HHS Public Access

Author manuscript

Liver Res. Author manuscript; available in PMC 2023 October 18.

Published in final edited form as:

Liver Res. 2023 September ; 7(3): 189–195. doi:10.1016/j.livres.2023.07.002.

Retinoic Acid Signaling in Fatty Liver Disease

Fathima N. Cassim Bawa,

Yanqiao Zhang

Department of Integrative Medical Sciences, Northeast Ohio Medical University, Rootstown, OH, USA 44272

Abstract

Retinoic acid (RA) is a metabolite of vitamin A and is essential for development and growth as well as cellular metabolism. Through genomic and nongenomic actions, RA regulates a variety of physiological functions. Dysregulation of RA signaling is associated with many diseases. Targeting RA signaling has been proven valuable to human health. All-trans retinoic acid (AtRA) and anthracycline-based chemotherapy are the standard treatment of acute promyelocytic leukemia (APL). Both human and animal studies have shown a significant relationship between RA signaling and the development and progression of nonalcoholic fatty liver disease (NAFLD). In this review article, we will first summarize vitamin A metabolism and then focus on the role of RA signaling in NAFLD. AtRA inhibits the development and progression of NAFLD via regulating lipid metabolism, inflammation, thermogenesis, etc.

Keywords

Retinoic acid; fatty liver disease; fatty acid oxidation; lipogenesis; obesity

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases ranging from simple steatosis, also known as nonalcoholic fatty liver (NAFL), to nonalcoholic steatohepatitis (NASH). The global NAFLD prevalence of NAFLD has reached 32.4% [1], and the prevalence rate is increasing due to obesity. Many people with NASH develop liver cirrhosis and hepatocellular carcinoma (HCC) as the disease progresses.[2,3] The pathogenic mechanisms of NAFLD are complex and may involve interactions among over-nutrition, genetics, gut microbiota, etc, leading to insulin resistance, lipotoxicity, apoptosis, mitochondrial dysfunction, oxidative stress, inflammation, and fibrogenesis.[2–4] So far, no drugs have been approved for the treatment of NASH.

Retinoids are metabolites of vitamin A (retinol) that include retinaldehyde/retinal, retinyl esters, oxidized retinol, retinoic acid, and conjugates of these compounds, which are essential for cell growth and differentiation.[5,6] Abnormal retinoid levels have been linked to a wide variety of clinical issues, including cardiovascular disease, diabetes, obesity,

Corresponding author: Dr. Yanqiao Zhang, Department of Integrative Medical Sciences, Northeast Ohio Medical University, 4209 State Route 44, Rootstown, Ohio 44272, USA. Phone 330.325.6693. yzhang@neomed.edu.

fatty liver disease, osteoporosis, skin illnesses, and cancer.[7–10] Mammals cannot synthesize vitamin A. Vitamin A is absorbed by intestinal epithelial cells, stored in the liver, and metabolized in target cells to more biologically active metabolites, retinoic acid (RA) and 4-oxo-RA.[11]

2. Vitamin A metabolism

Vitamin A is found in meat, dairy products, and β-carotene. In enterocytes, β-carotene is converted to retinal by β-C 15,15' oxygenase 1 (BCO1) and then reduced to retinol by a retinal reductase. Retinyl esters are hydrolyzed to form retinol by retinyl ester hydrolase (REH) prior to absorption. Retinol is then re-esterified with long-chain fatty acids by lecithin:retinol acyltransferase (LRAT) to regenerate retinyl esters, which are secreted with chylomicrons (CM) from the intestine and up-taken by hepatocytes in the form of CM remnants (Figure 1). In hepatocytes, retinyl esters are hydrolyzed by REH to produce retinol. Retinol binds to a retinol-binding protein (RBP) for release into the circulation and is up-taken by other cell types via one of the membrane receptors, such as the signaling receptor and transporter of retinol STRA6. Within cells, cellular retinol-binding proteins (CRBP) participate in the transport and metabolism of retinol. Retinol is converted to retinal by retinol dehydrogenase (RDH) or retinyl esters by LRAT.

More than 80 % of the vitamin A in the liver is stored in hepatic stellate cells (HSC).[12] Retinal is converted by retinal dehydrogenase, also known as retinaldehyde dehydrogenase (RALDH), to all-trans RA (AtRA), 9-cis RA, 13-cis-RA, 9,13-di-cis RA, and 11-cis-RA. AtRA and 9-cis RA are the major biologically active forms of RAs. Cellular retinoic acid-binding proteins (CRABP) transport RA into the nucleus, where AtRA and 9-cis RA bind to retinoic acid receptor (RAR) and retinoic X receptor (RXR), respectively, to regulate gene transcription (Figure 1). Excess RA is metabolized by P450 family enzymes (CYP26A1, CYP26B1, and CYP26C1) into polar chemicals, including 4-hydroxy-RA and 4-oxo-RA, which are glucuronidated and then removed from the body via the kidneys or liver into bile.[13]

3. Retinoic acid receptor (RAR)/retinoic X receptor (RXR)

RAR has three isoforms, RARα (NR1B1), RARβ (NR1B2), and RARγ (NR1B3). RXR also has three isoforms, RXRα (NR2B1), RXRβ (NR2B2), and RXRγ (NR2B3). RAR heterodimerizes with RXR and the dimers bind to the retinoic acid response element (RARE) in the target genes. Ligand binding to the RAR/RXR heterodimers results in the change in associated cofactors and activation or repression of gene transcription. More than 532 genes may be regulated by RA through the traditional genomic route.[14] In addition to the traditional genomic functions, RARs may also be engaged in nongenomic biological functions, such as the initiation of translation and kinase cascades,[15] e.g. the p38 or ERK mitogen-activated protein kinase.[16,17] The discovery of retinoic acid has been proved valuable to human health. For instance, AtRA and anthracycline-based chemotherapy are the standard treatment of acute promyelocytic leukemia (APL),[18,19] a highly curable disease.

4. Altered retinoid metabolism in NAFLD

Hepatic stellate cell (HSC) activation is associated with reduced hepatic retinyl esters and retinol concentrations and vitamin A metabolism.[20] In rats, vitamin A deficiency causes HSC activation to produce extracellular matrix[21] and potentiates carbon tetrachloride (CCl_4)-induced liver fibrosis[22]. In contrast, supplementation with vitamin A inhibits CCl_4-induced liver fibrosis in pigs.[23] Vitamin A is also shown to reduce mortality of animals with induced liver fibrosis by copper sulfate.[24] Clearly, vitamin A and its metabolites may play a key role in liver fibrogenesis.[25]

Multiple studies on patients have shown inverse relationship with serum retinol levels and the severity of NAFLD.[26–28] Chaves *et al.* show that serum and hepatic retinol levels decrease in NAFLD by 35.9% and 67.9%, respectively and that a significant association exists between hepatic retinol concentrations and the severity of NAFLD.[29] Similarly, serum RA levels are also shown to be inversely correlated with the severity of NAFLD.[30] Zhong *et al.* show that in NAFLD patients, hepatic vitamin A metabolites, including retinyl-palmitate esters, AtRA, 13-cis-RA, and 4-oxo-atRA, are reduced while the levels of retinol (the inactive form of vitamin A) do not change.[31] They suggest the levels of metabolites of vitamin A, rather than retinol, are more reliable for predicting the disease progression of NAFLD.[31]

In animal models of NAFLD, Trasino *et al.* show that hepatic retinol levels are decreased in high fat diet (HFD)-induced obese mice or genetically obese mice (*db/db* or *ob/ob* mice) accompanied by reduced RAR and RBP1 mRNA levels in HSC and elevated serum retinol levels.[32] Saeed *et al.* report that hepatic retinyl palmitate levels are significantly increased along with upregulated hepatic mRNA levels of genes related to retinol storage and metabolism in hepatocytes of high fat/high cholesterol diet-fed mice and *ob/ob* mice.[33] In rats fed a methionine-choline deficient (MCD) diet, hepatic and serum retinol levels are decreased.[34]

The changes in hepatic vitamin A and their metabolite levels are likely due to the change in genes involved in retinol metabolism. Another gene associated with NAFLD is aldo-keto reductase family 1 member B10 (AKR1B10), which is a key enzyme of retinol metabolism with a very efficient and high all-trans-retinaldehyde reductase activity in converting all-trans-retinaldehyde to retinol, is significantly overexpressed in human NASH liver and HCC tumors.[35] Pettinelli *et al.* show that NASH patients have highly induced AKR1B10 expression and reduced ALDH1A2 and ALDH1A3 expression in the liver as well as elevated plasma retinol levels.[36] 17-beta hydroxysteroid dehydrogenase 13 (HSD17B13) has RDH activity and a loss-of-function mutation in HSD17B13 reduces the progression of NAFLD.[37] Patatin-like phospholipase domain-containing 3 (PNPLA3), is reported to have retinyl-palmitate lipase activity, releasing retinol from lipid droplets in hepatic stellate cells.[38] The genetic association studies show that the genetic variant in I148M (rs738409), is a the risk factor for NAFLD as it reduces the lipase activity and decreases circulating serum retinol levels in NAFLD patients.[38–40] Thus, it is evident that disruption in the retinoid metabolism is often associated with NAFLD.

5. Mechanisms underlying the regulation of NAFLD by RA signaling

Hepatic lipid accumulation occurs from an imbalance between lipid absorption/uptake, synthesis, and secretion/disposal, which are regulated by several pathways, including uptake of circulating free fatty acids (FFAs), de novo lipogenesis (DNL), lipolysis, fatty acid oxidation (FAO), and secretion of lipids in very low-density lipoproteins (VLDL) or cholesterol to bile. Obesity is also associated with the development of NAFLD. Next, we will discuss how the RA signaling affects hepatic lipid metabolism, inflammation, fibrogenesis, and obesity.

5.1. RA signaling in hepatic lipid metabolism

Accumulation of FFAs may cause lipotoxicity. Amengual et al. show that AtRA treatment induces hepatic expression of peroxisome proliferator-activated receptor alpha (PPARα), retinoid X receptor alpha (RXRα), uncoupling protein 2 (UCP2), liver-type carnitine palmitoyltransferase 1 (CPT1), and carnitine/acylcarnitine carrier (CAC), and a reduction in the mRNA expression levels of sterol regulatory element binding protein 1c (SREBP1c) and fatty acid synthase (FASN),[41] and reduces hepatic triglyceride (TG) levels and VLDL secretion and increases circulating 3-hydroxybutyrate levels.[41] AtRA is also shown to induce FAO in HepG2 cells[42] and mouse primary hepatocytes.[43] We show that AtRA induces FAO independent of activation of RARα.[43] PPARα is a key regulator of FAO; activating PPARα protects from trans-fatty acid induced steatohepatitis while PPARα inhibition increases the susceptibility to steatohepatitis.[44] PPARα binds to DNA as a heterodimer with RXR. Both AtRA and 9-cis-RA can induce the expression of RXR which in turn activates PPAR:RXR heterodimers leading to the transcription of PPARα target genes.[45] In addition to reducing hepatic TG accumulation, activation of PPARα:RXR also decreases the production of TG-rich VLDL and plasma TG levels.[46] Peroxisome proliferator-activated receptor beta/delta (PPARβ/δ) is another transcription factor that is known to stimulate FAO. PPARβ/δ may prevent dyslipidemia, insulin resistance, obesity, and NAFLD by regulating hepatic glucose catabolism and FAO and by inhibiting DNL via AMPK signaling.[44] Apart from its canonical RARs, AtRA binds to PPARβ/δ with high affinity depending on the expression levels of CRABPII and FABP5 which delivers AtRA to RAR and PPARβ/δ respectively.[47]

Circulating FFA uptake is a major source of the FA pool in the liver. During fasting and insulin resistance, hepatocytes extract FFAs which increase lipogenesis and lipotoxicity. Fatty acid translocase (CD36/FAT) is a transmembrane glycoprotein that acts as scavenger receptor capable of binding several ligands, including long-chain fatty acids, lipoproteins, and oxidized lipids. Even though CD36 expression is considered low in the normal liver, its expression is increased in the liver of NAFLD patients.[48] It is well known that CD36 increases FFA uptake and drives hepatosteatosis onset and to its progression to NASH.[49] CD36 is a well-characterized PPARγ target.[50,51] It is reported recently that Alisol B, a natural compound isolated from a plant called *Alisma orientalis*, attenuates HFD and carbon tetrachloride (CCL4)-induced liver steatosis by inhibiting CD36 by regulating the RARα-HNF4α-PPARγ transcriptional cascade.[52] Tang *et al.* show that activating RARβ2 inhibits PPARγ and CD36 levels in HFD-fed mice.[53] We show that AtRA inhibits hepatocyte fatty

acid uptake and CD36 expression and that the inhibition of CD36 expression is dependent on activation of RARα.[43]

DNL is the process of the synthesis of endogenous fatty acids from acetyl-CoA produced by other metabolic pathways such as glycolysis. About 26% of TG in the livers of NAFLD patients come from DNL suggesting that impairment in DNL contributes to the pathogenesis of NAFLD.[54] Two major pathways downstream of the insulin receptor activates sterol regulatory element-binding protein 1C (SREBP1C), both involving the phosphoinositide-3 kinase (PI3K)/protein kinase B (PKB) pathway, one resulting in the phosphorylation of the nascent SREBP1c itself and the other in the activation of the liver X receptor (LXR).[55] Insulin resistance leads to hypertriglyceridemia and hepatic steatosis which is associated with increased SREBP1c activity. Therefore, inhibiting SREBP1C activation has the potential for treatment of hypertriglyceridemia and NAFLD.[56] Treatment of HFD-fed mice by RA reduces hepatosteatosis and this effect is suggested through sirtuin 1 (SIRT1)-mediated inhibition of SREBP1C.[57] Although AtRA inhibits lipogenic genes in the liver , DNL is not affected when mice are injected with heavy water followed by analysis of newly synthesized fatty acids or triglycerides,[43] suggesting that AtRA lowers hepatic TG levels likely independent of DNL.

Hepatic TG and cholesterol esters are secreted to the circulation in the form of VLDL. AtRA is shown to lower lipid contents in VLDL.[41] Nonetheless, controversial data have been reported on the role of AtRA in hepatic lipogenesis and VLDL secretion.[45] Retinoids have been reported to induce hypertriglyceridemia due to enhanced hepatic lipogenesis and VLDL production and secretion as well as VLDL clearance.[45]

5.2. RA signaling in hepatic inflammation

Retinoids have been known to possess anti-inflammatory effects for 40 years,[58,59] which may be mediated through downregulation of Th1 cytokines, such as tumor necrosis factor α (TNFα),[60,61] interferon gamma (IFNγ),[62] and IL-12.[63] In the THP-1 monocyte/macrophage cell line, AtRA reduces liposaccharide (LPS)-induced production of the proinflammatory cytokines TNFα and IL-12 and enhances IL-10 production.[64] Mechanistically, retinoids inhibit the phosphorylation of IκB kinase α/β (IKKα/β),[65] the nuclear factor kappa B (NFκB)-DNA interaction or its translocation to the nucleus.[63,66] Consistent with these observations, deletion of RARα in macrophages[67] or hepatocytes[43] aggravates inflammatory response whereas RARβ2 activation inhibits inflammatory cytokine secretion,[68] suggesting a critical role of RARα and RARβ2 in mediating retinoid's effects on inflammation.

5.3. RA in hepatic fibrosis and HSC activation

Fibrosis is a wound healing process characterized by extracellular matrix (ECM) accumulation that causes scarring and impaired liver function. The effects of RA on ECM accumulation and fibrosis are controversial. It is shown that loss of retinyl esters in hepatic stellate cells (HSC) is often a characteristic for HSC activation during liver injury.[69] Earlier studies show that 9-cis-RA enhanced plasminogen activator (PA)/plasmin levels and thereby induced proteolytic activation of TGF-β1, a strong fibrogenic cytokine, resulting in enhanced ECM production.[70] However, 9-cis-RA activates RXR, which can

form heterodimers with a variety of nuclear receptors to exert its functions. Later reports show a protective effect of RA signaling on liver fibrosis. Hisamori *et al.* show that AtRA is shown to attenuate CCl4-induced liver fibrosis by reducing the production of TGFβ, IL-6 and collagen from HSCs in mice.[71] They further show that AtRA inhibits TGFβ-dependent transdifferentiation of the cells and the activities of NFκB p65 and p38 mitogen-activated protein kinase [71]. Wang *et al.* also show that AtRA reduces liver fibrosis induced by common bile duct ligation via inhibition of TGFβ and connective tissue growth factor (CTGF) in rats.[72] In vitro studies show that AtRA inhibits HSC proliferation and collagen production via suppressing active protein-1, c-Jun N-terminal kinase signal, and expression of profibrogenic genes (TGF-β(1), CTGF, MMP-2, TIMP-1, TIMP-2, PAI-1), and inducing MMP-3 and MMP-13.[73] RA may also synergize with PPARγ to reverse fibrosis via modulating senescence of HSC.[74] In terms of specific RARs, expression of dominant negative form RARα is shown to induce fibrosis.[75] However, genetic ablation of RARα in the liver does not affect fibrogenesis.[43]

5.4. RA signaling in obesity and insulin resistance

Obesity and insulin resistance are among the most common risk factors for NAFLD as the majority of obese and diabetic patients have NAFLD.[76,77] Thus, treating insulin resistance may help to fight NAFLD. Circulating RA concentrations are lower in subjects with NAFLD and are associated with hepatic lipid metabolism and insulin resistance.[30] AtRA treatment is known to attenuate obesity and insulin resistance.[78] The effect of AtRA on obesity is likely through inhibition of adipogenesis and induction of energy expenditure.[79,80] At molecular levels, AtRA is suggested to inhibit obesity via activation of both PPARβ/δ and RAR.[81] We show that hepatic RARα plays an important role in mediating AtRA's effect on diet-induced obesity.[43] Tsuchiya *et al.* show that AtRA improves insulin sensitivity likely via induction of leptin receptor-mediated phosphorylation of signal transducer and activator of transcription 3 (STAT3) and insulin receptor substrate 1 (IRS1) and RARα activation is important for these effects.[82] Thus, the inhibition of obesity may play a role in AtRA-mediated amelioration of NAFLD.

6. Therapeutic potential of RA in NAFLD

Some studies have been aimed to identify the therapeutic potential of vitamin A metabolites in the treatment of NAFLD. Matsumoto *et al.* show that feeding obese Zucker (*fa/fa*) rats, an animal model of NAFLD, with brown rice increases RA synthesis which in turn, protects against NAFLD by increasing fatty acid oxidation (FAO) and VLDL secretion.[83] Zarei *et al.* report that AtRA significantly reduces liver steatosis in high fat diet (HFD)-fed rabbits.[84] We show that AtRA prevents and reverses Western diet-induced liver steatosis in mice.[43] Zhu *et al.*[85] and Kim *et al.*[86] also show that AtRA prevents HFD-induced liver steatosis in mice. Liu *et al.* report that RA levels are significantly reduced in NAFLD patients and correlated with hepatic TG levels.[30] It is also reported that the intake of β-carotene is inversely associated with liver steatosis in humans.[87] However, it remains to be investigated whether AtRA or other retinoids attenuates liver steatosis in humans.

7. Closing remarks and future directions

In this review, we primarily discuss the role of RA signaling in liver and to some extent in adipose tissue. However, RA signaling in other cells and tissues affects the progression of NAFLD. The gut-liver axis plays a key role in the pathogenesis of liver diseases, including NAFLD.[88,89] Dysregulation of gut microbiota, barrier and permeability contributes to the development of NAFLD.[90–92] There is a rich array of literature describing the role of RA signaling in reshaping gut microbiomes, inflammation, immunity, and barrier functions.[93,94] Serum retinol levels and gut permeability display an inverse relationship.[95,96] RA protects against a leaky gut likely through direct modulation of intestinal permeability and autoimmunity as well as regulating gut microbiota (e.g. *Lactobacillus spp.*) (see review [93]). RA inhibits gut microbiota dysbiosis,[94] which may in turn regulate nutrient absorption, gut permeability, and hepatic metabolism thus protecting against NAFLD.

Over the past decades, many studies from different groups investigated the role of retinoids, particularly AtRA, in metabolic homeostasis and cancer development. In addition to APL, AtRA is being used to treat a range of human cancers in clinical trials. [97,98] In rodents, AtRA attenuates Western diet-induced liver steatosis, inflammation, and fibrosis likely via inducing FAO and energy expenditure and inhibiting fatty acid uptake, NF-κB, and TGFβ (Figure 2). AtRA activates RARα, RARβ, and RARγ. The relative role of these RARs in the liver and other cell types/organs (e.g. adipocytes, intestine) in the development of NAFLD should be elucidated. Understanding the cell-specific effects of RA signaling and the functions of other less-studied retinoids may offer new therapeutic approaches to treatment of NAFLD.

Acknowledgements

This work is supported in part by NIH grants DK102619 and DK118805 to Y.Z. Both figures were created with BioRender.com and are original.

References

1. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, Swain MG, Congly SE, Kaplan GG, Shaheen AA. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7:851–861. doi: 10.1016/S2468-1253(22)00165-0 [PubMed: 35798021]
2. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell. 2021;184:2537–2564. doi: 10.1016/j.cell.2021.04.015 [PubMed: 33989548]
3. Pan X, Zhang Y. Hepatocyte nuclear factor 4alpha in the pathogenesis of non-alcoholic fatty liver disease. Chin Med J (Engl). 2022;135:1172–1181. doi: 10.1097/CM9.0000000000002092 [PubMed: 35191422]
4. Aamir Bashir AD, Arka De, Manu Mehta, Pramil Tiwari. Non-alcoholic fatty liver disease development: A multifactorial pathogenic phenomena. Liver Res. 2022;6:72–83. doi: 10.1016/j.livres.2022.05.002.
5. Samarut E, Rochette-Egly C. Nuclear retinoic acid receptors: conductors of the retinoic acid symphony during development. Mol Cell Endocrinol. 2012;348:348–360. doi: 10.1016/j.mce.2011.03.025 [PubMed: 21504779]
6. Mark M, Ghyselinck NB, Chambon P. Function of retinoic acid receptors during embryonic development. Nucl Recept Signal. 2009;7:e002. doi: 10.1621/nrs.07002 [PubMed: 19381305]

7. Yadav AS, Isoherranen N, Rubinow KB. Vitamin A homeostasis and cardiometabolic disease in humans: lost in translation? J Mol Endocrinol. 2022;69:R95–R108. doi: 10.1530/JME-22-0078 [PubMed: 35900842]
8. Saeed A, Dullaart RPF, Schreuder T, Blokzijl H, Faber KN. Disturbed Vitamin A Metabolism in Non-Alcoholic Fatty Liver Disease (NAFLD). Nutrients. 2017;10. doi: 10.3390/nu10010029 [PubMed: 29295506]
9. Olsen T, Blomhoff R. Retinol, Retinoic Acid, and Retinol-Binding Protein 4 are Differentially Associated with Cardiovascular Disease, Type 2 Diabetes, and Obesity: An Overview of Human Studies. Adv Nutr. 2020;11:644–666. doi: 10.1093/advances/nmz131 [PubMed: 31868199]
10. Brun PJ, Yang KJ, Lee SA, Yuen JJ, Blaner WS. Retinoids: Potent regulators of metabolism. Biofactors. 2013;39:151–163. doi: 10.1002/biof.1056 [PubMed: 23281051]
11. Gudas LJ. Retinoid metabolism: new insights. J Mol Endocrinol. 2022;69:T37–T49. doi: 10.1530/JME-22-0082 [PubMed: 35900851]
12. Blaner WS, Li Y, Brun PJ, Yuen JJ, Lee SA, Clugston RD. Vitamin A Absorption, Storage and Mobilization. Subcell Biochem. 2016;81:95–125. doi: 10.1007/978-94-024-0945-1_4 [PubMed: 27830502]
13. Li Y, Wongsiriroj N, Blaner WS. The multifaceted nature of retinoid transport and metabolism. Hepatobiliary Surg Nutr. 2014;3:126–139. doi: 10.3978/j.issn.2304-3881.2014.05.04 [PubMed: 25019074]
14. Balmer JE, Blomhoff R. Gene expression regulation by retinoic acid. J Lipid Res. 2002;43:1773–1808. doi: 10.1194/jlr.r100015-jlr200 [PubMed: 12401878]
15. Rochette-Egly C, Germain P. Dynamic and combinatorial control of gene expression by nuclear retinoic acid receptors (RARs). Nucl Recept Signal. 2009;7:e005. doi: 10.1621/nrs.07005 [PubMed: 19471584]
16. Al Tanoury Z, Piskunov A, Rochette-Egly C. Vitamin A and retinoid signaling: genomic and nongenomic effects. J Lipid Res. 2013;54:1761–1775. doi: 10.1194/jlr.R030833 [PubMed: 23440512]
17. Zanotto-Filho A, Cammarota M, Gelain DP, Oliveira RB, Delgado-Canedo A, Dalmolin RJ, Pasquali MA, Moreira JC. Retinoic acid induces apoptosis by a non-classical mechanism of ERK1/2 activation. Toxicol In Vitro. 2008;22:1205–1212. doi: 10.1016/j.tiv.2008.04.001 [PubMed: 18474417]
18. Grimwade D, Mistry AR, Solomon E, Guidez F. Acute promyelocytic leukemia: a paradigm for differentiation therapy. Cancer Treat Res. 2010;145:219–235. doi: 10.1007/978-0-387-69259-3_13 [PubMed: 20306254]
19. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood. 2008;111:2505–2515. doi: 10.1182/blood-2007-07-102798 [PubMed: 18299451]
20. Czuba LC, Wu X, Huang W, Hollingshead N, Roberto JB, Kenerson HL, Yeung RS, Crispe IN, Isoherranen N. Altered vitamin A metabolism in human liver slices corresponds to fibrogenesis. Clin Transl Sci. 2021;14:976–989. doi: 10.1111/cts.12962 [PubMed: 33382909]
21. Aguilar RP, Genta S, Oliveros L, Anzulovich A, Gimenez MS, Sanchez SS. Vitamin A deficiency injures liver parenchyma and alters the expression of hepatic extracellular matrix. J Appl Toxicol. 2009;29:214–222. doi: 10.1002/jat.1399 [PubMed: 18989869]
22. Seifert WF, Bosma A, Brouwer A, Hendriks HF, Roholl PJ, van Leeuwen RE, van Thiel-de Ruiter GC, Seifert-Bock I, Knook DL. Vitamin A deficiency potentiates carbon tetrachloride-induced liver fibrosis in rats. Hepatology. 1994;19:193–201. [PubMed: 8276355]
23. Senoo H, Wake K. Suppression of experimental hepatic fibrosis by administration of vitamin A. Lab Invest. 1985;52:182–194. [PubMed: 2578584]
24. Bozhkov AI, Novikova AV, Klimova EM, Ionov IA, Akzhyhitov RA, Kurhuzova NI, Bilovetska SG, Moskalov VB, Haiovyi SS. Vitamin A Reduces the Mortality of Animals with Induced Liver Fibrosis by Providing a Multi-level Body Defense System. J Clin Exp Hepatol. 2023;13:48–63. doi: 10.1016/j.jceh.2022.09.006 [PubMed: 36647402]
25. Schuppan D Vitamin A and liver fibrosis: cure or villain? J Lab Clin Med. 1992;119:590–591. [PubMed: 1593206]

26. Botella-Carretero JI, Balsa JA, Vazquez C, Peromingo R, Diaz-Enriquez M, Escobar-Morreale HF. Retinol and alpha-tocopherol in morbid obesity and nonalcoholic fatty liver disease. Obes Surg. 2010;20:69–76. doi: 10.1007/s11695-008-9686-5 [PubMed: 18830789]
27. Suano de Souza FI, Silverio Amancio OM, Saccardo Sarni RO, Sacchi Pitta T, Fernandes AP, Affonso Fonseca FL, Hix S, Ramalho RA. Non-alcoholic fatty liver disease in overweight children and its relationship with retinol serum levels. Int J Vitam Nutr Res. 2008;78:27–32. doi: 10.1024/0300-9831.78.1.27 [PubMed: 18654951]
28. Newsome PN, Beldon I, Moussa Y, Delahooke TE, Poulopoulos G, Hayes PC, Plevris JN. Low serum retinol levels are associated with hepatocellular carcinoma in patients with chronic liver disease. Aliment Pharmacol Ther. 2000;14:1295–1301. doi: 10.1046/j.1365-2036.2000.00849.x [PubMed: 11012474]
29. Chaves GV, Pereira SE, Saboya CJ, Spitz D, Rodrigues CS, Ramalho A. Association between liver vitamin A reserves and severity of nonalcoholic fatty liver disease in the class III obese following bariatric surgery. Obes Surg. 2014;24:219–224. doi: 10.1007/s11695-013-1087-8 [PubMed: 24101088]
30. Liu Y, Chen H, Wang J, Zhou W, Sun R, Xia M. Association of serum retinoic acid with hepatic steatosis and liver injury in nonalcoholic fatty liver disease. Am J Clin Nutr. 2015;102:130–137. doi: 10.3945/ajcn.114.105155 [PubMed: 25948673]
31. Zhong G, Kirkwood J, Won KJ, 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. doi: 10.1124/jpet.119.258517 [PubMed: 31043436]
32. Trasino SE, Tang XH, Jessurun J, Gudas LJ. Obesity Leads to Tissue, but not Serum Vitamin A Deficiency. Sci Rep. 2015;5:15893. doi: 10.1038/srep15893 [PubMed: 26522079]
33. Saeed A, Bartuzi P, Heegsma J, Dekker D, Kloosterhuis N, de Bruin A, Jonker JW, van de Sluis B, Faber KN. Impaired Hepatic Vitamin A Metabolism in NAFLD Mice Leading to Vitamin A Accumulation in Hepatocytes. Cell Mol Gastroenterol Hepatol. 2021;11:309–325 e303. doi: 10.1016/j.jcmgh.2020.07.006 [PubMed: 32698042]
34. Miyazaki H, Takitani K, Koh M, Inoue A, Kishi K, Tamai H. Retinol status and expression of retinol-related proteins in methionine-choline deficient rats. J Nutr Sci Vitaminol (Tokyo). 2014;60:78–85. doi: 10.3177/jnsv.60.78 [PubMed: 24975216]
35. Heringlake S, Hofdmann M, Fiebeler A, Manns MP, Schmiegel W, Tannapfel A. Identification and expression analysis of the aldo-ketoreductase1-B10 gene in primary malignant liver tumours. J Hepatol. 2010;52:220–227. doi: 10.1016/j.jhep.2009.11.005 [PubMed: 20036025]
36. Pettinelli P, Arendt BM, Teterina A, McGilvray I, Comelli EM, Fung SK, Fischer SE, Allard JP. Altered hepatic genes related to retinol metabolism and plasma retinol in patients with non-alcoholic fatty liver disease. PLoS One. 2018;13:e0205747. doi: 10.1371/journal.pone.0205747 [PubMed: 30379862]
37. Amangurbanova M, Huang DQ, Loomba R. Review article: the role of HSD17B13 on global epidemiology, natural history, pathogenesis and treatment of NAFLD. Aliment Pharmacol Ther. 2023;57:37–51. doi: 10.1111/apt.17292 [PubMed: 36349732]
38. Pirazzi C, Valenti L, Motta BM, Pingitore P, Hedfalk K, Mancina RM, Burza MA, Indiveri C, Ferro Y, Montalcini T, et al. PNPLA3 has retinyl-palmitate lipase activity in human hepatic stellate cells. Hum Mol Genet. 2014;23:4077–4085. doi: 10.1093/hmg/ddu121 [PubMed: 24670599]
39. Kovarova M, Konigsrainer I, Konigsrainer A, Machicao F, Haring HU, Schleicher E, Peter A. The Genetic Variant I148M in PNPLA3 Is Associated With Increased Hepatic Retinyl-Palmitate Storage in Humans. J Clin Endocrinol Metab. 2015;100:E1568–1574. doi: 10.1210/jc.2015-2978 [PubMed: 26439088]
40. Mondul A, Mancina RM, Merlo A, Dongiovanni P, Rametta R, Montalcini T, Valenti L, Albanes D, Romeo S. PNPLA3 I148M Variant Influences Circulating Retinol in Adults with Nonalcoholic Fatty Liver Disease or Obesity. J Nutr. 2015;145:1687–1691. doi: 10.3945/jn.115.210633 [PubMed: 26136587]
41. Amengual J, Ribot J, Bonet ML, Palou A. Retinoic acid treatment enhances lipid oxidation and inhibits lipid biosynthesis capacities in the liver of mice. Cell Physiol Biochem. 2010;25:657–666. doi: 10.1159/000315085 [PubMed: 20511711]

42. 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;44:2019–2027. doi: 10.1016/j.biocel.2012.07.026 [PubMed: 22871568]
43. Cassim Bawa FN, Xu Y, Gopoju R, Plonski NM, Shiyab A, Hu S, Chen S, Zhu Y, Jadhav K, Kasumov T, et al. Hepatic retinoic acid receptor alpha mediates all-trans retinoic acid's effect on diet-induced hepatosteatosis. Hepatol Commun. 2022;6:2665–2675. doi: 10.1002/hep4.2049 [PubMed: 35852305]
44. Wang Y, Nakajima T, Gonzalez FJ, Tanaka N. PPARs as Metabolic Regulators in the Liver: Lessons from Liver-Specific PPAR-Null Mice. Int J Mol Sci. 2020;21. doi: 10.3390/ijms21062061 [PubMed: 33375030]
45. Bonet ML, Ribot J, Palou A. Lipid metabolism in mammalian tissues and its control by retinoic acid. Biochim Biophys Acta. 2012;1821:177–189. doi: 10.1016/j.bbalip.2011.06.001 [PubMed: 21669299]
46. Duval C, Muller M, Kersten S. PPARalpha and dyslipidemia. Biochim Biophys Acta. 2007;1771:961–971. doi: 10.1016/j.bbalip.2007.05.003 [PubMed: 17604218]
47. Schug TT, Berry DC, Shaw NS, Travis SN, Noy N. Opposing effects of retinoic acid on cell growth result from alternate activation of two different nuclear receptors. Cell. 2007;129:723–733. doi: 10.1016/j.cell.2007.02.050 [PubMed: 17512406]
48. Miquilena-Colina ME, Lima-Cabello E, Sanchez-Campos S, Garcia-Mediavilla MV, Fernandez-Bermejo M, Lozano-Rodriguez T, Vargas-Castrillon J, Buque X, Ochoa B, Aspichueta P, et al. Hepatic fatty acid translocase CD36 upregulation is associated with insulin resistance, hyperinsulinaemia and increased steatosis in non-alcoholic steatohepatitis and chronic hepatitis C. Gut. 2011;60:1394–1402. doi: 10.1136/gut.2010.222844 [PubMed: 21270117]
49. Rada P, Gonzalez-Rodriguez A, Garcia-Monzon C, Valverde AM. Understanding lipotoxicity in NAFLD pathogenesis: is CD36 a key driver? Cell Death Dis. 2020;11:802. doi: 10.1038/s41419-020-03003-w [PubMed: 32978374]
50. Tontonoz P, Nagy L, Alvarez JG, Thomazy VA, Evans RM. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell. 1998;93:241–252. [PubMed: 9568716]
51. Nagy L, Tontonoz P, Alvarez JG, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARgamma. Cell. 1998;93:229–240. [PubMed: 9568715]
52. Zhao Z, Deng ZT, Huang S, Ning M, Feng Y, Shen Y, Zhao QS, Leng Y. Alisol B Alleviates Hepatocyte Lipid Accumulation and Lipotoxicity via Regulating RARalpha-PPARgamma-CD36 Cascade and Attenuates Non-Alcoholic Steatohepatitis in Mice. Nutrients. 2022;14. doi: 10.3390/nu14122411
53. Tang XH, Melis M, Lu C, Rappa A, Zhang T, Jessurun J, Gross SS, Gudas LJ. A retinoic acid receptor beta2 agonist attenuates transcriptome and metabolome changes underlying nonalcohol-associated fatty liver disease. J Biol Chem. 2021;297:101331. doi: 10.1016/j.jbc.2021.101331 [PubMed: 34688661]
54. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005;115:1343–1351. doi: 10.1172/JCI23621 [PubMed: 15864352]
55. Ferre P, Foufelle F. Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c. Diabetes Obes Metab. 2010;12 Suppl 2:83–92. doi: 10.1111/j.1463-1326.2010.01275.x [PubMed: 21029304]
56. Moon YA, Liang G, Xie X, Frank-Kamenetsky M, Fitzgerald K, Koteliansky V, Brown MS, Goldstein JL, Horton JD. The Scap/SREBP pathway is essential for developing diabetic fatty liver and carbohydrate-induced hypertriglyceridemia in animals. Cell Metab. 2012;15:240–246. doi: 10.1016/j.cmet.2011.12.017 [PubMed: 22326225]
57. Geng C, Xu H, Zhang Y, Gao Y, Li M, Liu X, Gao M, Wang X, Liu X, Fang F, et al. Retinoic acid ameliorates high-fat diet-induced liver steatosis through sirt1. Sci China Life Sci. 2017;60:1234–1241. doi: 10.1007/s11427-016-9027-6 [PubMed: 28667519]

58. Brinckerhoff CE, Coffey JW, Sullivan AC. Inflammation and collagenase production in rats with adjuvant arthritis reduced with 13-cis-retinoic acid. Science. 1983;221:756–758. doi: 10.1126/science.6308759 [PubMed: 6308759]

59. Orfanos CE, Bauer R. Evidence for anti-inflammatory activities of oral synthetic retinoids: experimental findings and clinical experience. Br J Dermatol. 1983;109 Suppl 25:55–60. [PubMed: 6222758]

60. Mehta K, McQueen T, Tucker S, Pandita R, Aggarwal BB. Inhibition by all-trans-retinoic acid of tumor necrosis factor and nitric oxide production by peritoneal macrophages. J Leukoc Biol. 1994;55:336–342. doi: 10.1002/jlb.55.3.336 [PubMed: 8120450]

61. Mathew JS, Sharma RP. Effect of all-trans-retinoic acid on cytokine production in a murine macrophage cell line. Int J Immunopharmacol. 2000;22:693–706. doi: 10.1016/s0192-0561(00)00032-1 [PubMed: 10884590]

62. Cantorna MT, Nashold FE, Chun TY, Hayes CE. Vitamin A down-regulation of IFN-gamma synthesis in cloned mouse Th1 lymphocytes depends on the CD28 costimulatory pathway. J Immunol. 1996;156:2674–2679. [PubMed: 8609382]

63. Na SY, Kang BY, Chung SW, Han SJ, Ma X, Trinchieri G, Im SY, Lee JW, Kim TS. Retinoids inhibit interleukin-12 production in macrophages through physical associations of retinoid X receptor and NFkappaB. J Biol Chem. 1999;274:7674–7680. doi: 10.1074/jbc.274.12.7674 [PubMed: 10075655]

64. Wang X, Allen C, Ballow M. Retinoic acid enhances the production of IL-10 while reducing the synthesis of IL-12 and TNF-alpha from LPS-stimulated monocytes/macrophages. J Clin Immunol. 2007;27:193–200. doi: 10.1007/s10875-006-9068-5 [PubMed: 17253143]

65. Nurrahmah QI, Madhyastha R, Madhyastha H, Purbasari B, Maruyama M, Nakajima Y. Retinoic acid abrogates LPS-induced inflammatory response via negative regulation of NF-kappa B/miR-21 signaling. Immunopharmacol Immunotoxicol. 2021;43:299–308. doi: 10.1080/08923973.2021.1902348 [PubMed: 33757404]

66. Wang R, Chen S, Liu Y, Diao S, Xue Y, You X, Park EA, Liao FF. All-trans-retinoic acid reduces BACE1 expression under inflammatory conditions via modulation of nuclear factor kappaB (NFkappaB) signaling. J Biol Chem. 2015;290:22532–22542. doi: 10.1074/jbc.M115.662908 [PubMed: 26240147]

67. Cassim Bawa FN, Gopoju R, Xu Y, Hu S, Zhu Y, Chen S, Jadhav K, Zhang Y. Retinoic Acid Receptor Alpha (RARalpha) in Macrophages Protects from Diet-Induced Atherosclerosis in Mice. Cells. 2022;11. doi: 10.3390/cells11203186

68. Melis M, Tang XH, Attarwala N, Chen Q, Prishker C, Qin L, Gross SS, Gudas LJ, Trasino SE. A retinoic acid receptor beta2 agonist protects against alcohol liver disease and modulates hepatic expression of canonical retinoid metabolism genes. Biofactors. 2022;48:469–480. doi: 10.1002/biof.1794 [PubMed: 34687254]

69. Friedman SL. Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. Physiol Rev. 2008;88:125–172. doi: 10.1152/physrev.00013.2007 [PubMed: 18195085]

70. Okuno M, Moriwaki H, Imai S, Muto Y, Kawada N, Suzuki Y, Kojima S. Retinoids exacerbate rat liver fibrosis by inducing the activation of latent TGF-beta in liver stellate cells. Hepatology. 1997;26:913–921. doi: 10.1053/jhep.1997.v26.pm0009328313 [PubMed: 9328313]

71. Hisamori S, Tabata C, Kadokawa Y, Okoshi K, Tabata R, Mori A, Nagayama S, Watanabe G, Kubo H, Sakai Y. All-trans-retinoic acid ameliorates carbon tetrachloride-induced liver fibrosis in mice through modulating cytokine production. Liver Int. 2008;28:1217–1225. doi: 10.1111/j.1478-3231.2008.01745.x [PubMed: 18397230]

72. Wang H, Dan Z, Jiang H. Effect of all-trans retinoic acid on liver fibrosis induced by common bile duct ligation in rats. J Huazhong Univ Sci Technolog Med Sci. 2008;28:553–557. doi: 10.1007/s11596-008-0514-x [PubMed: 18846337]

73. Ye Y, Dan Z. All-trans retinoic acid diminishes collagen production in a hepatic stellate cell line via suppression of active protein-1 and c-Jun N-terminal kinase signal. J Huazhong Univ Sci Technolog Med Sci. 2010;30:726–733. doi: 10.1007/s11596-010-0648-5 [PubMed: 21181362]

74. Panebianco C, Oben JA, Vinciguerra M, Pazienza V. Senescence in hepatic stellate cells as a mechanism of liver fibrosis reversal: a putative synergy between retinoic acid and PPAR-

gamma signalings. Clin Exp Med. 2017;17:269–280. doi: 10.1007/s10238-016-0438-x [PubMed: 27655446]

75. Yanagitani A, Yamada S, Yasui S, Shimomura T, Murai R, Murawaki Y, Hashiguchi K, Kanbe T, Saeki T, Ichiba M, et al. Retinoic acid receptor alpha dominant negative form causes steatohepatitis and liver tumors in transgenic mice. Hepatology. 2004;40:366–375. doi: 10.1002/hep.20335 [PubMed: 15368441]
76. Loomba R, Abraham M, Unalp A, Wilson L, Lavine J, Doo E, Bass NM, Nonalcoholic Steatohepatitis Clinical Research N. Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. Hepatology. 2012;56:943–951. doi: 10.1002/hep.25772 [PubMed: 22505194]
77. Lee YH, Cho Y, Lee BW, Park CY, Lee DH, Cha BS, Rhee EJ. Nonalcoholic Fatty Liver Disease in Diabetes. Part I: Epidemiology and Diagnosis. Diabetes Metab J. 2019;43:31–45. doi: 10.4093/dmj.2019.0011 [PubMed: 30793550]
78. Wolf G Retinoic acid activation of peroxisome proliferation-activated receptor delta represses obesity and insulin resistance. Nutr Rev. 2010;68:67–70. doi: 10.1111/j.1753-4887.2009.00261.x [PubMed: 20042001]
79. Berry DC, DeSantis D, Soltanian H, Croniger CM, Noy N. Retinoic acid upregulates preadipocyte genes to block adipogenesis and suppress diet-induced obesity. Diabetes. 2012;61:1112–1121. doi: 10.2337/db11-1620 [PubMed: 22396202]
80. Noy N The one-two punch: Retinoic acid suppresses obesity both by promoting energy expenditure and by inhibiting adipogenesis. Adipocyte. 2013;2:184–187. doi: 10.4161/adip.23489 [PubMed: 23991366]
81. Berry DC, Noy N. All-trans-retinoic acid represses obesity and insulin resistance by activating both peroxisome proliferation-activated receptor beta/delta and retinoic acid receptor. Mol Cell Biol. 2009;29:3286–3296. doi: 10.1128/MCB.01742-08 [PubMed: 19364826]
82. Tsuchiya H, Ikeda Y, Ebata Y, Kojima C, Katsuma R, Tsuruyama T, Sakabe T, Shomori K, Komeda N, Oshiro S, et al. Retinoids ameliorate insulin resistance in a leptin-dependent manner in mice. Hepatology. 2012;56:1319–1330. doi: 10.1002/hep.25798 [PubMed: 22531980]
83. Matsumoto Y, Fujita S, Yamagishi A, Shirai T, Maeda Y, Suzuki T, Kobayashi KI, Inoue J, Yamamoto Y. Brown Rice Inhibits Development of Nonalcoholic Fatty Liver Disease in Obese Zucker (fa/fa) Rats by Increasing Lipid Oxidation Via Activation of Retinoic Acid Synthesis. J Nutr. 2021;151:2705–2713. doi: 10.1093/jn/nxab188 [PubMed: 34224565]
84. Zarei L, Farhad N, Abbasi A. All-Trans Retinoic Acid (atRA) effectively improves liver steatosis in a rabbit model of high fat induced liver steatosis. Arch Physiol Biochem. 2022;128:1010–1015. doi: 10.1080/13813455.2020.1743725 [PubMed: 32202947]
85. Zhu S, Zhang J, Zhu D, Jiang X, Wei L, Wang W, Chen YQ. Adipose tissue plays a major role in retinoic acid-mediated metabolic homoeostasis. Adipocyte. 2022;11:47–55. doi: 10.1080/21623945.2021.2015864 [PubMed: 34957917]
86. Kim SC, Kim CK, Axe D, Cook A, Lee M, Li T, Smallwood N, Chiang JY, Hardwick JP, Moore DD, et al. All-trans-retinoic acid ameliorates hepatic steatosis in mice by a novel transcriptional cascade. Hepatology. 2014;59:1750–1760. doi: 10.1002/hep.26699 [PubMed: 24038081]
87. Liu X, Shen H, Chen M, Shao J. Clinical Relevance of Vitamins and Carotenoids With Liver Steatosis and Fibrosis Detected by Transient Elastography in Adults. Front Nutr. 2021;8:760985. doi: 10.3389/fnut.2021.760985 [PubMed: 34869532]
88. Tilg H, Adolph TE, Trauner M. Gut-liver axis: Pathophysiological concepts and clinical implications. Cell Metab. 2022;34:1700–1718. doi: 10.1016/j.cmet.2022.09.017 [PubMed: 36208625]
89. Plaza-Diaz J, Solis-Urra P, Rodriguez-Rodriguez F, Olivares-Arancibia J, Navarro-Oliveros M, Abadia-Molina F, Alvarez-Mercado AI. The Gut Barrier, Intestinal Microbiota, and Liver Disease: Molecular Mechanisms and Strategies to Manage. Int J Mol Sci. 2020;21. doi: 10.3390/ijms21218351
90. Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, Martin P, Philippe C, Walker F, Bado A, et al. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. Gut. 2013;62:1787–1794. doi: 10.1136/gutjnl-2012-303816 [PubMed: 23197411]

91. Safari Z, Gerard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cell Mol Life Sci. 2019;76:1541–1558. doi: 10.1007/s00018-019-03011-w [PubMed: 30683985]
92. Portincasa P, Bonfrate L, Khalil M, Angelis M, Calabrese FM, D'Amato M, Wang DQ, Di Ciaula A. Intestinal Barrier and Permeability in Health, Obesity and NAFLD. Biomedicines. 2021;10. doi: 10.3390/biomedicines10010083
93. Abdelhamid L, Luo XM. Retinoic Acid, Leaky Gut, and Autoimmune Diseases. Nutrients. 2018;10. doi: 10.3390/nu10081016
94. Lyu Y, Wu L, Wang F, Shen X, Lin D. Carotenoid supplementation and retinoic acid in immunoglobulin A regulation of the gut microbiota dysbiosis. Exp Biol Med (Maywood). 2018;243:613–620. doi: 10.1177/1535370218763760 [PubMed: 29534601]
95. Quadro L, Gamble MV, Vogel S, Lima AA, Piantedosi R, Moore SR, Colantuoni V, Gottesman ME, Guerrant RL, Blaner WS. Retinol and retinol-binding protein: gut integrity and circulating immunoglobulins. J Infect Dis. 2000;182 Suppl 1:S97–S102. doi: 10.1086/315920 [PubMed: 10944490]
96. Lima AA, Soares AM, Lima NL, Mota RM, Maciel BL, Kvalsund MP, Barrett LJ, Fitzgerald RP, Blaner WS, Guerrant RL. Effects of vitamin A supplementation on intestinal barrier function, growth, total parasitic, and specific Giardia spp infections in Brazilian children: a prospective randomized, double-blind, placebo-controlled trial. J Pediatr Gastroenterol Nutr. 2010;50:309–315. doi: 10.1097/MPG.0b013e3181a96489 [PubMed: 20038852]
97. Hanna GJ, A ON, Cutler JM, Flynn M, Vijaykumar T, Clark JR, Wirth LJ, Lorch JH, Park JC, Mito JK, et al. A phase II trial of all-trans retinoic acid (ATRA) in advanced adenoid cystic carcinoma. Oral Oncol. 2021;119:105366. doi: 10.1016/j.oraloncology.2021.105366 [PubMed: 34091189]
98. Kocher HM, Basu B, Froeling FEM, Sarker D, Slater S, Carlin D, deSouza NM, De Paepe KN, Goulart MR, Hughes C, et al. Phase I clinical trial repurposing all-trans retinoic acid as a stromal targeting agent for pancreatic cancer. Nat Commun. 2020;11:4841. doi: 10.1038/s41467-020-18636-w [PubMed: 32973176]

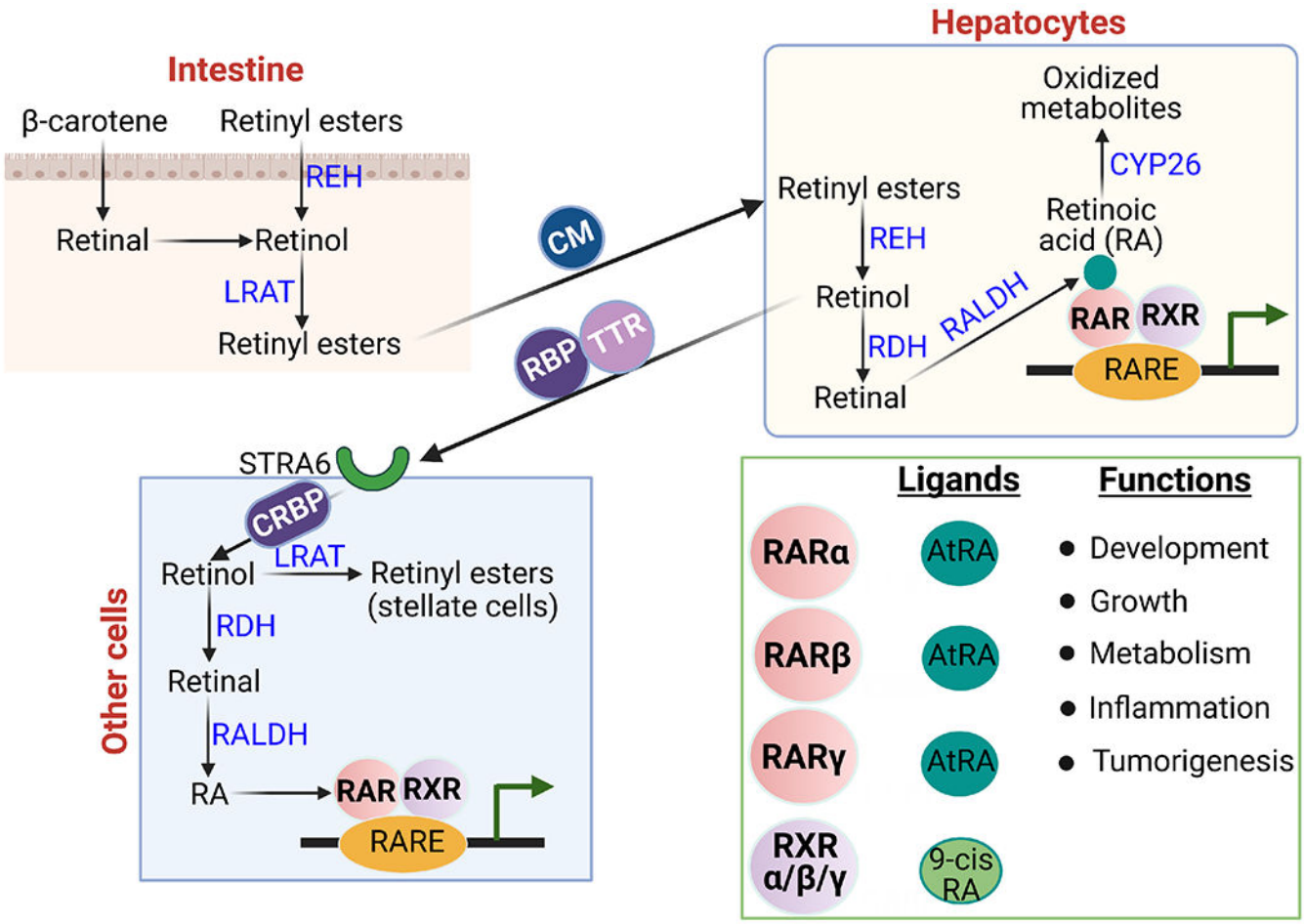

Figure 1. Overview of Vitamin A metabolism and RA signaling pathway

In the intestine, retinyl esters (RE) are hydrolyzed by RE hydrolase (REH) to form retinol. Retinal dervided from β-carotene is reduced to retinol by retinaldehyde reductase. Retinol is esterifed by lecithin retinol acyltransferase (LRAT) to form REs, which are assembled into chylomicron (CM) and secreted to the circulation. REs are uptaken by hepatocytes and are hydrolyzed to form retinol by hepatic REH. Retinol is secreted into the circulation and binds to the retinol binding protein (RBP)/transthyretin (TTR) complex. The membrane protein STRA6 recognizes RBP and transports retinol into cells. In the cells, retinol is converted to retinal by retinol dehydrogenase (RDH), which is further converted to retinoic acid (RA) by retinaldehyde dehydrogenase (RALDH). All-trans RA (AtRA) activates retinoic acid receptors (RAR) whereas 9-cis RA activates retinoic X receptors (RXR). RAR and RXR form heterodimers and bind to retinoic acid elements (RARE) to regulate gene transcription and a variety of pathways, e.g. development, growth, metabolism, inflammation, tumorigenesis. RAR or RXR has three isoforms, α, β, and γ. Retinol may also be esterifed to form REs by LRAT. About 80% REs are stored in hepatic stellate cells (HSC). Loss of REs from HSC may result in HSC activation. RA may be metabolized by CYP26A1, -B1, or -C1 to form 4-ox-RA, 4-OH-RA, etc.

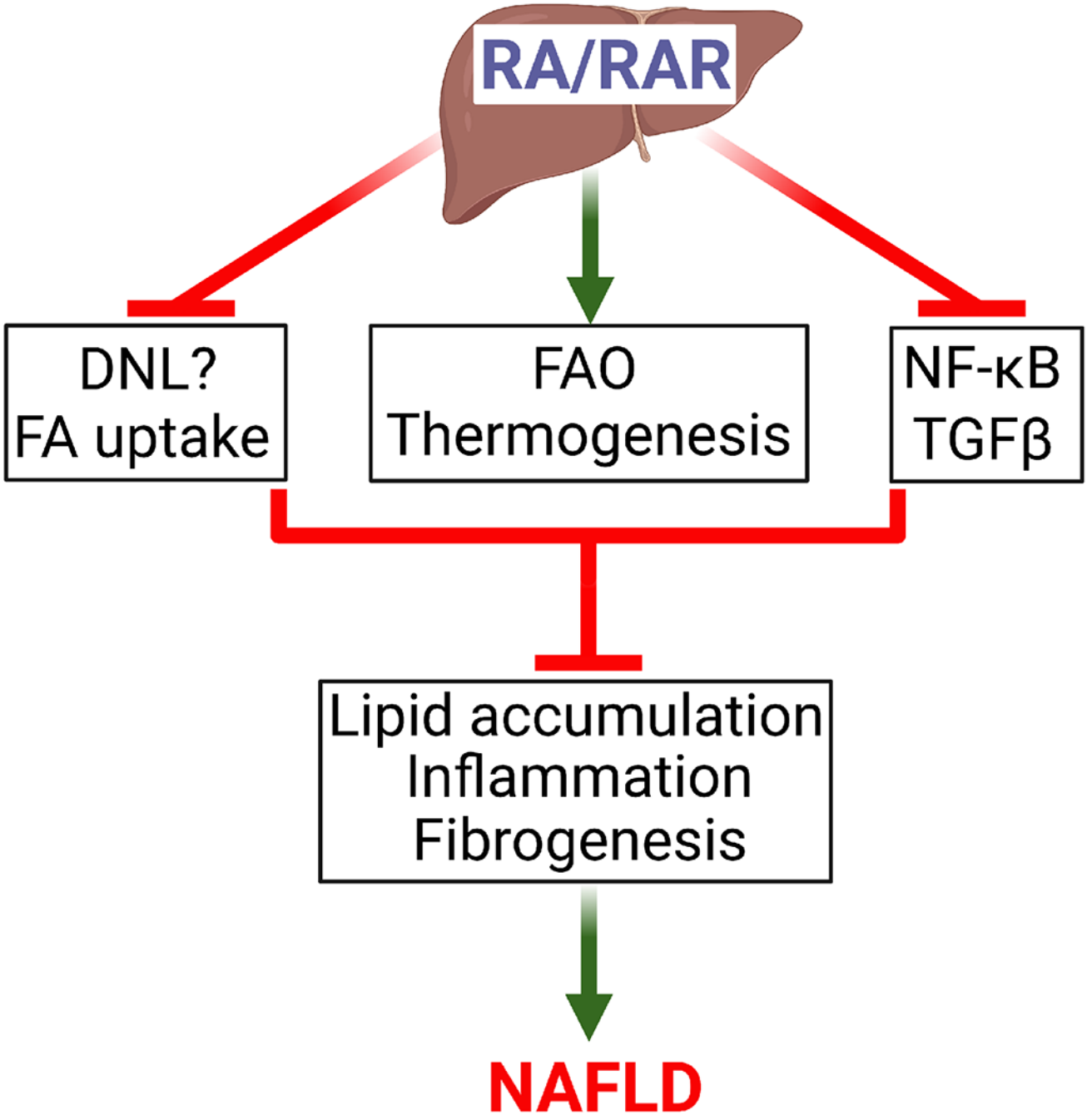

Figure 2. Regulation of the development of NAFLD by the RA/RAR signaling

Activation of RAR by RA inhibits the development of NAFLD likely via several pathways. Activation of RAR induces fatty acid oxidation (FAO) and thermogenesis and inhibits fatty acid (FA) uptake, NF-κB, and TGFβ, leading to a reduction in hepatic lipid accumulation, inflammation and fibrogenesis. The role of RAR activation in inhibiton of de novo lipogenesis (DNL) remains to be further clarified.