vivo induction of brown adipocyte uncoupling protein (thermogenin) by retinoic acid[J].Biochemical Journal,1996,317(3):827-833.
[14] FELIPE F,BONET M L,RIBOT J,et al.Up-regulation of muscle uncoupling protein 3 gene expression in mice following high fat diet,dietary vitamin A supplementation and acute retinoic acid-treatment[J].International Journal of Obesity,2003,27(1):60-69.
[15] REPA J J,LIANG G S,OU J F,et al.Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors,LXRα and LXRβ[J].Genes and Development,2000,14(22):2819-2830.
[16] YANG Q,GRAHAM T E,MODY N,et al.Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes[J].Nature,2005,436(7049):356-362.
[17] YOSHIKAWA T,IDE T,SHIMANO H,et al.Cross-talk between peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. .PPARs suppress sterol regulatory element binding protein-1c promoter through inhibition of LXR signaling[J].Molecular Endocrinology,2003,17(7):1240-1254.
[18] SHAW N,ELHOLM M,NOY N,et al.Retinoic acid is a high affinity selective ligand for the peroxisome proliferator-activated receptor α/β[J].Journal Biological Chemistry,2003,278(43):41589-41592.

[19] LUQUET S,GAUDEL C,HOLST D,et al.Roles of PPAR delta in lipid absorption and metabolism:a new target for the treatment of type 2 diabetes[J].Biochimica et Biophysica Acta (BBA): Molecular Basis of Disease,2005,1740(2):313-317.
[20] TANG Q Q,ZHANG J W,LANE M D.Sequential gene promoter interactions of C/EBPbeta,C/EBPalpha,and PPARgamma during adipogenesis[J].Biochemical and Biophysical Research Communications,2004,319(1):235-239.
[21] SCHWARZ E J,REGINATO M J,SHAO D,et al.Retinoic acid blocks adipogenesis by inhibiting C/EBPbeta-mediated transcription[J].Molecular and Cellular Biology,1997,17(3):1552-
[22] CADOUDAL T,GLORIAN M,MASSIAS A,et al.Retinoids upregulate phosphoenolpyruvate carboxykinase and glyceroneogenesis in human and rodent adipocytes[J].The Journal of Nutrition,2008,138(6):1004-1009.
[23] MILLER C W,WATERS K M,NTAMBI J M.Regulation of hepatic stearoyl-CoA desaturase vitamin A[J].Biochemical Biophysical Research Communications,1997,231(1):206-210.
[24] RAISHER B D,GULICK T,ZHANG Z,et al.Identification of a novel retinoid-responsive element in the promoter region of the medium chain acyl-coenzyme A dehydrogenase gene[J].Journal of Biological Chemistry,1992,267(28):20264-20269.
[25] VU-DAC N,GERVOIS P,TORRA I P,et al.Retinoids increase human apo C-III expression at transcriptional level via retinoid X receptor[J].Journal of Clinical Investigation,1998,102(3):625-632.
[26] TANIGUCHI D,MIZOGUCHI Y.Retinoic acids change gene expression profiles of bovine intramuscular adipocyte differentiation,based on microarray analysis[J].Animal Science Journal,2015,86(6):579-587.
[27] BERRY D C,JIN H,MAJUMDAR A,et al.Signaling by vitamin A and retinol-binding protein regulates gene expression to inhibit insulin responses[J].Proceedings of the National Academy of Sciences of the United States of America,2011,108(11):4340-4345.
[28] KANG H W,BHIMIDI G R,ODOM D P,et al.Altered lipid catabolism in the vitamin A deficient liver[J].Molecular and Cellular Endocrinology,2007,271(1/2):18-27.
[29] XIONG Y,COLLINS Q F,AN J,et al.p38 mitogen-activated protein kinase plays an inhibitory role in hepatic lipogenesis[J].Journal of Biological Chemistry,2007,282(7):4975-4982.
[30] BARGER P M,BROWNING A C,GARNER A N,et al.p38 mitogen-activated protein kinase activates peroxisome proliferator-activated receptor α:a potential role in the cardiac metabolic stress response[J].Journal of Biological Chemistry,2001,276(48):44495-44501.
[31] 刘洋.ATRA 调控 BMP9 诱导 3T3-L1 前脂肪细胞成骨和成脂分化的作用及机制研究[D]. 博士学位论文. 重庆: 重庆医科大学,2014.
[32] KIM D M,CHOI H R,PARK A,et al.Retinoic acid inhibits adipogenesis via activation of Wnt signaling pathway in 3T3-L1 preadipocytes[J].Biochemical and Biophysical Research Communications,2013,434(3):455-459.

[33] TAKADA I,MIHARA M,SUZAWA M,et al.A histone lysine methyltransferase activated by non-canonical Wnt signalling suppresses PPAR-γ transactivation[J].Nature Cell Biology,2007,9(11):1273-1285.
[34] OSEI-SARFO K,GUDAS L J.Retinoic acid suppresses the canonical Wnt signaling pathway in embryonic stem cells and activates the noncanonical Wnt signaling pathway[J].Stem Cells,2014,32(8):2061-2071.
[35] HISADA K,HATA K,ICHIDA F,et al.Retinoic acid regulates commitment of undifferentiated mesenchymal stem cells into osteoblasts and adipocytes[J].Journal of Bone & Mineral Metabolism,2013,31(1):53-63.
[36] MARCHILDON F,ST-LOUIS C,AKTER R,et al.Transcription factor Smad3 is required for inhibition of adipogenesis by retinoic acid[J].Journal Biological Chemistry,2010,285(17):13274-13284.
[37] STEPPAN C M,BAILEY S T,BHAT S,et al.The hormone resistin links obesity to diabetes[J].Nature,2001,409(6818):307-312.
[38] HOLLUNG K,RISE C P,DREVON C A,et al.Tissue-specific regulation of leptin expression and secretion by all-trans retinoic acid[J].Journal of Cellular Biochemistry,2004,92(2):307-315.
[39] SONG H Y,SHOJIMA N,Sakoda H,et al.Resistin is regulated by C/EBPs,PPARs,and signal-transducing molecules[J].Biochemical Biophysical Research Communications,2002,299(2):291-298.
[40] HUANG Y,DAS A K,YANG Q Y,et al.Zfp423 promotes adipogenic differentiation of bovine stromal vascular cells[J].PLoS One,2012,7(10):e47496.
[41] WANG B,YANG Q Y,HARRIS C L,et al.Nutrigenomic regulation of adipose tissue development-role of retinoic acid:a review[J].Meat Science,2016,120:100-106.

Note: Figure translations are in progress. See original paper for figures.