JAST (Journal of Animal Science and Technology) TITLE PAGE

Upload this completed form to website with submission

ARTICLE INFORMATION	Fill in information in each box below
Article Type	Review article
Article Title (within 20 words without abbreviations)	Vitamin A signaling in Adipocyte Differentiation: From Molecular Mechanisms to Livestock Production
Running Title (within 10 words)	Effect of atRA in vitro and in vivo
Author	Geumyoung Sok1, Zhijie Deng2, Dong-Hwan Kim1, Kichoon Lee2
Affiliation	1 Department of Animal Science, College of Natural Resources & Life Science, Pusan National University, Miryang 50463, South Korea 2 Department of Animal Sciences, The Ohio State University, Columbus, OH 43210, USA
ORCID (for more information, please visit https://orcid.org)	Geumyoung Sok (https://orcid.org/0009-0004-0501-1857) Zhijie Deng (https://orcid.org/0009-0007-6628-8712) Dong-Hwan Kim (https://orcid.org/0000-0002-3993-4025) Kichoon Lee (https://orcid.org/0000-0001-6169-7516)
Competing interests	No potential conflict of interest relevant to this article was reported.
Funding sources State funding sources (grants, funding sources, equipment, and supplies). Include name and number of grant if available.	This work was supported by a 2-Year Research Grant of Pusan National University
Acknowledgements	We are grateful to Michelle Milligan for her invaluable assistance by proofreading this manuscript.
Availability of data and material	Upon reasonable request, the datasets of this study can be available from the corresponding author.
Authors' contributions Please specify the authors' role using this form.	Conceptualization: Kim DH, Lee K. Methodology: Sok G, Deng Z. Validation: Sok G, Deng Z. Writing - original draft: Sok G, Deng Z, Kim DH. Writing - review & editing: Kim DH, Lee K.
Ethics approval and consent to participate	This article does not require IRB/IACUC approval because there are no human and animal participants.

CORRESPONDING AUTHOR CONTACT INFORMATION

For the corresponding author (responsible for correspondence, proofreading, and reprints)	Fill in information in each box below
First name, middle initial, last name	Kichoon Lee
Email address – this is where your proofs will be sent	lee.2626@osu.edu
Secondary Email address	donghwank@pusan.ac.kr
Address	Department of Animal Sciences, The Ohio State University, Columbus, OH 43210, USA
Cell phone number	
Office phone number	+1-614-688-7963
Fax number	

Vitamin A signaling in Adipocyte Differentiation: From Molecular Mechanisms to Livestock Production

Geumyoung Sok[1], Zhijie Deng[2], Dong-Hwan Kim[1,*], Kichoon Lee[2,*]

[1] Department of Animal Science, College of Natural Resources & Life Science, Pusan National University, Miryang 50463, South Korea

[2] Department of Animal Sciences, The Ohio State University, Columbus, OH 43210, USA

[*] Corresponding author: Dong-Hwan Kim (donghwank@pusan.ac.kr), Kichoon Lee (lee.2626@osu.edu)

Abstract

Adipogenesis, the differentiation of fibroblast-like precursor cells into mature adipocytes, is a complex process governed by transcriptional networks and nutrient signaling. Among micronutrients, vitamin A and its active metabolites, all-trans retinoic acid (atRA), have emerged as potent regulators of adipocyte development, linking nutritional status to metabolic and physiological outcomes. atRA is generated from retinol through sequential oxidation by retinol and aldehyde dehydrogenases and exerts transcriptional control primarily via retinoic acid receptors (RARs) and retinoid X receptors (RXRs). It functions in dynamic crosstalk with Wnt/b-catenin and other signaling pathways to influence the expression of key adipogenic transcription factors, including PPARγ and C/EBPα. In vitro evidence from 3T3-L1 and other mammalian cell models demonstrates that low concentrations of atRA (0.01 to 100 nM) promote adipogenic commitment and lipid accumulation, whereas higher concentrations (over 1 μM) inhibit differentiation and stimulate apoptosis through mitochondrial pathways. Comparative in vitro studies across livestock species reveal that atRA exerts species-specific effects which suppresses adipogenesis in porcine and bovine cells, while promoting PPARγ-mediated transdifferentiation of avian myoblasts into adipocytes. In vivo, atRA modulates adipose tissue development in a developmental stage-dependent manner, enhancing intramuscular fat deposition during fetal and neonatal stages but suppressing white adipose tissue expansion in adults. Collectively, these finding highlight atRA as a critical integrator of micronutrient signaling, gene regulation, and adipose tissue plasticity. Understanding the mechanisms of atRA-mediated adipogenesis provides key insights into the prevention of metabolic disorders and offers practical strategies in improve meat quality and feed efficiency in animal production system.

Keywords: Vitamin A; all-trans retinoic acid; Adipocyte; Adiposity; Livestock

INTRODUCTION

Adipogenesis, the biological process in which fibroblast-like precursor cells differentiate into fully developed adipocytes, is a tightly controlled process primarily by transcription factors such as peroxisome proliferator-activated receptor gamma (PPAR-γ) and the CCAAT/enhancer-binding protein (C/EBP) family members [1]. Beyond energy storage, adipocytes act as endocrine organs, regulating systemic metabolism and inflammatory responses. Changes in adipose tissue mass occur through hypertrophy [2] or hyperplasia [3], both closely linked with conditions such as obesity, cardiovascular diseases, and diabetes [4] Therefore, understanding adipogenesis is fundamental for elucidating metabolic disorders and therapeutic strategies. Its regulation is also crucial for livestock production, directly affecting meat quality, flavor, and feed efficiency [5,6]. Ultimately, clarifying adipogenesis mechanisms benefits both human health and advancements in animal agriculture.

Vitamin A (also known as retinol) of which active form is all-trans retinoic acid (atRA) is an essential fat-soluble nutrient [7]. It plays essential roles in maintaining visual function [8], immune regulation [9], reproduction, and epithelial tissue homeostasis [10,11]. Vitamin A is acquired through dietary sources, either as preformed vitamin A from animal products or as provitamin A carotenoids derived from plant foods, which are converted into active forms within the body [12]. Maintaining an optimal balance of vitamin A is crucial; deficiency leads to severe health problems, such as night blindness [13,14], impaired immune function [11], and growth retardation [15,16], while hypervitaminosis A can result in toxicity, characterized by symptoms such as liver damage and teratogenicity [17,18]. In addition to its systemic effects, the regulation of adipocyte differentiation by vitamin A metabolism highlights its broad significance, impacting not only the prevention and management of metabolic diseases but also various aspects of animal agriculture.

In this review, we discuss previously reported studies focusing on the functions of vitamin A in adipogenesis both in vitro and in vivo. In particular, we delve into the molecular mechanisms underlying regulatory effects of vitamin A on adipocyte differentiation, encompassing both its pro-adipogenic and anti-adipogenic actions, and their implications for metabolic health and animal agriculture.

BIOSYNTHESIS, METABOLISM, AND MECHANISM OF ACTION

atRA Biosynthesis and Metabolic Pathways

atRA is a major bioactive form of retinol. It serves as a critical signaling molecule involved in various cellular activities such as cell growth, lineage commitment [19], apoptosis [20], and metabolic regulation [21]. The biosynthesis of atRA is tightly regulated within cells through a two-step oxidative process (Fig. 1a). In the first step, retinol is reversibly oxidized to retinaldehyde by retinol dehydrogenases (RDHs), is

considered the rate-limiting step in the pathway, and its efficiency is influenced by the availability of cofactors and binding proteins [22]. In the second, irreversible step, retinaldehyde is further oxidized to atRA by aldehyde dehydrogenases (ALDHs), particularly those expressed selectively depending on the type of tissue. This step represents a crucial regulatory point to produce active atRA biologically [22,23]. Unlike other retinoic acid derivatives, atRA binds with high affinity to retinoic acid receptors (RARs), through which it directly regulates the transcription of specific target genes via retinoic acid response elements (RAREs) [19].

In the storage pathway, lecithin: retinol acyltransferase (LRAT) facilitates the conversion of retinol to retinyl esters through esterification, which are subsequently stored in lipid droplets [24]. This process indirectly limits the availability of retinol for atRA synthesis. The activity of LRAT itself is tightly regulated, being rapidly and markedly upregulated by atRA [25]. When the intracellular concentration of atRA increases excessively, cytochrome P450 family 26 enzymes (CYP26) are upregulated and become actively involved in the breakdown of atRA into hydroxylated inactive metabolites [26,27]. This serves as a key negative feedback mechanism to regulate RA signaling tightly (Fig. 1b). Dysregulation of this feedback may lead to retinoid toxicity or impaired differentiation processes, especially in tissues with high retinoid turnover.

The regulation of the retinoid metabolic network is further refined by cellular retinol-binding proteins (CRBPs) and cellular retinoic acid-binding proteins (CRABPs), which play essential roles in transporting retinoids within the cell, facilitating their storage, transport, and targeted delivery to specific enzymes or nuclear receptors. CRBPs primarily bind retinol, directing it either toward storage via esterification or toward oxidation for atRA biosynthesis, depending on the cell's physiological needs. CRABPs, which are structurally and immunologically distinct from CRBPs, bind retinoic acid [28] and determine its fate by mediating its interaction with nuclear receptors like RARs [29] or targeting it for catabolism via CYP26 enzymes [30–32]. The distribution and levels of CRBPs and CRABPs vary across tissues and are subject to independent regulation. The precise balance of retinoids, maintained by these binding proteins, is crucial. If these binding proteins do not work properly, the balance of retinoids in the cell can be disturbed, which may affect how cells grow, develop, and respond to the immune system. Together, these pathways and binding proteins help control atRA levels in specific tissues [33,34] and keep retinoid balance stable, making sure that RA signals are precisely regulated in different biological processes and stages of development.

Recent multi-omics studies have revealed complex molecular signaling networks through which atRA regulates adipocyte differentiation in livestock species. An integrated analysis of transcriptome and metabolome in bovine preadipocytes identified 5,257 differentially expressed genes (DEGs) and 328 differentially expressed metabolites (DEMs) during adipogenic differentiation, highlighting key lipid metabolic regulators such as FADS2, ACOT7, and ACOT2, while revealing that distinct FADS2 isoforms differentially influence unsaturated fatty acid biosynthesis and adipogenic regulation [35]. Meanwhile, in

bovine skeletal muscle-derived cells, atRA treatment exhibited a development-phase specific effect on adipogenic and myogenic gene expression, such as up-regulation of ZFP423 and PPAR γ in the proliferative phase, but suppression of adipogenic markers during differentiation [36]. These results illustrate that retinoid signaling in livestock is not simply a linear regulation of RAR/RXR to target gene but rather integrates with broader lipid and energy metabolic pathways, and its impact depends on the developmental stage and cellular context. Moreover, such omics-driven insights pave the way identifying novel biomarkers and species-specific retinoid-responsive modules that could optimize intramuscular fat deposition or adipose tissue composition in production animals.

Nuclear Receptors and Signaling Pathways

atRA functions as an important signaling molecule involved in diverse cellular activities. Within the cell, atRA binds with high affinity to RARα, β, and γ, as well as retinoid X receptors (RXR) α, β, and γ. These nuclear receptors form heterodimers that directly bind to RAREs, enabling precise regulation of gene expression. These complexes orchestrate diverse transcriptional programs tailored to the physiological functions of specific tissues, including liver [37,38], adipose tissue [39], skin [40], and immune cells [41]. Moreover, their transcriptional activities are finely tuned through dynamic interactions with a variety of coactivators, such as the NCoA family (SRC-1, TIF2/GRIP1, AIB1) and histone acetyltransferases like CBP/p300, which promote chromatin remodeling and gene activation [42]. Conversely, in the absence of ligand binding, RAR/RXR complexes recruit corepressors like NCoR and SMRT to induce chromatin condensation and repress target gene expression [43]. These regulatory mechanisms enable context-dependent and precise control of gene expression by retinoic acid signaling across different tissues and cell types.

At higher concentrations (≥1 μM), atRA activates the Wnt/β-catenin signaling pathway, which is closely associated with the inhibition of adipocyte differentiation [44]. Binding of Wnt ligands to their receptors inhibits phosphorylation of β-catenin by CK1 and GSK3β, leading to its stabilization and nuclear accumulation of β-catenin [45–47]. In the nucleus, β-catenin interacts with LEF/TCF transcription factors to induce the expression of Wnt target genes, such as Axin2 [48]. In this context, atRA, acting through RARγ, enhances Axin2 expression [49]. Axin2 suppresses the transcription of key adipogenic regulators, including C/EBPα and PPARγ, thereby reinforcing the anti-adipogenic effects [50]. Additionally, atRA inhibits the expression of PPARγ and C/EBPα, delaying or blocking adipocyte differentiation [51,52]. This functional crosstalk between atRA and Wnt signaling represents a critical regulatory mechanism in adipocyte differentiation (Fig. 1a).

The functional interaction between atRA and Wnt signaling is mediated by the RAR/β-catenin/Axin2 axis, which plays a key role in cell fate determination. Wnt signaling is known to inhibit adipogenesis [53], while atRA can antagonize or modulate this inhibitory effect. This regulatory interplay is closely connected to the physiological development of adipocytes [54,55]. atRA also directly influences adipocyte fate by

regulating the expression of crucial adipogenic transcription factors such as PPARγ and C/EBPα through the nuclear RAR/RXR heterodimer. The transcriptional effects of atRA depend on its concentration and timing of exposure [44,56,57], which affects adipocyte maturation and function. Therefore, understanding the crosstalk between atRA and Wnt signaling is fundamental to revealing the complex mechanisms governing adipocyte differentiation.

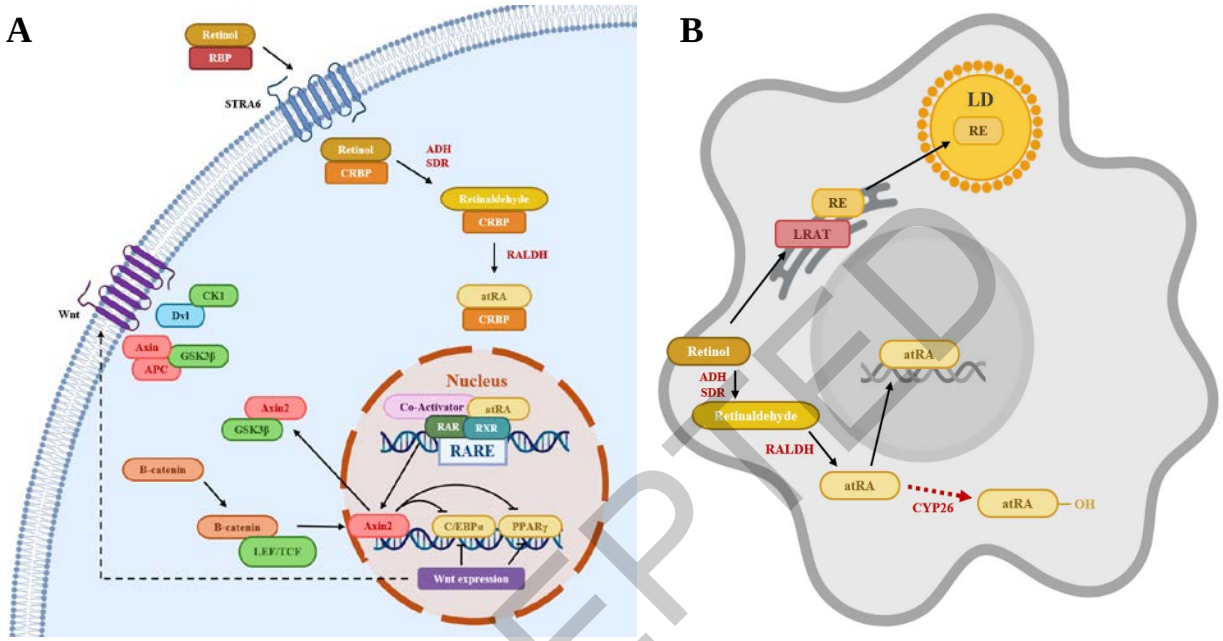

Fig. 1 An Illustrative Overview of atRA Biosynthesis and Metabolic Regulation. A. atRA Action and Crosstalk with Wnt Signaling. Retinol is enzymatically converted to atRA, which binds to RARs and regulates gene transcription by interacting with DNA response elements. atRA inhibits the expression of key adipogenic factors such as C/EBPα and PPARγ, while activating Wnt signaling pathways, thereby playing a crucial role in controlling cell differentiation. **B.** atRA Biosynthesis and Metabolism. Retinol can be stored as retinyl esters (RE) in lipid droplets (LD) via the enzyme LRAT. A crucial negative feedback loop is shown, where excessive atRA is inactivated by CYP26 enzymes to maintain retinoid homeostasis.

IN VITRO STUDIES OF atRA

Effects on Cell Proliferation, Differentiation, and Apoptosis

Most in vitro studies investigating atRA's role in adipogenesis have been conducted using mammalian models [58–61], particularly a mouse-derived preadipocyte cell line, 3T3-L1 cells [44,62–64]. These studies have revealed that atRA exerts opposing effects on adipocyte differentiation depending on the treatment concentration and timing, promoting differentiation within certain concentration ranges while inhibiting it at others [44,64] (Fig. 2). In 3T3-L1 adipocytes, atRA exerts cell type-specific effects through a sequential process ranging from the uptake of extracellular retinol to the activation of nuclear receptors.

High concentrations of atRA (≥1 μM) suppress the expression of the key adipogenic transcription factors PPARγ and C/EBPα [44] and activate the Wnt/β-catenin signaling pathway [65,66], thereby inhibiting the differentiation of preadipocytes. High concentrations of atRA inhibit adipocyte differentiation during the early stages by selectively activating RARγ [67,68]. Activation of RARγ promotes the maintenance of a stem-like state [69,70]. Low concentrations of atRA (0.01-100 nM) promote lipid accumulation and increase the expression of mature adipocyte marker genes such as FABP4 [44], adiponectin [71], and LPL [72] (Fig. 2a).

The process of adipocyte differentiation can be broadly divided into three stages: the early transcriptional phase, the mitotic clonal expansion (MCE) phase, and the late terminal differentiation phase [73]. Among these, the MCE phase is characterized by cells re-entering the cell cycle and proliferating after the activation of early transcription factors [73], thereby increasing cell number to establish a sufficient cellular pool necessary for subsequent adipocyte differentiation. Multiple studies have demonstrated that MCE is an essential prerequisite for adipogenesis, emphasizing that precise regulation of cell cycle entry and exit critically influences differentiation efficiency [74–76]. Notably, atRA has been reported to exert a significant regulatory effect on the MCE phase in the 3T3-L1 cell model [44]. Treatment with a low concentration of atRA (1 nM) resulted in the highest proliferation rate and simultaneous G0/G1 cell cycle arrest observed at day 2, suggesting a dual mechanism by which atRA coordinates cell division and growth inhibition to secure an adequate cell number during MCE and activate the differentiation program. Furthermore, atRA concentrations ranging from 0.01 to 100 nM progressively increased the expression of S/G2 phase-related proteins such as Cdk1 and Cdk2, which are likely to promote DNA synthesis and entry into cell division, thereby maximizing proliferative capacity in the early MCE stage. Conversely, high concentrations of atRA (1 to 10 μM) led to dominant expression of G0/G1 phase marker proteins, including Cdk4, a key regulator of the G1/S transition through its interaction with Cyclin D, when overexpressed, can cause prolonged retention of cells in the G1 phase before S phase entry. Combined with changes in Cdk1 expression, this results in cells being arrested in G1 rather than progressing through S/G2/M phases, ultimately inhibiting DNA synthesis and cell division and delaying or blocking the adipogenic differentiation program (Fig. 2b).

Although direct reports on atRA-induced apoptosis in mature adipocytes are limited [77], studies on adipose-derived stem cells (ADSCs) have shown that atRA treatment notably increases the expression of pro-apoptotic proteins, such as BAX and BAK, and promotes caspase-3 expression. It also alters the expression of anti-apoptotic proteins, such as BCL-2, and increases mitochondrial membrane permeability, indicating apoptosis via the intrinsic mitochondrial pathway [78]. This trend is like mechanisms reported in acute promyelocytic leukemia (APL) cells [78–80] and other cancer cell models [20,81,82], where atRA induces upregulation of BAX, suppression of BCL-2 expression, triggers activation of the caspase signaling cascade, and facilitates the release of cytochrome c. These findings suggest that atRA triggers apoptosis

primarily through mitochondrial functional alterations and regulation of BCL-2 family proteins. These findings suggest that atRA influences adipose tissue by regulating adipocyte numbers and remodeling metabolism, yet the specific stages of adipogenesis and the signaling pathways involved remain to be fully understood.

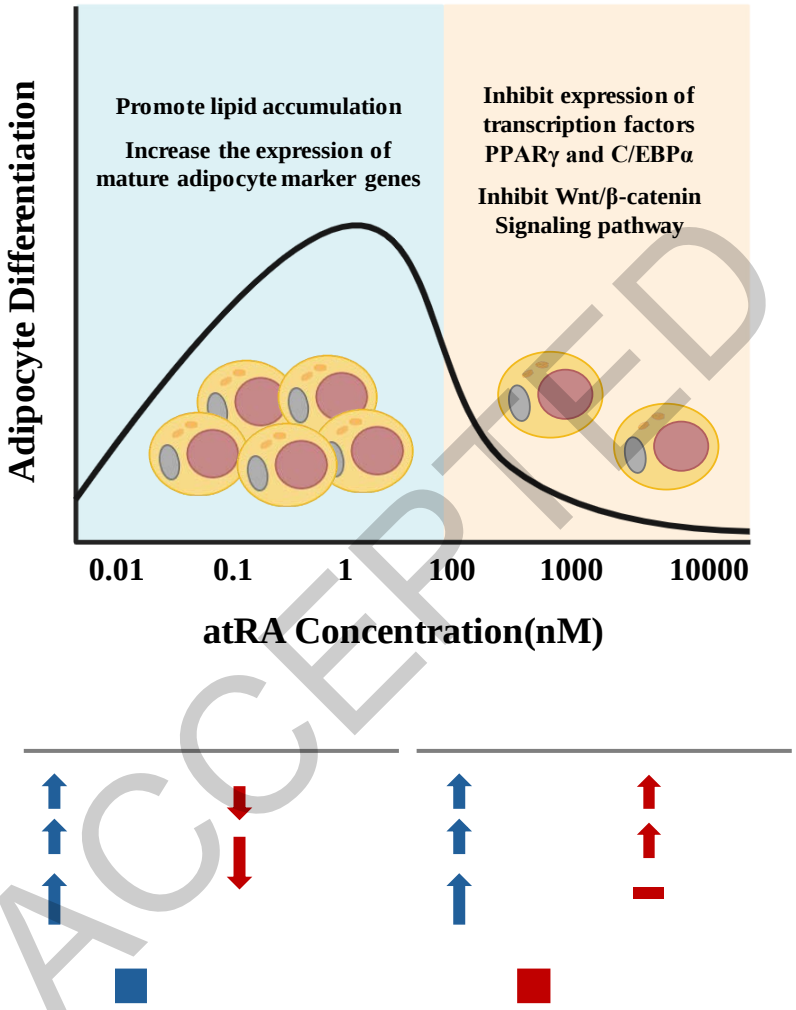

Fig. 2. Dual Regulation of Adipocyte Differentiation by atRA Concentration. **A.** At low atRA concentrations (approximately 0.01-100 nM), atRA promotes adipocyte differentiation by enhancing lipid accumulation and increasing the expression of mature adipocyte marker genes. Conversely, at high atRA concentrations (approximately >100 nM), atRA inhibits adipocyte differentiation by suppressing the expression of key transcription factors PPARγ and C/EBPα, and by inhibiting the Wnt/β-catenin signaling pathway. **B.** atRA modulates gene expression and cell cycle progression during adipocyte differentiation. During the Early transcriptional phase, low atRA (blue) upregulates C/EBP family transcription factors, while high atRA (red) suppresses. In the MCE phase, low atRA increases Cdk1 and Cdk2 expression,

facilitating G2/M phase entry. Conversely, high atRA reduces Cdk4 and Cdk1 levels, resulting in a pronounced G1 arrest.

Disease Modeling in Culture Systems

Using atRA in cell culture systems allows for precise explanation of molecular mechanisms related to metabolic diseases. In the 3T3-L1 adipocyte culture model, atRA exhibits dual effects depending on treatment concentration, timing, and the stage of cell differentiation. Low-dose or late-stage treatment promotes adipocyte differentiation by increasing the expression of mature adipocyte markers such as FABP4 and adiponectin, whereas high-dose treatment strongly inhibits lipid accumulation and differentiation by suppressing the expression of PPARγ and C/EBPα [44]. In the hepatocyte cell model (HepG2 cells), atRA suppresses the expression of SREBP-1c and FASN genes involved in de novo lipogenesis [83,84], increases the transcription factor C/EBPα leading to inhibition of cell proliferation, and reduces PLAU (involved in expansion and remodeling of adipose tissue) expression, thereby blocking pro-growth signals and decreasing hepatic lipid accumulation [85]. These results highlight the promise of atRA as a candidate treatment for non-alcoholic fatty liver disease (NAFLD). Additionally, in cardiovascular disease models, atRA inhibits excessive proliferation of vascular smooth muscle cells (VSMCs) and acts through activation of the AMPK signaling pathway to suppress mTOR signaling [86], demonstrating its influence on atherosclerosis and related cardiovascular conditions. atRA promotes myofiber formation and mitochondrial biogenesis in mouse myoblasts [87], and enhances insulin synthesis and secretion in the pancreatic beta-cell model, contributing to glucose homeostasis [88]. Furthermore, in inflammation-related disease models, atRA plays a key role in regulating macrophage M1/M2 polarization [89]. Studies in murine macrophage cells have shown that atRA suppresses the NF-κB signaling pathway, leading to decreased expression of pro-inflammatory cytokines IL-6 and TNF-α, thereby alleviating metabolic inflammation [90]. Collectively, these results indicate that atRA exerts specific and context-dependent regulatory effects across diverse cell types and pathological environments, highlighting its value as a useful in vitro model for studying metabolic and inflammatory diseases as well as for potential therapeutic development.

To date, researches on disease modeling related to atRA have primarily focused on human and rodent cell lines; however, expanding studies to livestock species such as pigs, cattle, sheep, and chickens is critically important. Livestock play a vital role as food sources and provide more realistic models for studying metabolic and inflammatory diseases due to their distinct physiological characteristics and environmental exposures compared to humans. For example, atRA strongly inhibits differentiation of porcine preadipocytes by reducing the mRNA expression of PPARγ, RXRα, SREBP-1c, and FABP4 through activation of retinoic acid receptors [61]. Additionally, atRA induces muscle fiber type switching in cultured bovine satellite cells (BSCs), increasing expression of oxidative metabolism-related MHC I and

decreasing MHC IIX via the PPARδ pathway [91]. In ovine myoblasts, atRA suppresses cell proliferation while increasing expression of myogenin and myosin heavy chain proteins; this process involves elevated H3K4me3 and reduced H3K27me3, modulating transcriptional activation, and further activates GLUT4 expression and mTOR signaling pathways to influence muscle metabolism and growth [92].

Studies on primary cultured preadipocytes from Holstein cattle showed that atRA inhibits proliferation and induces apoptosis in pre-confluent preadipocytes. In post-confluent preadipocytes, atRA suppressed differentiation by reducing PPARγ and C/EBPα protein expression. In mature adipocytes, atRA (conc.: 0.2, 2, and 20 nM) stimulated basal lipolysis but did not affect epinephrine-stimulated lipolysis[59]. These results suggest that atRA regulates lipid accumulation and breakdown in bovine adipocytes, potentially playing a role in modulating lipid metabolism and preventing metabolic diseases in over-conditioned dry cows [59]. In avian myoblasts, atRA treatment increased intracellular lipid accumulation and adipogenic gene expression, notably by directly inducing PPARγ expression[93]. The extent of transdifferentiation was dependent on PPARγ activation, and treatment with PPARγ agonists alone was insufficient to trigger adipocyte transdifferentiation in the absence of atRA[93]. These findings indicate that atRA-driven PPARγ expression is critical for the conversion of myoblasts into adipocytes and highlight atRA as a potential novel regulator to improve marbling in poultry production [93].Collectively, these findings suggest that atRA exerts species-specific yet consist of regulatory functions on lipid metabolism and muscle development in livestock cells. For instance, atRA-mediated induction of PPARγ is essential for transdifferentiation of myoblast into adipocyte in avian systems [93], while in porcine and bovine cells, atRA predominantly suppresses adipogenesis and modulates muscle fiber characteristics through nuclear receptor pathways [91]. Such comparative evidence highlights atRA as a central molecular determinant orchestrating the balance between myogenesis and adipogenesis across livestock species, linking its relevance not only to human metabolic disorders but also to meat quality traits in animal production.

Such livestock-based in vitro models are invaluable for specifically understanding the molecular mechanisms regulated by atRA in agriculturally important species. Research on atRA-related signaling and gene expression regulation in livestock cells contributes not only to improving animal health, productivity, meat quality, and resistance to metabolic diseases but also enhances comparative biological insights into atRA biology across mammals. Furthermore, these livestock models hold promise as platforms applicable to both human and animal studies for exploring nutritional or pharmacological interventions aimed at preventing or treating metabolic disorders.

THE EFFECT OF RETINOIC ACID ON ADIPOSE TISSUE OF ANIMAL

To extend cellular observations to physiological contexts, subsequent studies have investigated the effects of retinoic acid in animal models. In rodent studies, daily subcutaneous injection of atRA in adult

mice reduces adipocyte size and decreases white adipose tissue (WAT) mass in epididymal, inguinal, and retroperitoneal fat [94]. This morphological change is accompanied by upregulation of central regulators of fatty acid oxidation, including PGC-1α, PPARα, and CPT1, suggesting an enhanced capacity for lipid catabolism. Similarly, atRA treatment to adult obese mice promotes weight loss, reduces WAT mass, and alleviates hepatic lipid accumulation [95]. Moreover, atRA administration partially reverses the adiposity of mice induced by a vitamin A-deficient diet and downregulates PPARγ2 expression level in WAT, a key marker of lipogenesis and adipogenesis [96]. Collectively, these findings indicate that retinoic acid functions as an inhibitor of adipogenesis in mature mice.

In livestock, manipulating vitamin A status – through dietary supplementation, restriction, or intramuscular injection of retinoic acid – has emerged as a strategy to modulate intramuscular fat (marbling), a critical determinant of beef flavor and tenderness. In pregnant beef cattle, vitamin A supplementation from day 180 of gestation until parturition increases intramuscular fat deposition in the offspring throughout postnatal life, with elevated expression of the preadipocyte marker DLK1, and the adipogenic marker PPARγ in neonatal skeletal muscle [97]. Likewise, intramuscular injection of vitamin A at birth and at 1 month of age in Black Angus steers enhances PDGFRα^{+} adipose progenitors and improves marbling scores [98,99]. By contrast, in later life stages, vitamin A restriction is required to enhance marbling: mature steers fed low- or no-vitamin A diets exhibit greater intramuscular fat deposition largely through adipocyte hyperplasia [100–103]. Comparable effects have been reported in pigs and sheep. Lambs receiving vitamin A supplementation or intramuscular injections during early postnatal development show increased numbers of preadipocytes and intramuscular adipocytes, alongside upregulation of adipogenic markers such as CEBPα and CEBPβ in the longissimus dorsi muscle [104,105]. In female pigs, restricting vitamin A intake during the grower and finisher phase enhances intramuscular fat levels in the longissimus muscle [106].

In avian species, vitamin A has long been implicated in adipogenesis, the direct effects of embryonic atRA exposure on adipose development have only recently been investigated. In quail embryos, in ovo administration of atRA at embryonic day (E) 7 led to increased inguinal fat mass and enlarged adipocytes by E14, accompanied by upregulation of pro-adipogenic genes (PPARγ, Fabp4) and downregulation of the preadipocyte marker Dlk1 [56]. Similarly, in broiler chickens, in ovo injection of 500 nM atRA at E10 enhanced adipose tissue accumulation and adipocyte hypertrophy during embryogenesis, although these effects did not persist after hatching [107]. Beyond its roles in proliferation and apoptosis, atRA exerts distinct metabolic and transcriptional effects on white, beige, and brown adipocytes across both rodent and livestock species. In white adipocytes, high concentrations of atRA (≥1 μM) generally suppress differentiation by downregulating PPARγ and C/EBPα, thereby maintaining cells in a preadipocyte-like state [94]. Conversely, brown and beige adipocytes exhibit enhanced thermogenic activity in response to atRA exposure, characterized by the upregulation of UCP1, CIDEA and mitochondrial biogenesis genes [108]. Recent findings in bovine [109] and porcine [110] adipose tissues demonstrate that dietary vitamin A restriction or pharmacological modulation of retinoid signaling alters the mRNA expression levels of

UCP1, PGC-1α, and ZFP423, suggesting that RA metabolism contributes to the recruitment of beige-like adipocytes even in livestock species [55,109]. Furthermore, chronic atRA treatment promotes oxidative metabolism, as evidenced by increased TCA cycle intermediates and glucose oxidation, coupled with the downregulation of glycolytic enzymes such as PFKP and G6PDH. This metabolic shift implies enhanced mitochondrial activation and fatty acid oxidation, particularly in metabolically active depots [55,111].

Retinoid signaling via RARα and its metabolic enzyme RDH1 is essential for maintaining BAT atRA levels, mitochondrial integrity, and systemic glucose homeostasis [112]. Disruption of this regulatory axis, through RARα inhibition or RDH1 deficiency[112,113], reduces UCP1 expression[108]. However, the mechanistic basis linking atRA to adipogenic fate determination (white vs. beige vs. brown) remains poorly defined in livestock. Species-specific differences in RAR/RXR sensitivity, local retinoid metabolism, and adipose depot–dependent signaling likely underlie the divergent adipogenic and metabolic outcomes observed among ruminants, pigs, and rodents. Thus, comparative in vitro and in vivo analyses are required to elucidate how atRA coordinates cellular differentiation, mitochondrial remodeling, and lipid metabolism across species knowledge that could ultimately inform nutritional or pharmacological strategies to modulate adipose plasticity in livestock.

In summary, these findings collectively indicate that the influence of retinoic acid on adipose development is both stage and species dependent. atRA promotes adipogenesis during early developmental stages particularly in embryos and neonates while in later life it generally suppresses adipogenesis. In avian embryos, however, their adipogenic effects appear largely restricted to the prenatal period.

338 **Table 1. Summary of the effect of retinoic acid on adipose tissue of mammals.**

Species	Age	Administration	VitA dose or concentration	Main effects	Overall adipogenic outcome	Reference
NMRI male mice	12-week-old	atRA s.c., once daily for 4 days	10, 50, 100 mg/kg	iWAT, eWAT, rWAT mass↓ WAT UCP1/2, PGC-1α, PPARα and CPT1 mRNA↑	Inhibit	[94]
C57BL/6Ntac mice	>16-week-old	subcutaneous implantation of RA pellet, 5 weeks	NA	eWAT and aWAT mass↓ Adipocyte size↓ Liver lipid accumulation↓	Inhibit	[95]
NMRI male mice	3-week-old	VitA-deficient diet for 10 weeks followed by atRA s.c. (once daily for 4 days)	VitA-deficient diet: <0.38 IU/kcal atRA s.c.: 100 mg/kg	VitA-deficient diet: iWAT and eWAT mass↑, adiposity index↑, eWAT PPARγ2, ADD1/SREBP1c and C/EBPα mRNA↑ atRA sc injection: body weight↓, eWAT mass↓, iWAT and eWAT PPARγ2 mRNA↓, eWAT ADD1/SREBP1c and C/EBPα mRNA↓	VitA-deficient diet: Promote atRA sc injection: Inhibit	[96]
Pregnant Angus-Simmental cross bred multiparous cows	Day 180 of gestation	Basal diet enriched with pure VitA until parturition	12200 IU VitA/kg in feed	Offspring calves: IMF%↑, skeletal muscle DLK1, PPARγ↑	Promote	[97]
Angus steer calves	Newborn	VitA i.m. at birth and 1-month-old	150000 IU	IMF%↑, marbling score↑, subcutaneous adipocyte diameter↓, *Biceps femoris* muscle PDGFRα, PPARγ, and ZFP423 mRNA↑	Promote	[99]
Angus steer calves	Newborn	VitA i.m. at birth and 1-month-old	150000 or 300000 IU	IMF%↑, marbling score↑, *Biceps femoris* muscle PPARγ and ZFP423 mRNA↑	Promote	[114]
Angus steers	12-month-old	Standard commercial feedlot ratios without VitA over 300 days	NA	IMF%↑	Promote	[115]

Holstein steers	NA	VitA-restricted diet for 131 or 243 days	~950 IU of VitA equivalents/kg of DM	VitA-restricted diet for 243 days: IMF%↑	Promote	[100]
Angus-cross steers	NA	No VitA supplementation in high-moisture or dry corn for 145 days	High-moisture corn: 1300 IU/kg VitA Dry corn: 1100 IU/kg VitA	Marbling score↑	Promote	[101]
Angus steers	12-month-old	Non VitA-supplemented diet for 10 months	NA	IMF%↑, marbling score↑, cell number per IMF fleck↑	Promote	[103]
Hu sheep lambs	Newborn	VitA or RA i.m. at 1, 7, 14, and 21 days of age	VitA i.m.: 7500 IU RA i.m.: 7500 IU	VitA i.m.: intramuscular SVF cells formed adipocytes↑, adipocyte numbers of LD and ST muscle↑, LD C/EBPα and C/EBPβ mRNA↑	Promote	[104]
Rasa Aragonesa lambs	Newborn	VitA supplementation by capsule, twice a week until 58 days of age	500000 IU	IMF mass↑, the number of adipocytes in the perirenal depot↑	Promote	[105]
Crossbred (Large White × Landrace × Duroc) pigs	NA	Non VitA-supplemented diet during grower (68-124 days) and finisher (124-159 days) phase	NA	LD IMF%↑	Promote	[106]

s.c., subcutaneous injection; i.m., intramuscular injection; WAT, white adipose tissue; eWAT, epididymal WAT; iWAT, inguinal WAT; rWAT, retroperitoneal WAT; aWAT, abdominal WAT; RA, retinoic acid; atRA, *all-trans* retinoic acid; VitA, vitamin A; IMF, intramuscular fat; LD, Longissimus dorsi; ST, semitendinosus; SVF, stromal vascular fraction; NA, not available.

CONCLUSION

Significant progress has been made in understanding the effects of atRA on adipogenesis, yet several critical knowledge gaps remain. Current knowledge is largely derived from murine cell lines, particularly 3T3-L1 preadipocytes, which cannot fully recapitulate the complexity of adipose biology across different species [44,63,116–119]. The different responses to atRA in rodents, ruminants, and poultry emphasize the importance of studying multiple species to identify which mechanisms are universal and which are specific to each species. Another major challenge lies in resolving the temporal and concentration-dependent effects of atRA. Evidence suggests that the stage of adipocyte differentiation and the local microenvironment strongly influence atRA signaling outcomes, yet systematic analyses across developmental stages and tissue contexts remain limited.

Moreover, while atRA has been shown to interact with nuclear receptors (RAR/RXR) [120,121] and signaling cascades such as Wnt/β-catenin [122,123], MAPK [124], and PI3K/AKT [125], the context-dependent hierarchy and cross-regulation of these pathways are poorly understood. Advances in single-cell multi-omics, spatial transcriptomics, and metabolomics are likely to provide powerful tools to address these questions.

Understanding the regulatory role of atRA also holds important applied value. In livestock, targeted modulation of retinoid signaling can improve feed efficiency [6,56], meat quality [58], and metabolic regulation. In human medicine, selective manipulation of retinoid pathways may offer novel therapeutic strategies for obesity [21], diabetes [126], and nonalcoholic fatty liver disease [127]. Accordingly, the development of tissue-selective RAR/RXR agonists and antagonists, alongside nutritional interventions aimed at modulating endogenous retinoid metabolism, represents a promising frontier for future research.

However, practical applications of vitamin A modulation in livestock must carefully balance efficacy with safety. Excessive or prolonged supplementation can lead to hepatic toxicity, impaired growth, or reproductive disorders, while insufficient levels may compromise immune and metabolic function. For instance, in broiler breeders, dietary supplementation exceeding 45,000–135,000 IU vitamin A/kg feed induced liver dysfunction could reduce fertility and alter immune responses [128]. Excessive vitamin A intake in cattle has been associated with decreased feed intake, hepatic dysfunction, and abnormal bone growth, particularly when intake levels greatly exceed recommended dietary requirement [129]. These findings highlight the narrow physiological window required for optimal vitamin A status in livestock. Therefore, precise dose optimization, adherence to regulatory limits, and long-term safety evaluations are essential for translating retinoid signaling research into sustainable livestock production strategies.

Adipogenesis is a complex, tightly regulated process that integrates endocrine, nutritional, and molecular cues to maintain energy homeostasis and influence metabolic health. Among these regulatory factors, atRA emerges as a broadly acting and condition-dependent regulator. In vitro evidence suggests that low concentrations (approximately 0.01-100 nM) of atRA may facilitate early adipogenic commitment, whereas

higher concentrations (approximately ≥1 μM) generally suppress differentiation through nuclear receptor–mediated transcriptional repression and activation of inhibitory signaling cascades [44]. atRA modulates fat accumulation in a stage- and timing-dependent manner in vivo, enhancing intramuscular fat and adipogenic marker expression (DLK1, PPARγ, PDGFRα) during fetal and early postnatal stages [98,114], while reducing white adipose tissue and inhibiting adipogenesis in adults [94]. In avian, in ovo atRA treatment increases adipocyte hypertrophy and pro-adipogenic gene expression, though these effects do not persist after hatching [56,107].

Collectively, these findings position atRA as a critical link between micronutrient status, gene regulation, and adipose tissue biology. However, the complexity of its effects—depending on dose, timing, species, and developmental context—underscores the need for further mechanistic and translational studies. A comprehensive understanding of atRA-mediated adipogenesis will not only deepen our insight into fundamental adipose biology but also provide novel opportunities for improving livestock production and developing targeted interventions for metabolic disorders.

From an applied perspective, several strategies could advance the use of atRA in livestock production. Nutritional and developmental modulation involves optimizing dietary vitamin A or carotenoid intake and timing atRA or analog supplementation during key developmental stages to fine-tune fat deposition, enhance marbling, and improve feed efficiency. Selective RAR/RXR-targeted interventions use tissue-specific agonists or regulators of retinoid metabolism to differentially modulate adipogenesis in muscle versus subcutaneous depots. Integrating these approaches with genomic and metabolomic monitoring could enable precision control of adiposity, productivity, and meat quality in livestock.

Funding sources

This work was supported by a 2-Year Research Grant of Pusan National University.

Acknowledgments

We are grateful to Michelle Milligan for her invaluable assistance by proofreading this manuscript.

References

1. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor. Cell. 1994;79:1147–56. https://doi.org/10.1016/0092-8674(94)90006-X

2. Wang QA, Tao C, Gupta RK, Scherer PE. Tracking adipogenesis during white adipose tissue development, expansion and regeneration. Nat Med. 2013;19:1338–44. https://doi.org/10.1038/nm.3324

3. Shepherd PR, Gnudi L, Tozzo E, Yang H, Leach F, Kahn BB. Adipose cell hyperplasia and enhanced glucose disposal in transgenic mice overexpressing GLUT4 selectively in adipose tissue. Journal of Biological Chemistry. 1993;268:22243–6. https://doi.org/10.1016/S0021-9258(18)41516-5

4. Diff M, Median Diff O. Educational Level, Relative Body Weight, and Changes in Their Association Over 10 Years: An International Perspective From the WHO MONICA Project. Am J Public Health. 2000.

5. Horodyska J, Reyer H, Wimmers K, Trakooljul N, Lawlor PG, Hamill RM. Transcriptome analysis of adipose tissue from pigs divergent in feed efficiency reveals alteration in gene networks related to adipose growth, lipid metabolism, extracellular matrix, and immune response. Molecular Genetics and Genomics. Springer Verlag; 2019;294:395–408. https://doi.org/10.1007/s00438-018-1515-5

6. Kim D-H, Lee J, Suh Y, Cressman M, Lee K. Research Note: All-trans retinoic acids induce adipogenic differentiation of chicken embryonic fibroblasts and preadipocytes. Poult Sci. 2020;99:7142–6 . https://doi.org/10.1016/j.psj.2020.09.006

7. Bates CJ. Vitamin A. The Lancet. 1995;345:31–5. https://doi.org/10.1016/S0140-6736(95)91157-X

8. Bello S MMMERI, Oduwole O. Routine vitamin A supplementation for the prevention of blindness due to measles infection in children. Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2014; https://doi.org/10.1002/14651858.CD007719.pub3

9. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008;8:685–98. https://doi.org/10.1038/nri2378

10. Aamir A, Kuht HJ, Grønskov K, Brooks BP, Thomas MG. Clinical utility gene card for oculocutaneous (OCA) and ocular albinism (OA)—an update. European Journal of Human Genetics. 2021;29:1577–83. https://doi.org/10.1038/s41431-021-00809-w

11. Obers A, Poch T, Rodrigues G, Christo SN, Gandolfo LC, Fonseca R, et al. Retinoic acid and TGF-β orchestrate organ-specific programs of tissue residency. Immunity. 2024;57:2615-2633.e10. https://doi.org/10.1016/j.immuni.2024.09.015

12. Chungchunlam SMS, Moughan PJ. Comparative bioavailability of vitamins in human foods sourced from animals and plants. Crit Rev Food Sci Nutr. Taylor and Francis Ltd.; 2024. p. 11590–625. https://doi.org/10.1080/10408398.2023.2241541

13. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. The Lancet. 2006;368:1795–809. https://doi.org/10.1016/S0140-6736(06)69740-7

14. Bernal S, Ayuso C, Antiñolo G, Gimenez A, Borrego S, Trujillo MJ, et al. Mutations in USH2A in Spanish patients with autosomal recessive retinitis pigmentosa: high prevalence and phenotypic variation. J Med Genet. 2003;40. https://doi.org/10.1136/jmg.40.1.e8

15. Arballo J, Rutkowsky JM, Haskell MJ, De Las Alas K, Engle-Stone R, Du X, et al. Pre- and Postnatal Vitamin A Deficiency Impairs Motor Skills without a Consistent Effect on Trace Mineral Status in Young Mice. Int J Mol Sci. Multidisciplinary Digital Publishing Institute (MDPI); 2024;25. https://doi.org/10.3390/ijms251910806

16. Mcmenamy KR, Zachman RD. Effect of Gestational Age and Retinol (Vitamin A) Deficiency on Fetal Rat Lung Nuclear Retinoic Acid Receptors. Pediatr Res. 1993;33:251–5. https://doi.org/10.1203/00006450-199303000-00009
17. Geubel AndréP, De Galocsy C, Alves N, Rahier J, Dive C. Liver damage caused by therapeutic vitamin A administration: Estimate of dose-related toxicity in 41 cases. Gastroenterology. 1991;100:1701–9. https://doi.org/10.1016/0016-5085(91)90672-8
18. Enneth K, Othman JR, Oore YLM, Inger ARS, Guyen Y-SADTN, Alvatore S, et al. Teratogenicity of High Vitamin A Intake. 1995. https://doi.org/10.1056/NEJM199511233332101
19. Brown G. Retinoic acid receptor regulation of decision-making for cell differentiation. Front Cell Dev Biol. Frontiers Media SA; 2023. https://doi.org/10.3389/fcell.2023.1182204
20. Butsri S, Kukongviriyapan V, Senggunprai L, Kongpetch S, Prawan A. All-trans-retinoic acid induces RARB-dependent apoptosis via ROS induction and enhances cisplatin sensitivity by NRF2 downregulation in cholangiocarcinoma cells. Oncol Lett. Spandidos Publications; 2022;23. https://doi.org/10.3892/ol.2022.13299
21. Rubinow KB, Zhong G, Czuba LC, Chen JY, Williams E, Parr Z, et al. Evidence of depot-specific regulation of all-trans-retinoic acid biosynthesis in human adipose tissue. Clin Transl Sci. John Wiley and Sons Inc; 2022;15:1460–71. https://doi.org/10.1111/cts.13259
22. Belyaeva O V., Adams MK, Popov KM, Kedishvili NY. Generation of retinaldehyde for retinoic acid biosynthesis. Biomolecules. MDPI AG; 2020. https://doi.org/10.3390/biom10010005
23. Kedishvili NY. Retinoic acid synthesis and degradation. Subcell Biochem. Springer New York; 2016;81:127–61. https://doi.org/10.1007/978-94-024-0945-1_5
24. O'Byrne SM, Wongsiriroj N, Libien J, Vogel S, Goldberg IJ, Baehr W, et al. Retinoid Absorption and Storage Is Impaired in Mice Lacking Lecithin:Retinol Acyltransferase (LRAT)*. Journal of Biological Chemistry. 2005;280:35647–57. https://doi.org/10.1074/jbc.M507924200
25. Randolph RK, Ross AC. Vitamin A status regulates hepatic lecithin: retinol acyltransferase activity in rats. Journal of Biological Chemistry. 1991;266:16453–7. https://doi.org/10.1016/S0021-9258(18)55321-7
26. Wu Z, Zhang X, An Y, Ma K, Xue R, Ye G, et al. CLMP is a tumor suppressor that determines all-trans retinoic acid response in colorectal cancer. Dev Cell. 2023;58:2684-2699.e6. https://doi.org/10.1016/j.devcel.2023.10.006
27. Lee S-J, Perera L, Coulter SJ, Mohrenweiser HW, Jetten A, Goldstein JA. The discovery of new coding alleles of human CYP26A1 that are potentially defective in the metabolism of all-trans retinoic acid and their assessment in a recombinant cDNA expression system. https://doi.org/10.1097/FPC.0b013e32801152d6
28. Takase S, Ong DE, Chytil F. Transfer of retinoic acid from its complex with cellular retinoic acid-binding protein to the nucleus. Arch Biochem Biophys. 1986;247:328–34. https://doi.org/10.1016/0003-9861(86)90591-6
29. Nugent P, Greene RM. Antisense oligonucleotides to CRABP I and II alter the expression of TGF-β3, RAR-β, and tenascin in primary cultures of embryonic palate cells. In Vitro Cell. Dev. Biol.-Animal. 1995 Feb. https://doi.org/10.1007/BF02634034
30. Won JY, Nam E-C, Yoo SJ, Kwon HJ, Um SJ, Han HS, et al. The effect of cellular retinoic acid binding protein-I expression on the CYP26-mediated catabolism of all-trans retinoic acid and cell proliferation in head and neck squamous cell carcinoma. Metabolism. 2004;53:1007–12. https://doi.org/10.1016/j.metabol.2003.12.015
31. Kim SY, Yoo SJ, Kwon HJ, Kim SH, Byun Y, Lee K-S. Retinoic acid 4-hydroxylase-mediated catabolism of all-trans retinoic acid and the cell proliferation in head and neck squamous cell carcinoma. Metabolism. 2002;51:477–81. https://doi.org/10.1053/meta.2002.31335

32. Kashyap V, Laursen KB, Brenet F, Viale AJ, Scandura JM, Gudas LJ. RARγ is essential for retinoic acid induced chromatin remodeling and transcriptional activation in embryonic stem cells. J Cell Sci. 2013;126:999–1008. https://doi.org/10.1242/jcs.119701
33. Sapin V, Ward SJ, Bronner S, Chambon P, Dollé P. Differential expression of transcripts encoding retinoid binding proteins and retinoic acid receptors during placentation of the mouse. Developmental Dynamics. 1997;208:199–210. https://doi.org/10.1002/(SICI)1097-0177(199702)208:2<199::AID-AJA7>3.0.CO;2-D
34. Dolle P, Ruberte E, Leroy P, Morriss-Kay G, Chambon' P. Retinoic acid receptors and cellular retinoid binding proteins I. A systematic study of their differential pattern of transcription during mouse organogenesis. Development. 1990. https://doi.org/10.1242/dev.110.4.1133
35. Zhang X, Li F, Peng L, Huang W, Du Y, Yang L, et al. Integrated multi-omics analysis of metabolome and transcriptome profiles during bovine adipocyte differentiation reveals functional divergence of FADS2 isoforms in lipid metabolism regulation. BMC Genomics. BioMed Central Ltd; 2025;26. https://doi.org/10.1186/s12864-025-11650-6
36. Jin XC, Peng DQ, Kim WS, Park JS, Lee JH, Brad Kim YH, et al. All-Trans Retinoic Acid Drives Development Phase-Specific Response to Adipogenic and Myogenic Processes in Bovine Skeletal Muscle-Derived Cells. Meat and Muscle Biology. Iowa State University Digital Press; 2024;8:1–13. https://doi.org/10.22175/mmb.16978
37. Li B, Cai S-Y, Boyer JL. The role of the retinoid receptor, RAR/RXR heterodimer, in liver physiology. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2021;1867:166085. https://doi.org/10.1016/j.bbadis.2021.166085
38. He Y, Gong L, Fang Y, Zhan Q, Liu H-X, Lu Y, et al. The role of retinoic acid in hepatic lipid homeostasis defined by genomic binding and transcriptome profiling. BMC Genomics. 2013;14:575. https://doi.org/10.1186/1471-2164-14-575
39. Teruel T, Hernandez R, Benito M, Lorenzo M. Rosiglitazone and Retinoic Acid Induce Uncoupling Protein-1 (UCP-1) in a p38 Mitogen-activated Protein Kinase-dependent Manner in Fetal Primary Brown Adipocytes*. Journal of Biological Chemistry. 2003;278:263–9. https://doi.org/10.1074/jbc.M207200200
40. Mihály J, Gericke J, Lucas R, de Lera AR, Alvarez S, Törőcsik D, et al. TSLP expression in the skin is mediated via RARγ-RXR pathways. Immunobiology. Elsevier GmbH; 2016;221:161–5. https://doi.org/10.1016/j.imbio.2015.09.013
41. Szondy Z, Reichert U, Fésüs L. Retinoic acids regulate apoptosis of T lymphocytes through an interplay between RAR and RXR receptors. Cell Death Differ. 1998;5:4–10. https://doi.org/10.1038/sj.cdd.4400313
42. Rochette-Egly C, Germain P. Dynamic and combinatorial control of gene expression by nuclear retinoic acid receptors (RARs). Nucl Recept Signal. 2009. https://doi.org/10.1621/nrs.07005
43. Cordeiro TN, Sibille N, Germain P, Barthe P, Boulahtouf A, Allemand F, et al. Interplay of Protein Disorder in Retinoic Acid Receptor Heterodimer and Its Corepressor Regulates Gene Expression. Structure. 2019;27:1270-1285.e6. https://doi.org/10.1016/j.str.2019.05.001
44. Kim DH, Lee JW, Lee K. Supplementation of All-Trans-Retinoic Acid Below Cytotoxic Levels Promotes Adipogenesis in 3T3-L1 Cells. Lipids. John Wiley and Sons Inc.; 2019;54:99–107. https://doi.org/10.1002/lipd.12123
45. Shah K, Kazi JU. Phosphorylation-Dependent Regulation of WNT/Beta-Catenin Signaling. Front Oncol. Frontiers Media S.A.; 2022. https://doi.org/10.3389/fonc.2022.858782
46. Cruciat CM. Casein kinase 1 and Wnt/β-catenin signaling. Curr Opin Cell Biol. Elsevier Ltd; 2014. p. 46–55. https://doi.org/10.1016/j.ceb.2014.08.003

47. Lin J, Song T, Li C, Mao W. GSK-3β in DNA repair, apoptosis, and resistance of chemotherapy, radiotherapy of cancer. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2020;1867:118659. https://doi.org/10.1016/j.bbamcr.2020.118659
48. Jho E, Zhang T, Domon C, Joo C-K, Freund J-N, Costantini F. Wnt/β-Catenin/Tcf Signaling Induces the Transcription of Axin2, a Negative Regulator of the Signaling Pathway. Mol Cell Biol. Taylor & Francis; 2002;22:1172–83. https://doi.org/10.1128/MCB.22.4.1172-1183.2002
49. Green AC, Kocovski P, Jovic T, Walia MK, Chandraratna RAS, Martin TJ, et al. Retinoic acid receptor signalling directly regulates osteoblast and adipocyte differentiation from mesenchymal progenitor cells. Exp Cell Res. 2017;350:284–97. https://doi.org/10.1016/j.yexcr.2016.12.007
50. Li Y, Yao L, Lu J. IL-35 inhibits adipogenesis via PPARγ-Wnt/β-catenin signaling pathway by targeting Axin2. Int Immunopharmacol. 2023;122:110615. https://doi.org/10.1016/j.intimp.2023.110615
51. Sharvit E, Abramovitch S, Reif S, Bruck R. Amplified Inhibition of Stellate Cell Activation Pathways by PPAR-γ, RAR and RXR Agonists. PLoS One. Public Library of Science; 2013;8:e76541-. https://doi.org/10.1371/journal.pone.0076541
52. Sun F, Pan Q, Wang J, Liu S, Li Z, Yu Y. Contrary effects of BMP-2 and ATRA on adipogenesis in mouse mesenchymal fibroblasts. Biochem Genet. 2009;47:789–801. https://doi.org/10.1007/s10528-009-9277-8
53. Tang QQ, Lane MD. Adipogenesis: From stem cell to adipocyte. Annu Rev Biochem. 2012;81:715–36. https://doi.org/10.1146/annurev-biochem-052110-115718
54. Xue J-C, Schwarz EJ, Chawla A, Lazar MA. Distinct Stages in Adipogenesis Revealed by Retinoid Inhibition of Differentiation after Induction of PPARγ. Mol Cell Biol. Taylor & Francis; 1996;16:1567–75. https://doi.org/10.1128/MCB.16.4.1567
55. Suzuki M, Chen HJ, Tomonaga S, Hashimoto O, Kawada T, Matsui T, et al. Chronic retinoic acid treatment induces differentiation and changes in the metabolite levels of brown (pre)adipocytes. Cell Biochem Funct. John Wiley and Sons Ltd; 2019;37:377–84. https://doi.org/10.1002/cbf.3416
56. Kim DH, Lee J, Kim S, Lillehoj HS, Lee K. Hypertrophy of Adipose Tissues in Quail Embryos by in ovo Injection of All-Trans Retinoic Acid. Front Physiol. Frontiers Media S.A.; 2021;12. https://doi.org/10.3389/fphys.2021.681562
57. Chung KY, Kim J, Johnson BJ. All-trans retinoic acid alters the expression of adipogenic genes during the differentiation of bovine intramuscular and subcutaneous adipocytes. J Anim Sci Technol. Korean Society of Animal Sciences and Technology; 2021;63:1397–410. https://doi.org/10.5187/jast.2021.e125
58. Taniguchi D, Mizoguchi Y. Retinoic acids change gene expression profiles of bovine intramuscular adipocyte differentiation, based on microarray analysis. Animal Science Journal. John Wiley & Sons, Ltd; 2015;86:579–87. https://doi.org/10.1111/asj.12338
59. Xu Q, Fan Y, Loor JJ, Liang Y, Sun X, Jia H, et al. All-trans retinoic acid controls differentiation, proliferation, and lipolysis in isolated subcutaneous adipocytes from peripartal Holstein cows. J Dairy Sci. 2021;104:4999–5008. https://doi.org/10.3168/jds.2020-19408
60. Zhou H, Chen Y, Hu Y, Gao S, Lu W, He Y. Administration of All-Trans Retinoic Acid to Pregnant Sows Improves the Developmental Defects of Hoxa1−/− Fetal Pigs. Front Vet Sci. Frontiers Media S.A.; 2021;7. https://doi.org/10.3389/fvets.2020.618660
61. Brandebourg TD, Hu CY. Regulation of differentiating pig preadipocytes by retinoic acid. J Anim Sci. 2005;83:98–107. https://doi.org/10.2527/2005.83198x
62. Wang X, Yang P, Liu J, Wu H, Yu W, Zhang T, et al. RARγ-C-Fos-PPARγ2 signaling rather than ROS generation is critical for all-trans retinoic acid-inhibited adipocyte differentiation. Biochimie. 2014;106:121–30. https://doi.org/10.1016/j.biochi.2014.08.009

63. Tourniaire F, Musinovic H, Gouranton E, Astier J, Marcotorchino J, Arreguin A, et al. All-trans retinoic acid induces oxidative phosphorylation and mitochondria biogenesis in adipocytes. J Lipid Res. 2015;56:1100–9. https://doi.org/10.1194/jlr.M053652
64. Stoecker K, Sass S, Theis FJ, Hauner H, Pfaffl MW. Inhibition of fat cell differentiation in 3T3-L1 pre-adipocytes by all-trans retinoic acid: Integrative analysis of transcriptomic and phenotypic data. Biomol Detect Quantif. Elsevier GmbH; 2017;11:31–44. https://doi.org/10.1016/j.bdq.2016.11.001
65. Zhu X, Wang W, Zhang X, Bai J, Chen G, Li L, et al. All-Trans Retinoic Acid-Induced Deficiency of the Wnt/β-Catenin Pathway Enhances Hepatic Carcinoma Stem Cell Differentiation. PLoS One. Public Library of Science; 2015;10:e0143255-. https://doi.org/10.1371/journal.pone.0143255
66. Zhang S, Chen X, Hu Y, Wu J, Cao Q, Chen S, et al. All-trans retinoic acid modulates Wnt3A-induced osteogenic differentiation of mesenchymal stem cells via activating the PI3K/AKT/GSK3β signalling pathway. Mol Cell Endocrinol. 2016;422:243–53. https://doi.org/10.1016/j.mce.2015.12.018
67. Samarut E, Gaudin C, Hughes S, Gillet B, de Bernard S, Jouve P-E, et al. Retinoic Acid Receptor Subtype-Specific Transcriptotypes in the Early Zebrafish Embryo. Molecular Endocrinology. 2014;28:260–72. https://doi.org/10.1210/me.2013-1358
68. Purton LE, Dworkin S, Olsen GH, Walkley CR, Fabb SA, Collins SJ, et al. RARγ is critical for maintaining a balance between hematopoietic stem cell self-renewal and differentiation. Journal of Experimental Medicine. 2006;203:1283–93. https://doi.org/10.1084/jem.20052105
69. Ying Q-L, Stavridis M, Griffiths D, Li M, Smith A. Conversion of embryonic stem cells into neuroectodermal precursors in adherent monoculture. Nat Biotechnol. 2003;21:183–6. https://doi.org/10.1038/nbt780
70. Wai HA, Kawakami K, Wada H, Müller F, Vernallis AB, Brown G, et al. The Development and Growth of Tissues Derived from Cranial Neural Crest and Primitive Mesoderm Is Dependent on the Ligation Status of Retinoic Acid Receptor γ: Evidence That Retinoic Acid Receptor γ Functions to Maintain Stem/Progenitor Cells in the Absence of Retinoic Acid. Stem Cells Dev. Mary Ann Liebert, Inc., publishers; 2014;24:507–19. https://doi.org/10.1089/scd.2014.0235
71. Kalisz M, Chmielowska M, Martyńska L, Domańska A, Bik W, Litwiniuk A. All-trans-retinoic acid ameliorates atherosclerosis, promotes perivascular adipose tissue browning, and increases adiponectin production in Apo-E mice. Sci Rep. 2021;11:4451. https://doi.org/10.1038/s41598-021-83939-x
72. Kim J, Wellmann KB, Smith ZK, Johnson BJ. All-trans retinoic acid increases the expression of oxidative myosin heavy chain through the PPARδ pathway in bovine muscle cells derived from satellite cells1. J Anim Sci. 2018;96:2763–76. https://doi.org/10.1093/jas/sky155
73. Nobushi Y, Wada T, Miura M, Onoda R, Ishiwata R, Oikawa N, et al. Effects of Flavanone Derivatives on Adipocyte Differentiation and Lipid Accumulation in 3T3-L1 Cells. Life. Multidisciplinary Digital Publishing Institute (MDPI); 2024;14. https://doi.org/10.3390/life14111446
74. Chen Q, Hao W, Xiao C, Wang R, Xu X, Lu H, et al. SIRT6 Is Essential for Adipocyte Differentiation by Regulating Mitotic Clonal Expansion. Cell Rep. 2017;18:3155–66. https://doi.org/10.1016/j.celrep.2017.03.006
75. Fajas L, Landsberg RL, Huss-Garcia Y, Sardet C, Lees JA, Auwerx J. E2Fs Regulate Adipocyte Differentiation. Dev Cell. 2002;3:39–49. https://doi.org/10.1016/S1534-5807(02)00190-9
76. Liu D-W, Ye Y-S, Huang C-G, Lu Q, Yang L, Wang Q, et al. Sampsonione F suppresses adipogenesis via activating p53 pathway during the mitotic clonal expansion progression of

adipocyte differentiation. Eur J Pharmacol. 2022;925:175002.
https://doi.org/10.1016/j.ejphar.2022.175002
77. Josep Mercader LMFFAPKK and MLB. All-Trans Retinoic Acid Increases Oxidative Metabolism in Mature Adipocytes. 2007. https://doi.org/10.1159/000110717
78. Schweich L de C, Oliveira EJT de, Pesarini JR, Hermeto LC, Camassola M, Nardi NB, et al. All-trans retinoic acid induces mitochondria-mediated apoptosis of human adipose-derived stem cells and affects the balance of the adipogenic differentiation. Biomedicine and Pharmacotherapy. Elsevier Masson SAS; 2017;96:1267–74.
https://doi.org/10.1016/j.biopha.2017.11.087
79. Gianni M, Ponzanelli I, Mologni L, Reichert U, Rambaldi A, Terao M, et al. Retinoid-dependent growth inhibition, differentiation and apoptosis in acute promyelocytic leukemia cells. Expression and activation of caspases. Cell Death Differ. 2000;7:447–60.
https://doi.org/10.1038/sj.cdd.4400673
80. Wang R, Xia L, Gabrilove J, Waxman S, Jing Y. Sorafenib inhibition of Mcl-1 accelerates ATRA-induced apoptosis in differentiation-responsive AML cells. Clinical Cancer Research. American Association for Cancer Research Inc.; 2016;22:1211–21. https://doi.org/10.1158/1078-0432.CCR-15-0663
81. Pettersson F, Dalgleish AG, Bissonnette RP, Colston KW. Retinoids cause apoptosis in pancreatic cancer cells via activation of RAR-γ and altered expression of Bcl-2/Bax. Br J Cancer. 2002;87:555–61. https://doi.org/10.1038/sj.bjc.6600496
82. Zhang H, Satyamoorthy K, Herlyn M, Rosdahl I. All- trans retinoic acid (atRA) differentially induces apoptosis in matched primary and metastatic melanoma cells – a speculation on damage effect of atRA via mitochondrial dysfunction and cell cycle redistribution. Carcinogenesis. 2003;24:185–91. https://doi.org/10.1093/carcin/24.2.185
83. Amengual J, Petrov P, Bonet ML, Ribot J, Palou A. Induction of carnitine palmitoyl transferase 1 and fatty acid oxidation by retinoic acid in HepG2 cells. Int J Biochem Cell Biol. 2012;44:2019–27. https://doi.org/10.1016/j.biocel.2012.07.026
84. Zhang W, Huang J, Tang Y, Yang Y, Hu H. Inhibition of fatty acid synthase (FASN) affects the proliferation and apoptosis of HepG2 hepatoma carcinoma cells via the β-catenin/C-myc signaling pathway. Ann Hepatol. 2020;19:411–6. https://doi.org/10.1016/j.aohep.2020.03.005
85. Nakanishi M, Tomaru Y, Miura H, Hayashizaki Y, Suzuki M. Identification of transcriptional regulatory cascades in retinoic acid-induced growth arrest of HepG2 cells. Nucleic Acids Res. 2008;36:3443–54. https://doi.org/10.1093/nar/gkn066
86. Zhang J, Deng B, Jiang X, Cai M, Liu N, Zhang S, et al. All-trans-retinoic acid suppresses neointimal hyperplasia and inhibits vascular smooth muscle cell proliferation and migration via activation of AMPK signaling pathway. Front Pharmacol. Frontiers Media S.A.; 2019;10.
https://doi.org/10.3389/fphar.2019.00485
87. Kaur H, Carrillo O, Garcia I, Ramos I, St. Vallier S, De La Torre P, et al. Differentiation activates mitochondrial OPA1 processing in myoblast cell lines. Mitochondrion. 2024;78:101933. https://doi.org/10.1016/j.mito.2024.101933
88. Krell S, Hamburg A, Gover O, Molakandov K, Leibowitz G, Sharabi K, et al. Beta cells intrinsically sense and limit their secretory activity via mTORC1-RhoA signaling. Cell Rep. 2025;44:115647. https://doi.org/10.1016/j.celrep.2025.115647
89. Feng Q, Xu M, Yu YY, Hou Y, Mi X, Sun YX, et al. High-dose dexamethasone or all-trans-retinoic acid restores the balance of macrophages towards M2 in immune thrombocytopenia. Journal of Thrombosis and Haemostasis. 2017;15:1845–58. https://doi.org/10.1111/jth.13767
90. Hong K, Zhang Y, Guo Y, Xie J, Wang J, He X, et al. All-trans retinoic acid attenuates experimental colitis through inhibition of NF-κB signaling. Immunol Lett. Elsevier; 2014;162:34–40. https://doi.org/10.1016/j.imlet.2014.06.011

91. Kim J, Wellmann KB, Smith ZK, Johnson BJ. All-trans retinoic acid increases the expression of oxidative myosin heavy chain through the PPARδ pathway in bovine muscle cells derived from satellite cells1. J Anim Sci. 2018;96:2763–76. https://doi.org/10.1093/jas/sky155
92. Li Q, Zhang T, Zhang R, Qin X, Zhao J. All-trans retinoic acid regulates sheep primary myoblast proliferation and differentiation in vitro. Domest Anim Endocrinol. 2020;71:106394. https://doi.org/10.1016/j.domaniend.2019.106394
93. Kim DH, Lee J, Suh Y, Ko JK, Lee K. Transdifferentiation of Myoblasts Into Adipocytes by All-Trans-Retinoic Acid in Avian. Front Cell Dev Biol. Frontiers Media S.A.; 2022;10. https://doi.org/10.3389/fcell.2022.856881
94. Mercader J, Ribot J, Murano I, Felipe F, Cinti S, Bonet ML, et al. Remodeling of White Adipose Tissue after Retinoic Acid Administration in Mice. Endocrinology. 2006;147:5325–32. https://doi.org/10.1210/en.2006-0760
95. Berry DC, Noy N. All-trans-Retinoic Acid Represses Obesity and Insulin Resistance by Activating both Peroxisome Proliferation-Activated Receptor β/δ and Retinoic Acid Receptor. Mol Cell Biol. Taylor & Francis; 2009;29:3286–96. https://doi.org/10.1128/MCB.01742-08
96. Ribot J, Felipe F, Bonet ML, Palou A. Changes of adiposity in response to vitamin A status correlate with changes of PPARγ2 expression. Obes Res. North American Assoc. for the Study of Obesity; 2001;9:500–9. https://doi.org/10.1038/oby.2001.65
97. Dean S, Gomes M, Silva W, Steele M, Wood K, Du M, et al. Vitamin A–Enriched Diet at Late Gestation Affects Intramuscular Fat Deposition in Beef Offspring. Meat and Muscle Biology. Iowa State University Digital Press; 2024;8. https://doi.org/10.22175/mmb.17646
98. Yu X, Ma Y, Luo Y, Tang G, Jiang Z, Zhang J, et al. Neonatal vitamin A administration increases intramuscular fat by promoting angiogenesis and preadipocyte formation. Meat Sci. 2022;191:108847. https://doi.org/10.1016/j.meatsci.2022.108847
99. Harris CL, Wang B, Deavila JM, Busboom JR, Maquivar M, Parish SM, et al. Vitamin A administration at birth promotes calf growth and intramuscular fat development in Angus beef cattle. J Anim Sci Biotechnol. 2018;9:55. https://doi.org/10.1186/s40104-018-0268-7
100. Gorocica-Buenfil MA, Fluharty FL, Reynolds CK, Loerch SC. Effect of dietary vitamin A restriction on marbling and conjugated linoleic acid content in Holstein steers. J Anim Sci. 2007;85:2243–55. https://doi.org/10.2527/jas.2006-781
101. Gorocica-Buenfil MA, Fluharty FL, Bohn T, Schwartz SJ, Loerch SC. Effect of low vitamin A diets with high-moisture or dry corn on marbling and adipose tissue fatty acid composition of beef steers. J Anim Sci. 2007;85:3355–66. https://doi.org/10.2527/jas.2007-0172
102. Takase S, Ong DE, Chytil F. Transfer of retinoic acid from its complex with cellular retinoic acid-binding protein to the nucleus. Arch Biochem Biophys. 1986;247:328–34. https://doi.org/10.1016/0003-9861(86)90591-6
103. Kruk ZA, Bottema MJ, Reyes-Veliz L, Forder REA, Pitchford WS, Bottema CDK. Vitamin A and marbling attributes: Intramuscular fat hyperplasia effects in cattle. Meat Sci. 2018;137:139–46. https://doi.org/10.1016/j.meatsci.2017.11.024
104. Huang Z, Yu X, Jiang Z, Tang G, Gao S, Xiang Y, et al. Neonatal vitamin A but not retinoic acid administration increases intramuscular adipocyte number in sheep by promoting vascularization. Animal Nutrition. 2024;19:215–25. https://doi.org/10.1016/j.aninu.2024.08.006
105. Arana A, Mendizabal JA, Alzón M, Soret B, Purroy A. The effect of vitamin A supplementation on postnatal adipose tissue development of lambs1. J Anim Sci. 2008;86:3393–400. https://doi.org/10.2527/jas.2008-0889
106. D'Souza DN, Pethick DW, Dunshea FR, Pluske JR, Mullan BP. Nutritional manipulation increases intramuscular fat levels in the Longissimus muscle of female finisher pigs. Aust J Agric Res. 2003;54:745–9. https://doi.org/10.1071/AR03009

107. Kim D-H, Lee J, Lee C, Shin B-J, Ryu B-Y, Lee K. Short communication: In ovo injection of all-trans retinoic acid causes adipocyte hypertrophy in embryos but lost its effect in posthatch chickens. animal. 2023;17:100750. https://doi.org/10.1016/j.animal.2023.100750
108. Murholm M, Isidor MS, Basse AL, Winther S, Sørensen C, Skovgaard-Petersen J, et al. Retinoic acid has different effects on UCP1 expression in mouse and human adipocytes. BMC Cell Biol. 2013;14:41. https://doi.org/10.1186/1471-2121-14-41
109. Peng DQ, Smith SB, Lee HG. Vitamin A regulates intramuscular adipose tissue and muscle development: promoting high-quality beef production. J Anim Sci Biotechnol. BioMed Central Ltd; 2021. https://doi.org/10.1186/s40104-021-00558-2
110. M. Ayuso AFBIARRBADCJL-B and CÓ. Long term vitamin A restriction improves meat quality parameters and modifies gene expression in Iberian pigs. American Society of Animal Science. 2015;6:2730–44.
111. Wang B, Fu X, Liang X, Deavila JM, Wang Z, Zhao L, et al. Retinoic acid induces white adipose tissue browning by increasing adipose vascularity and inducing beige adipogenesis of PDGFRα+ adipose progenitors. Cell Discov. Nature Publishing Groups; 2017;3. https://doi.org/10.1038/celldisc.2017.36
112. Krois CR, Vuckovic MG, Huang P, Zaversnik C, Liu CS, Gibson CE, et al. RDH1 suppresses adiposity by promoting brown adipose adaptation to fasting and re-feeding. Cellular and Molecular Life Sciences. 2019;76:2425–47. https://doi.org/10.1007/s00018-019-03046-z
113. Kiefer FW, Vernochet C, O'Brien P, Spoerl S, Brown JD, Nallamshetty S, et al. Retinaldehyde dehydrogenase 1 regulates a thermogenic program in white adipose tissue. Nat Med. 2012;18:918–25. https://doi.org/10.1038/nm.2757
114. Harris CL, Wang B, Deavila JM, Busboom JR, Maquivar M, Parish SM, et al. Vitamin A administration at birth promotes calf growth and intramuscular fat development in Angus beef cattle. J Anim Sci Biotechnol. BioMed Central Ltd.; 2018;9. https://doi.org/10.1186/s40104-018-0268-7
115. Siebert BD, Kruk ZA, Davis J, Pitchford WS, Harper GS, Bottema CDK. Effect of low vitamin a status on fat deposition and fatty acid desaturation in beef cattle. Lipids. 2006;41:365–70. https://doi.org/10.1007/s11745-006-5107-5
116. Takahashi K, Uchida N, Kitanaka C, Sagara C, Imai M, Takahashi N. Inhibition of ASCT2 is essential in all-trans retinoic acid-induced reduction of adipogenesis in 3T3-L1 cells. FEBS Open Bio. Elsevier; 2015;5:571–8. https://doi.org/10.1016/j.fob.2015.06.012
117. Hussain J, Mabood F, Al-Harrasi A, Ali L, Rizvi TS, Jabeen F, et al. New robust sensitive fluorescence spectroscopy coupled with PLSR for estimation of quercetin in Ziziphus mucronata and Ziziphus sativa. Spectrochim Acta A Mol Biomol Spectrosc. 2018;194:152–7. https://doi.org/10.1016/j.saa.2018.01.002
118. Seo J, Kim J, Nam KA, Zheng Z, Oh BH, Chung KY. Reconstruction of large wounds using a combination of negative pressure wound therapy and punch grafting after excision of acral lentiginous melanoma on the foot. Journal of Dermatology. Blackwell Publishing Ltd; 2016;43:79–84. https://doi.org/10.1111/1346-8138.13017
119. Liu Y, Liu Y, Zhang R, Wang X, Huang F, Yan Z, et al. All-trans retinoic acid modulates bone morphogenic protein 9-induced osteogenesis and adipogenesis of preadipocytes through BMP/Smad and Wnt/β-catenin signaling pathways. Int J Biochem Cell Biol. 2014;47:47–56. https://doi.org/10.1016/j.biocel.2013.11.018
120. Meester-Smoor MA, Janssen MJFW, Grosveld GC, de Klein A, van IJcken WFJ, Douben H, et al. MN1 affects expression of genes involved in hematopoiesis and can enhance as well as inhibit RAR/RXR-induced gene expression. Carcinogenesis. 2008;29:2025–34. https://doi.org/10.1093/carcin/bgn168

121. Yoo HS, Moss KO, Cockrum MA, Woo W, Napoli JL. Energy status regulates levels of the RAR/RXR ligand 9-cis-retinoic acid in mammalian tissues: Glucose reduces its synthesis in β-cells. Journal of Biological Chemistry. 2023;299:105255. https://doi.org/10.1016/j.jbc.2023.105255
122. Yao XT, Li P pei, Liu J, Yang YY, Luo ZL, Jiang HT, et al. Wnt/β-Catenin Promotes the Osteoblastic Potential of BMP9 Through Down-Regulating Cyp26b1 in Mesenchymal Stem Cells. Tissue Eng Regen Med. Korean Tissue Engineering and Regenerative Medicine Society; 2023;20:705–23. https://doi.org/10.1007/s13770-023-00526-z
123. Xi H-M, Lu H, Weng X-Q, Sheng Y, Wu J, Li L, et al. Combined Application of Salinomycin and ATRA Induces Apoptosis and Differentiation of Acute Myeloid Leukemia Cells by Inhibiting WNT/β-Catenin Pathway. Anticancer Agents Med Chem. Bentham Science Publishers Ltd.; 2023;23:1074–84. https://doi.org/10.2174/1871520623666230110121629
124. Ni X, Hu G, Cai X. The success and the challenge of all-trans retinoic acid in the treatment of cancer. Crit Rev Food Sci Nutr. Taylor & Francis; 2019;59:S71–80. https://doi.org/10.1080/10408398.2018.1509201
125. Wang K, Ou Z, Deng G, Li S, Su J, Xu Y, et al. The Translational Landscape Revealed the Sequential Treatment Containing ATRA plus PI3K/AKT Inhibitors as an Efficient Strategy for AML Therapy. Pharmaceutics. MDPI; 2022;14. https://doi.org/10.3390/pharmaceutics14112329
126. Hrabak P, Zelenkova M, Krechler T, Soupal J, Vocka M, Hanus T, et al. Levels of retinol and retinoic acid in pancreatic cancer, type-2 diabetes and chronic pancreatitis. Biomedical Papers. Palacky University Olomouc; 2024;168:132–8. https://doi.org/10.5507/bp.2023.049
127. Zhong G, Kirkwood J, Won K-J, Tjota N, Jeong H, Isoherranen N. Characterization of Vitamin A Metabolome in Human Livers With and Without Nonalcoholic Fatty Liver Disease. J Pharmacol Exp Ther. 2019;370:92–103. https://doi.org/10.1124/jpet.119.258517
128. Yuan J, Roshdy AR, Guo Y, Wang Y, Guo S. Effect of dietary vitamin a on reproductive performance and immune response of broiler breeders. PLoS One. 2014;9. https://doi.org/10.1371/journal.pone.0105677
129. Jenkins OP. Balancing Vitamin A Supply for Cattle: A Review of the Current Knowledge. Advances in Animal Science and Zoology; 2024.