

# Thoughts on Vitamin A, IBD and PSC

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PSC Partners Seeking a Cure



**Jorgensen RA, Lindor KD, Sartin JS, LaRusso NF, Wiesner RH (1995) Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis. J. Clin. Gastroenterol. 20: 215-219.**

“In patients in the therapeutic trial\*, **vitamin A deficiency was seen in 40%**, vitamin D deficiency in 14%, and vitamin E deficiency in 2% of those tested. More prominent deficiencies of fat-soluble vitamins occurred in the pretransplant group of patients, with **82% deficient in vitamin A**, 57% deficient in vitamin D, and 43% deficient in vitamin E. We conclude that hypercholesterolemia and fat-soluble vitamin deficiencies are frequent in patients with PSC and are more common with more severe disease. Patients with PSC, especially with advanced liver disease, should be screened for fat-soluble vitamin deficiencies and supplemented accordingly.”

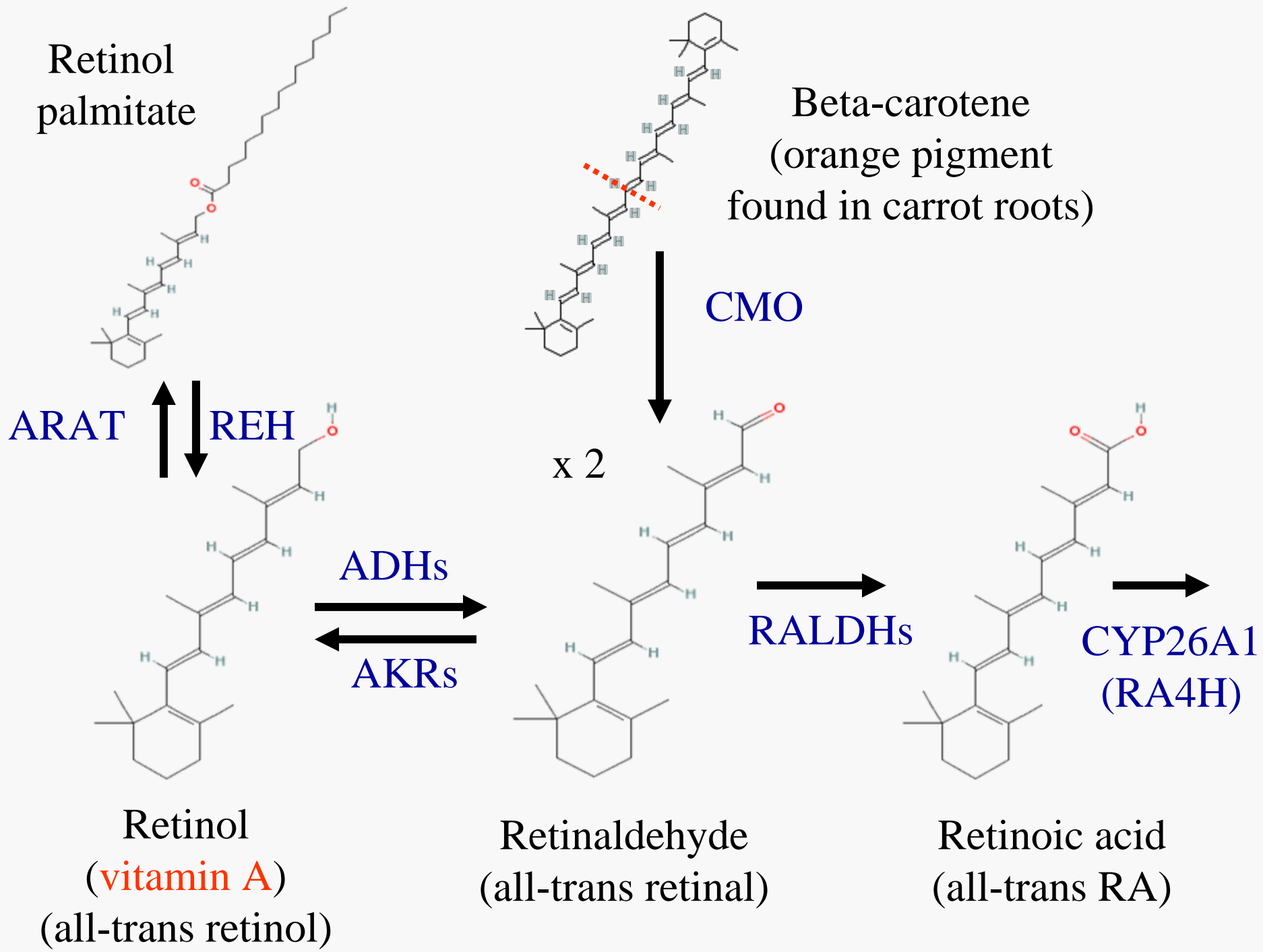
\* A placebo-controlled trial evaluating ursodeoxycholic acid in PSC.

# Question

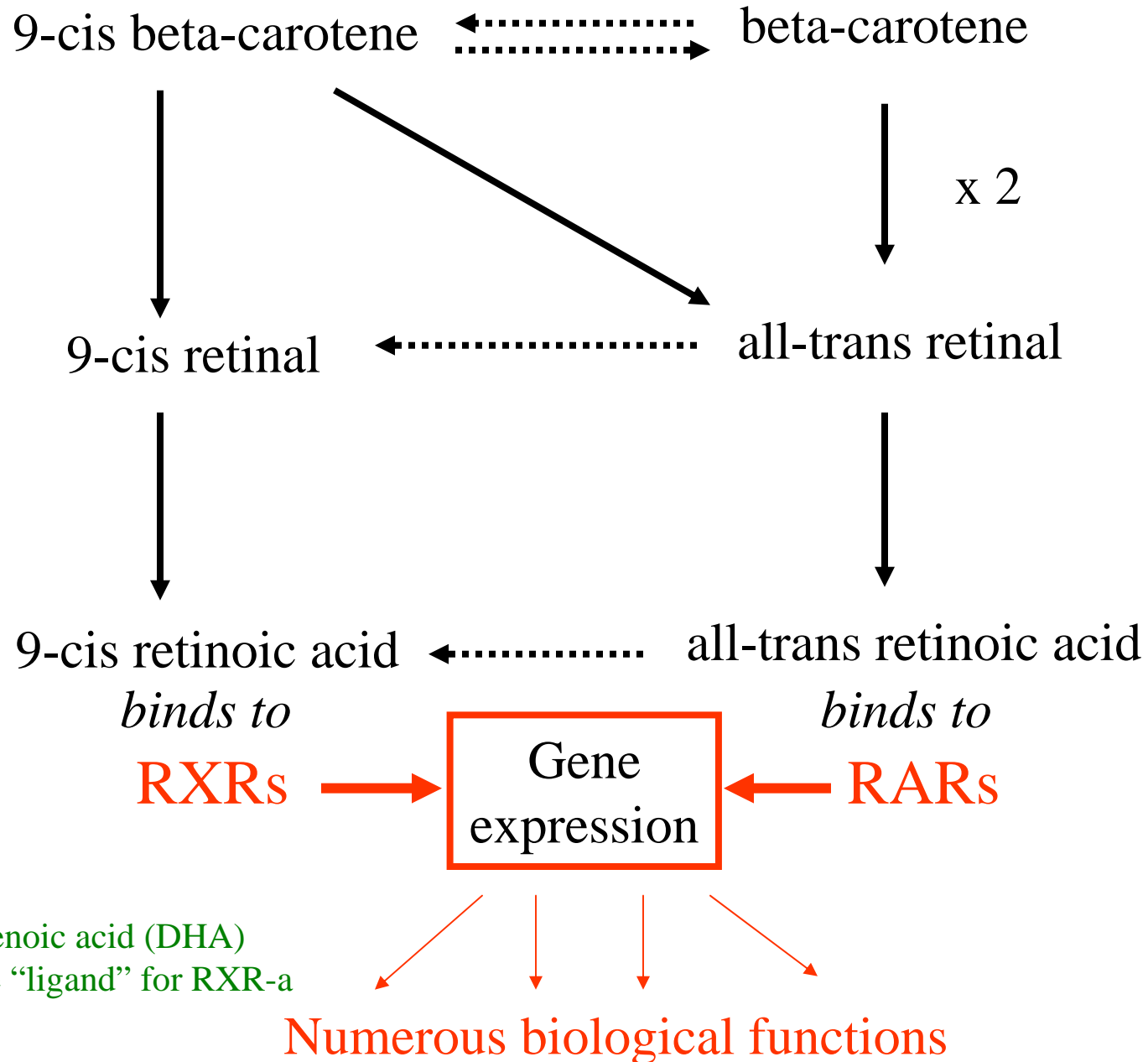
Could vitamin A deficiency contribute to the rate of progression and/or severity of IBD/PSC?

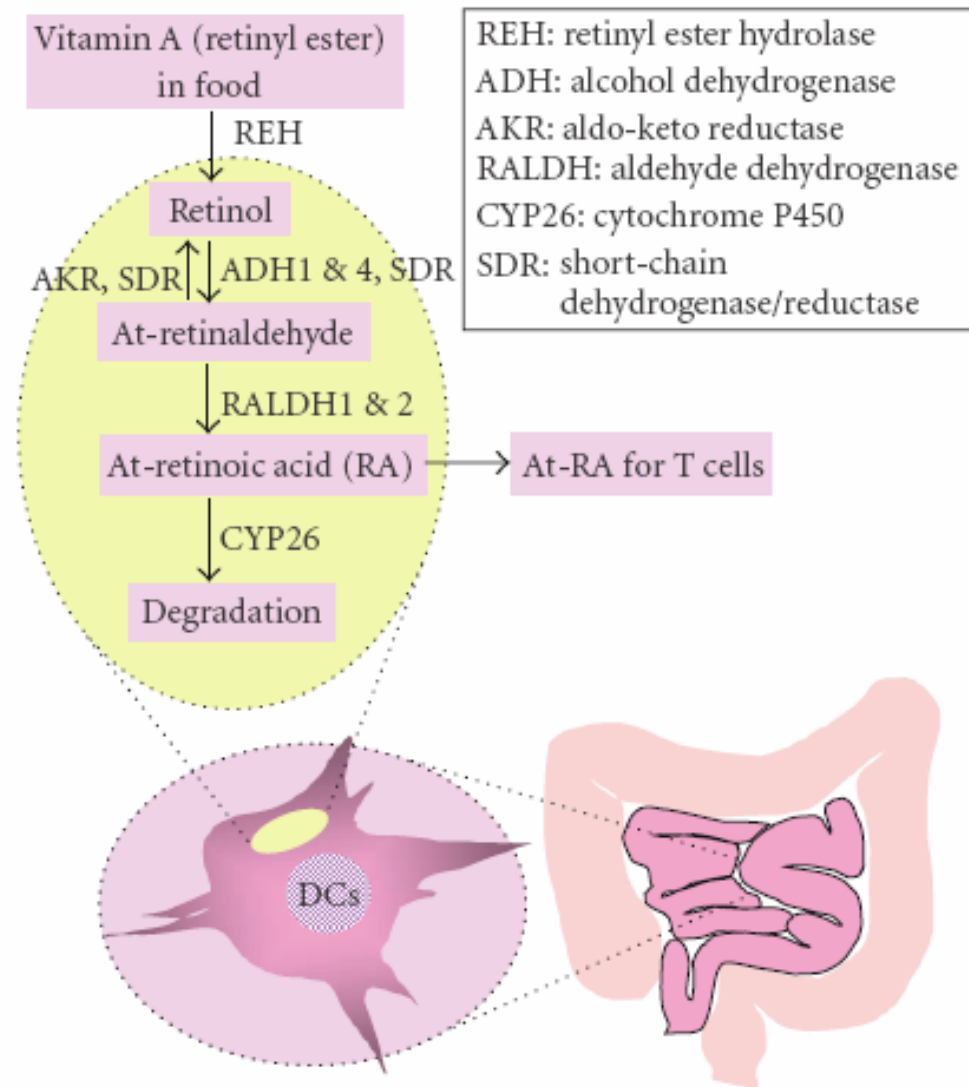
# Overview

- Synthesis of vitamin A, and metabolism to retinoic acid.
- Biological actions of retinoic acid are mediated by nuclear receptors, RXRs and RARs.
- Retinoic acid controls immune cells in gut associated lymphoid tissue (GALT).
- Retinoic acid controls gut permeability.
- Bacterial toxins reaching the liver via a permeable gut interfere with hepatic bile acid metabolism and transport via inhibition of RXR.
- Insults to the liver activate hepatic stellate cells, causing release of vitamin A stores and switch to collagen synthesis (→ liver fibrosis).
- Additional factors potentially contributing to retinoic acid deficiency (ethanol consumption; alternative pathways of beta-carotene metabolism; analogs of retinoic acid; cancer).



# Isomers of carotene, retinal, and retinoic acid

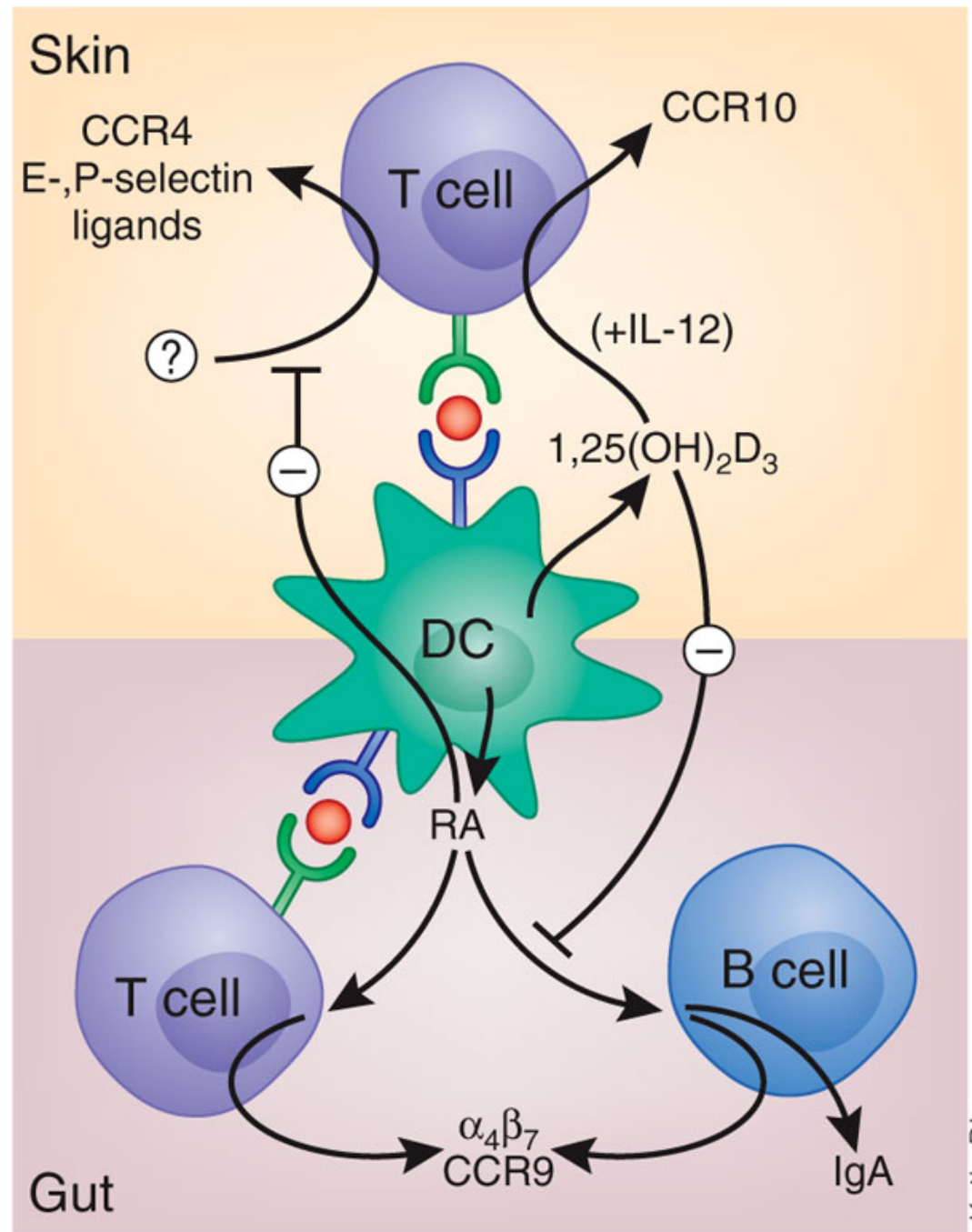




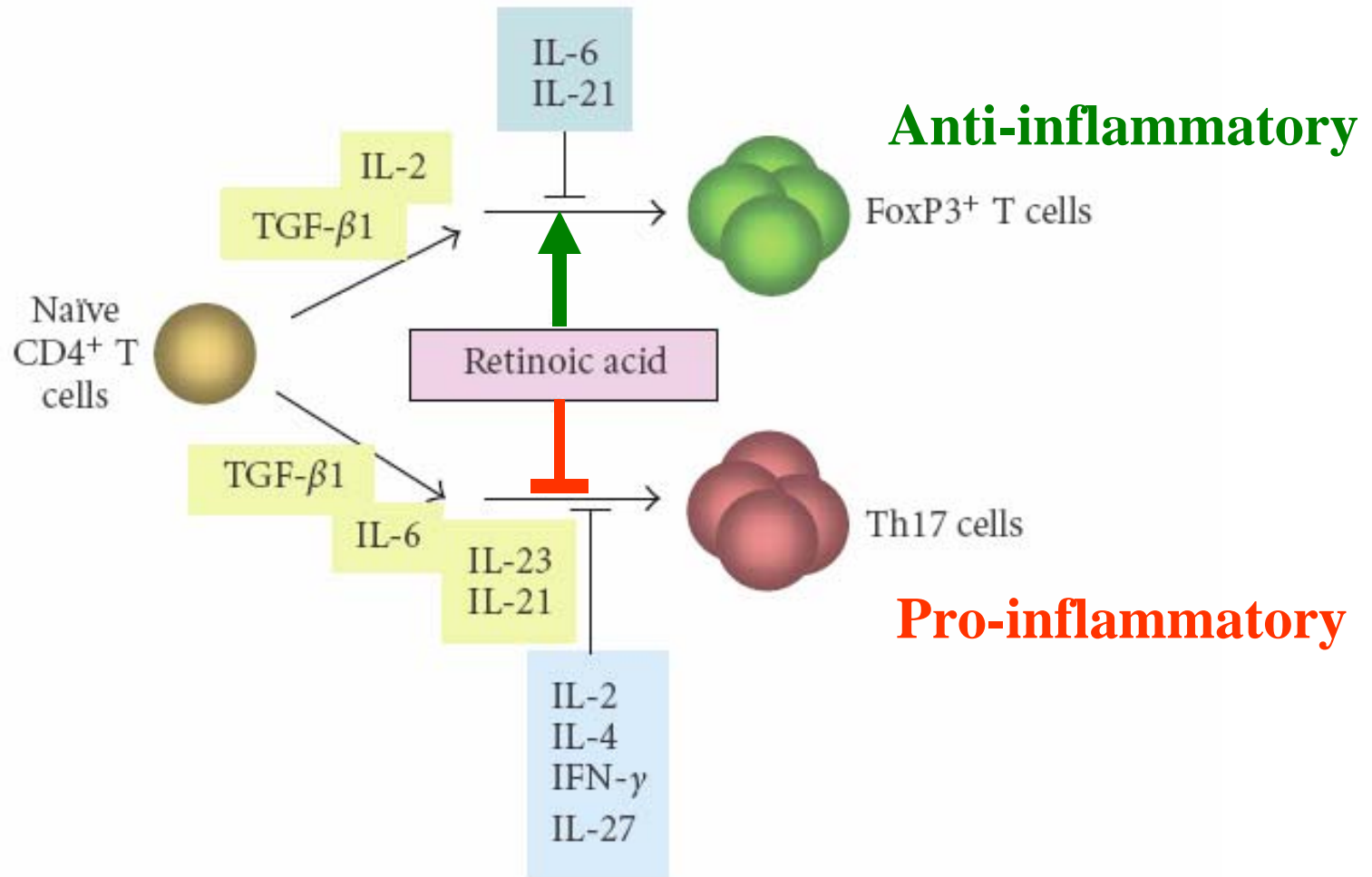
DC's = dendritic cells in gut associated lymphoid tissue (GALT)

Kim CH (2008) Regulation of FoxP3<sup>+</sup> regulatory T cells and Th17 cells by retinoids. Clin. Dev. Immunol. 2008: 416910.

All-trans retinoic acid (RA) produced by dendritic cells in the gut associated lymphoid tissue (GALT) “educates” immune cells. It imparts to T cells “gut-homing” characteristics. RA also primes B cells with “gut-homing” characteristics and ability to produce IgA. IgA is secreted from the gut mucosal surfaces, keeping bacterial populations in check. [Mebius RE \(2007\) Vitamins in control of lymphocyte migration. Nat. Immunol. 8: 229-230.](#)

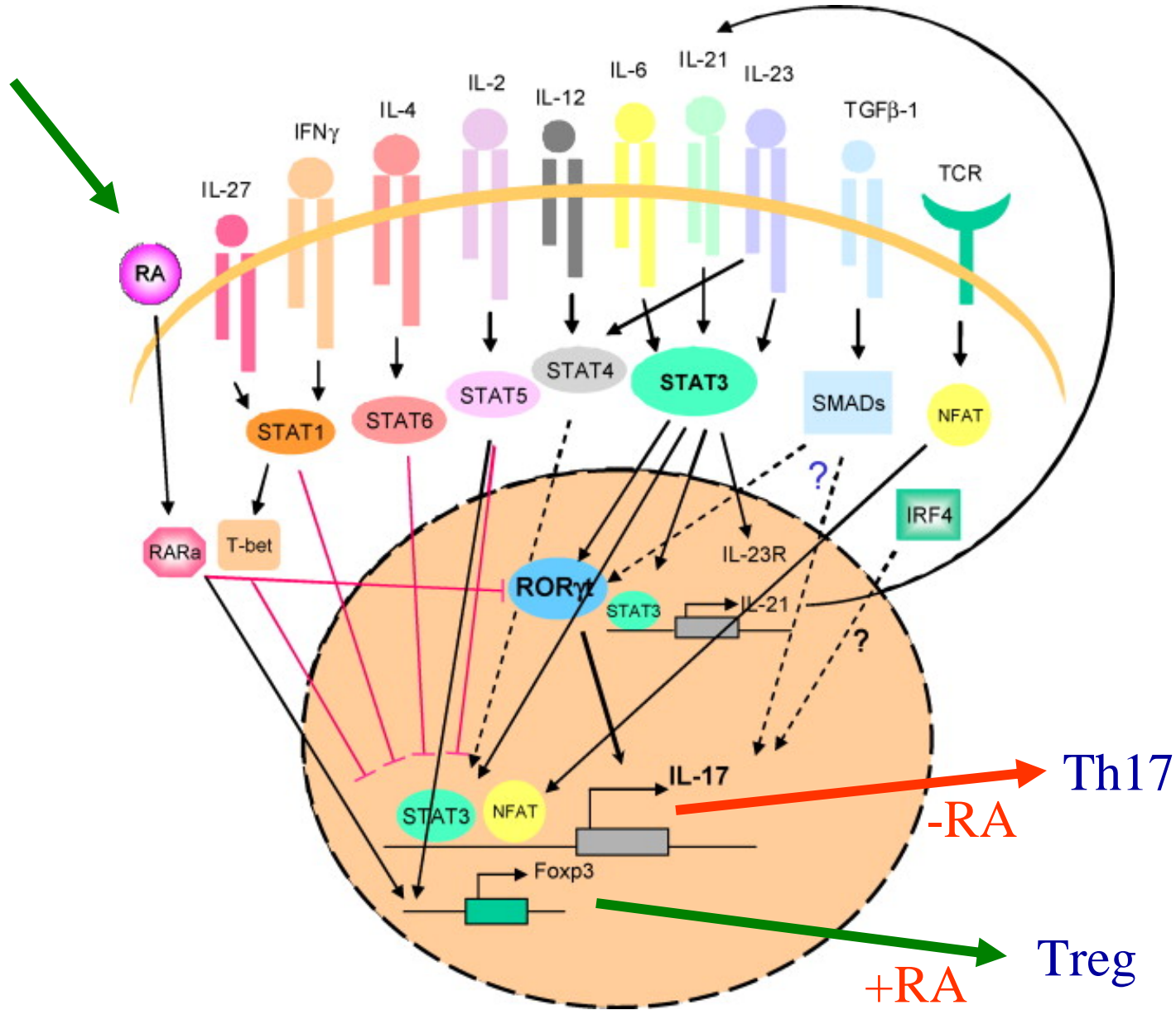






## Reciprocal regulation of Th17 and Treg cells by retinoic acid

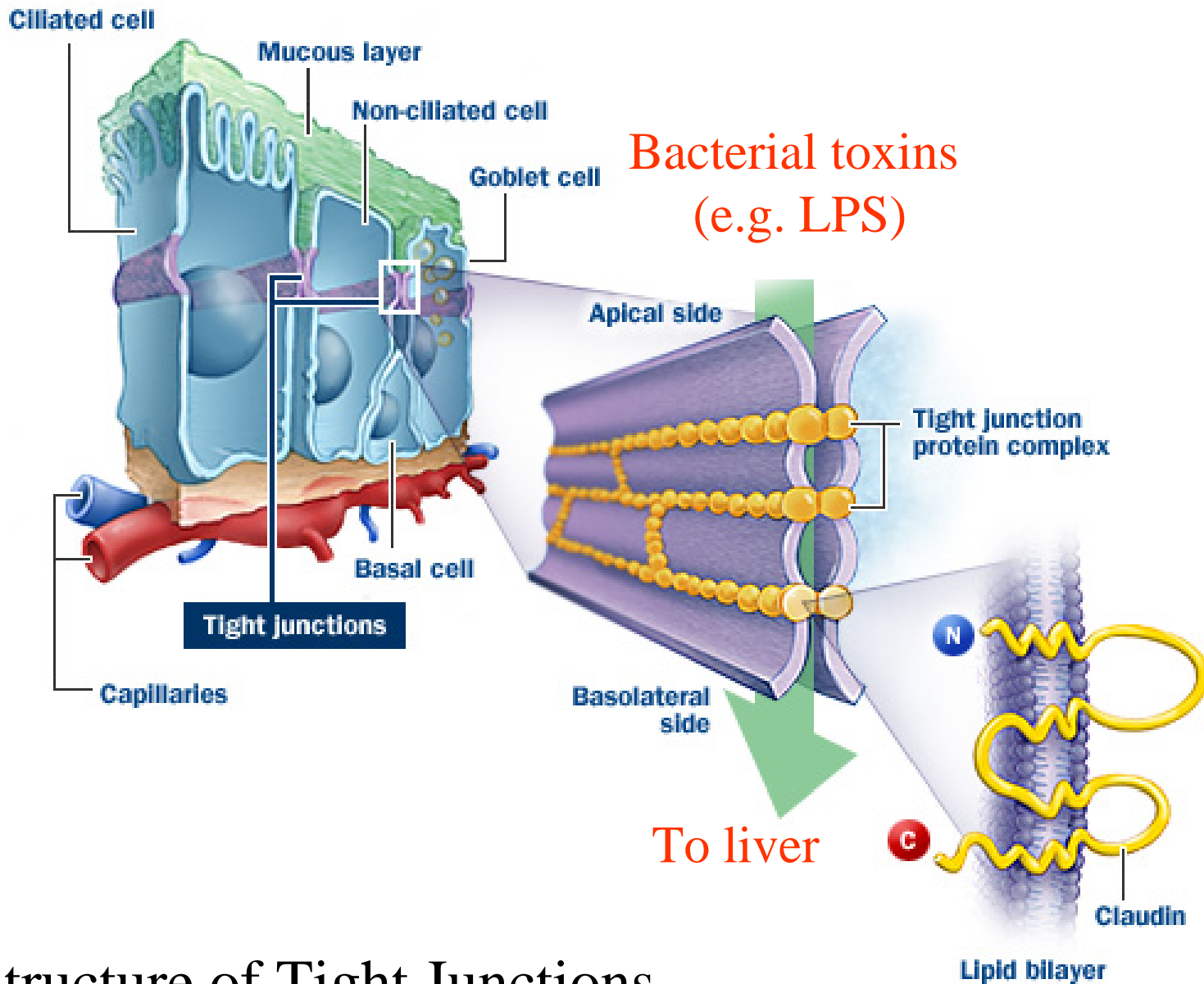
Kim (2008)



Chen Z, Laurence A, O'Shea JJ (2007) Signal transduction pathways and transcriptional regulation in the control of Th17 differentiation. *Semin. Immunol.* 19: 400-408.

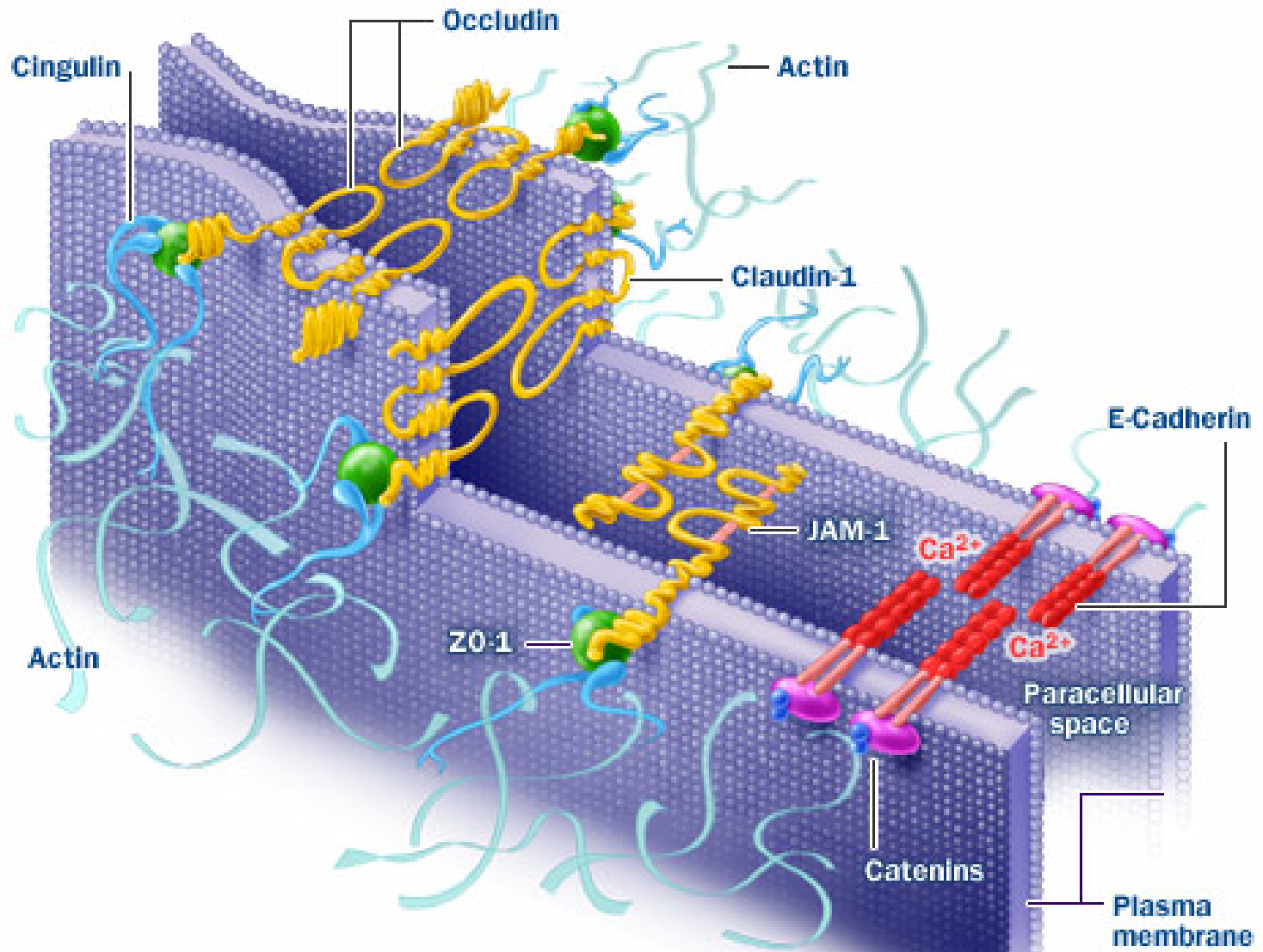
Osanai M, Nishikiori N, Murata M, Chiba H, Kojima T, Sawada N (2007) Cellular retinoic acid bioavailability determines epithelial integrity: role of retinoic acid receptor alpha agonists in colitis. *Mol. Pharmacol.* 71: 250-258.

“The epithelial barrier is determined primarily by intercellular tight junctions (TJs). We have demonstrated previously that all-trans retinoic acid (atRA) plays an important role in forming functional TJs through a specific retinoic acid receptor (RAR)/retinoid X receptor (RXR) heterodimer in epithelial cells..... Here, we show that several types of RA, including atRA, promote the barrier function of epithelial TJs. Conversely, RA depletion in the cells by overexpressing CYP26s, cytochrome P450 enzymes specifically involved in the metabolic inactivation of RAs, induces an increase of permeability as measured by two differently sized tracer molecules, inulin and mannitol. **This RA-mediated enhancement of barrier function is potentially associated with the increased expression of TJ-associated genes such as occludin, claudin-1, claudin-4, and zonula occludens-1.** We also found that RARalpha is a preferential regulator of the epithelial barrier in vitro. Studies of murine experimental colitis, which is characterized by increased gut permeability, reveal that **RARalpha stimulation significantly attenuates the loss of the epithelial barrier during colitis in vivo.** Our results suggest that cellular RA bioavailability determines the epithelial integrity, because it is a critical regulator for barrier protection during mucosal injuries.”



## Structure of Tight Junctions

[www.nastech.com/nastech/junctions\\_biology](http://www.nastech.com/nastech/junctions_biology)



Hadj-Rabia S, Baala L, Vabres P, Hamel-Teillac D, Jacquemin E, Fabre M, Lyonnet S, De Prost Y, Munnich A, Hadchouel M, Smahi A (2004) Claudin-1 gene mutations in neonatal sclerosing cholangitis associated with ichthyosis: a tight junction disease. *Gastroenterology* 127: 1386-1390.

Gene Symbol: CLAUDIN 1; CLDN1

OMIM# 603718

Location: 3q28-q29

Disease: NEONATAL ICHTHYOSIS-SCLEROSING  
CHOLANGITIS SYNDROME

All-trans RA  
Omega-3 s  
Nicotine



Tight  
Junctions

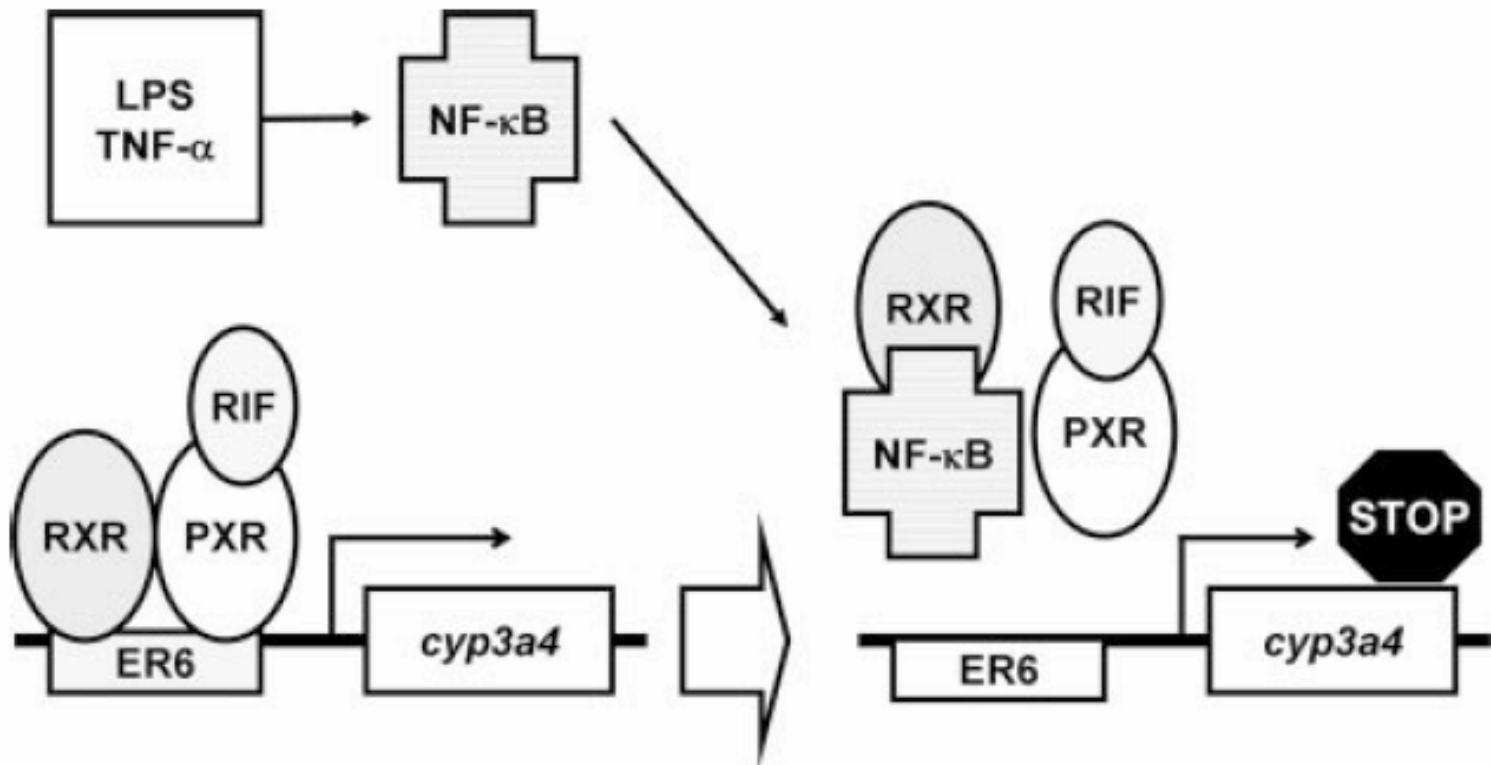


LPS  
TNF-alpha  
IL-17

Ghose R, Zimmerman TL, Thevananther S, Karpen SJ (2004) Endotoxin leads to rapid subcellular re-localization of hepatic RXRalpha: a novel mechanism for reduced hepatic gene expression in inflammation. Nucl. Recept. 2: 4.

Lipopolysaccharide (LPS) treatment of animals down-regulates the expression of hepatic genes involved in a broad variety of physiological processes, collectively known as the negative hepatic acute phase response (APR). **Retinoid X receptor alpha (RXRalpha), the most highly expressed RXR isoform in liver, plays a central role in regulating bile acid, cholesterol, fatty acid, steroid and xenobiotic metabolism and homeostasis.** Many of the genes regulated by RXRalpha are repressed during the negative hepatic APR, although the underlying mechanism is not known.

The subcellular localization of native RXRalpha rapidly changes in response to LPS administration, correlating with induction of cell signaling pathways, providing a novel and broad-ranging molecular mechanism for the suppression of RXRalpha-regulated genes in hepatic inflammation.

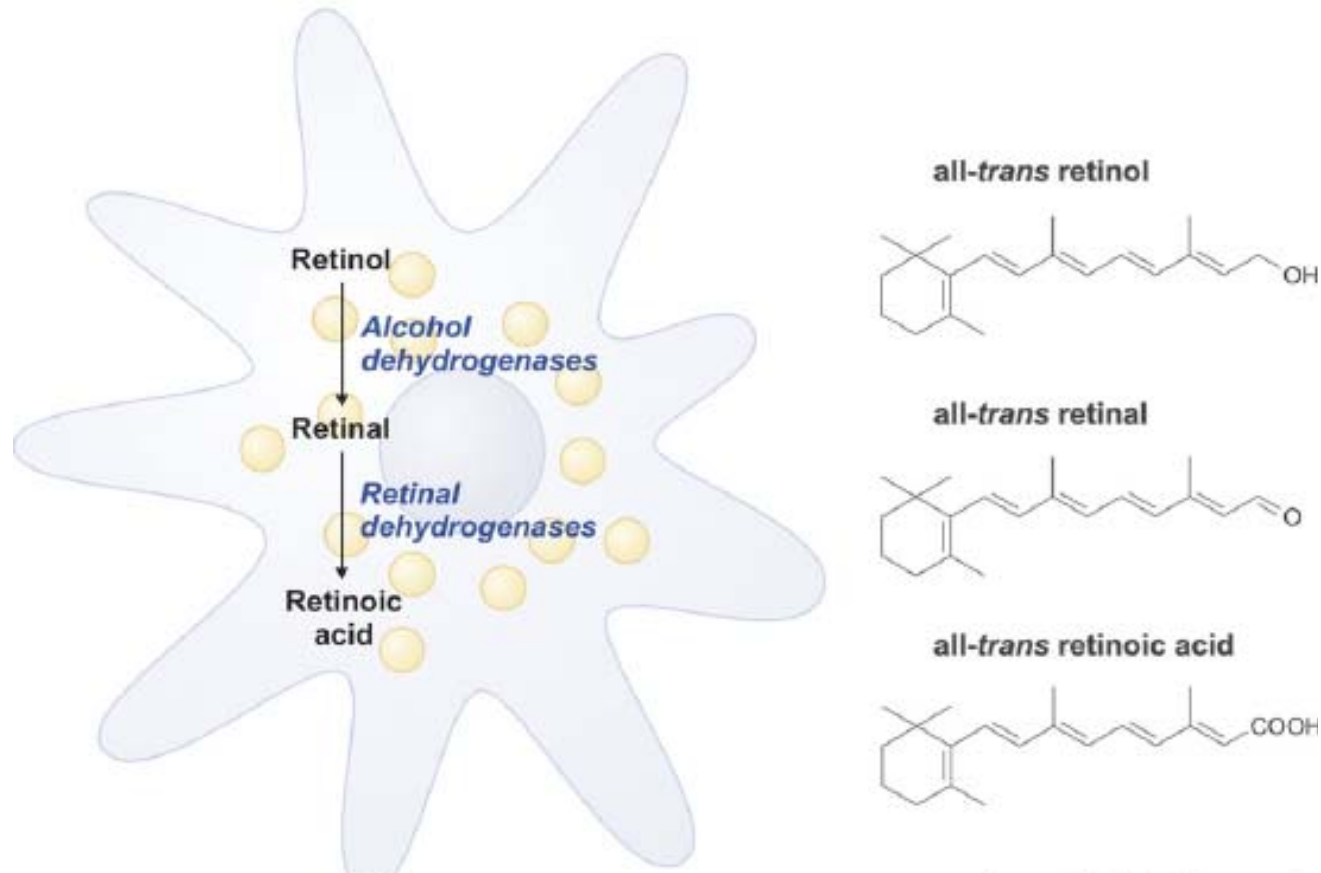


Schematic illustration of the suppression of CYP3A4 gene expression by NF-κB. (From: Gu X, Ke S, Liu D, Sheng T, Thomas PE, Rabson AB, Gallo MA, Xie W, Tian Y 2006 Role of NF-kappaB in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. J. Biol. Chem. 281: 17882- 17889).

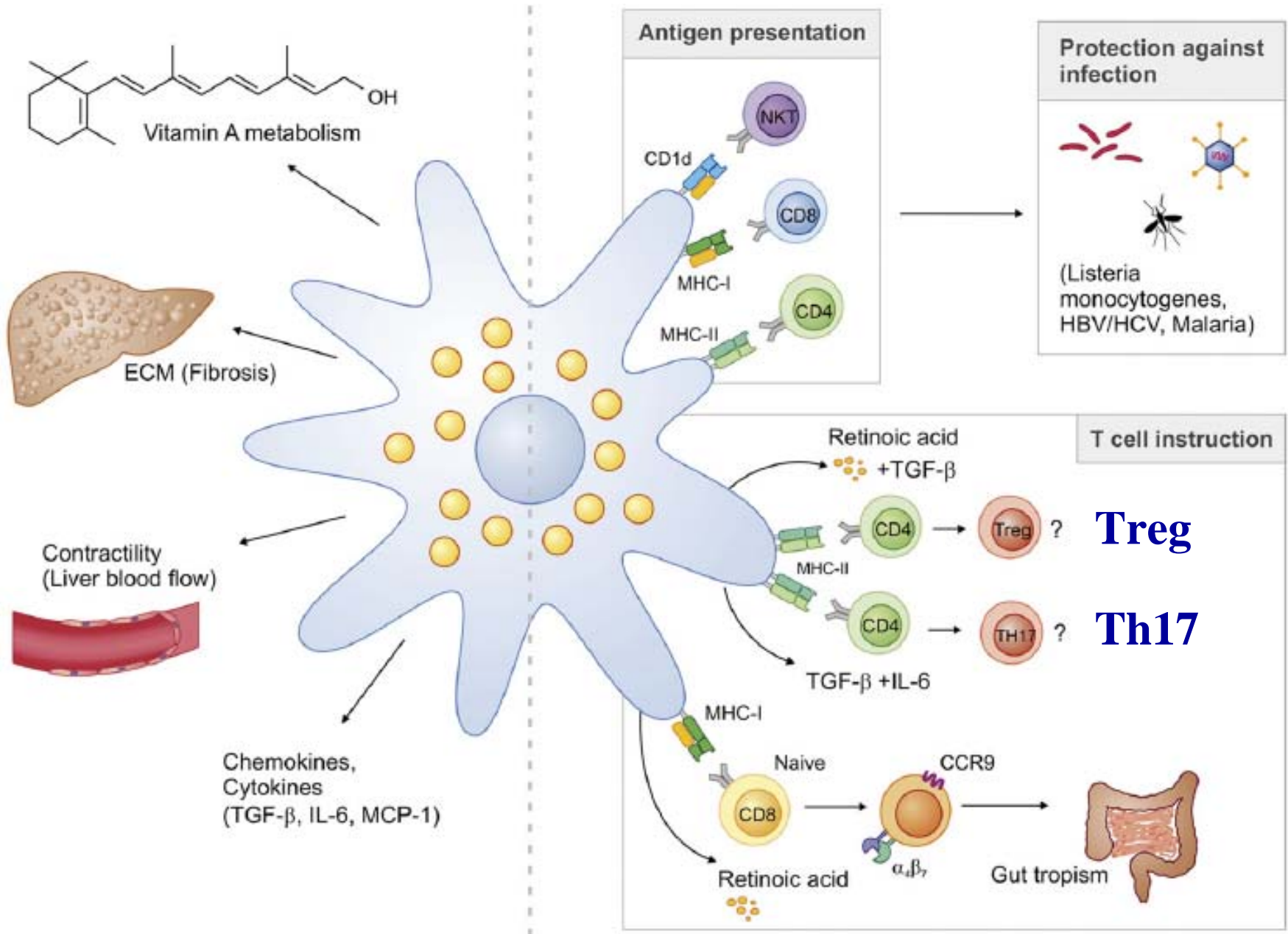
Upon activation of NF-κB by TNF-α or LPS, NF-κB p65 translocates into the nucleus and disrupts the binding of the PXR-RXRα heterodimer to its regulatory sites by interacting with RXRα, which is the obligate partner of PXR, thereby suppressing *cyp3a4* expression. RIF = rifampin.



Winau F, Quack C, Darmoise A, Kaufmann SH (2008) Starring stellate cells in liver immunology. *Curr. Opin. Immunol.* 20: 68-74.



## Vitamin A metabolism in hepatic stellate cells



**Diverse functions of hepatic stellate cells (Winau et al (2008))**

**Various insults to the liver (excessive alcohol consumption, infection, lipopolysaccharide treatment) will “activate” hepatic stellate cells. The activated hepatic stellate cells release their vitamin A stores, and they then differentiate to myofibroblasts and start producing a large amount of collagen (fibrosis).**

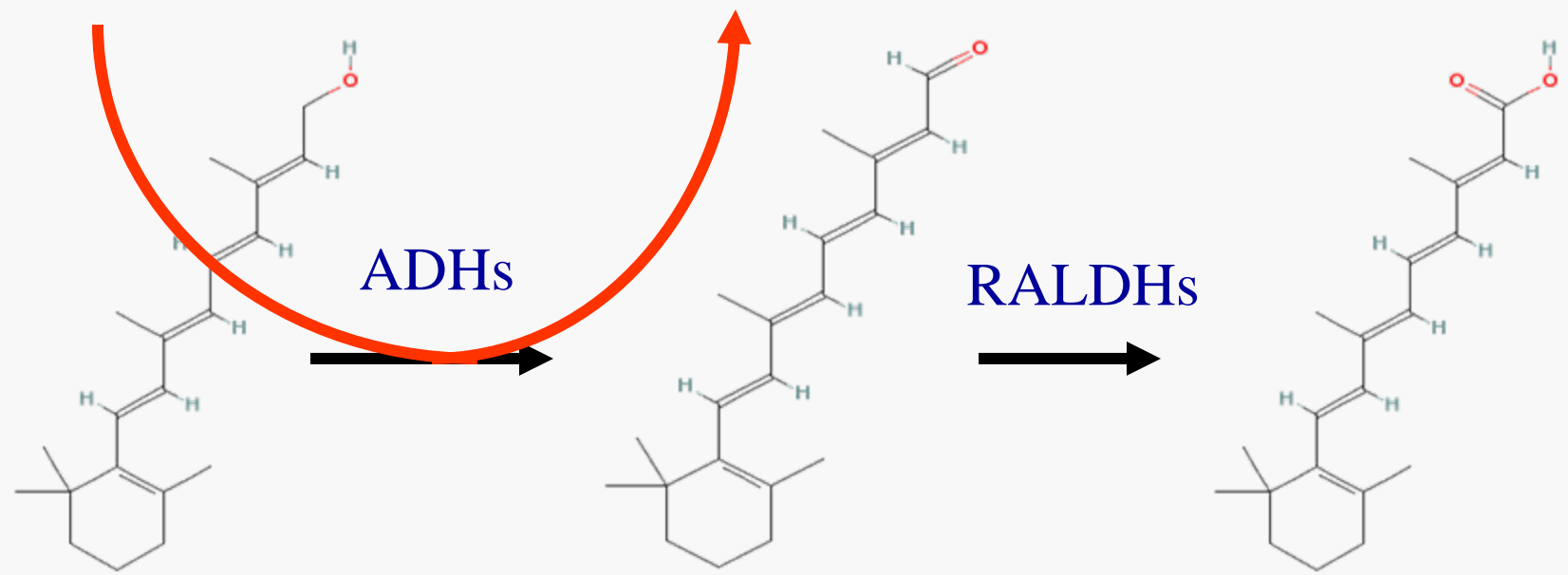
**Recent studies show that hepatic stellate cells can be coaxed into taking up a collagen synthesis inhibitor (using vitamin A-coupled liposomes), thereby reversing cirrhosis in a rat model.**

Sato Y, Murase K, Kato J, Kobune M, Sato T, Kawano Y, Takimoto R, Takada K, Miyanishi K, Matsunaga T, Takayama T, Niitsu Y (2008) Resolution of liver cirrhosis using vitamin A-coupled liposomes to deliver siRNA against a collagen-specific chaperone. *Nat. Biotechnol.* 26: 431-442.

Ethanol is toxic in part because it is metabolized to acetaldehyde, but also because it competes with retinol, diminishing retinaldehyde and retinoic acid synthesis. Retinol is metabolized to retinaldehyde by alcohol dehydrogenases (ADHs) in hepatic stellate cells.

**Ethanol**

**Acetaldehyde**

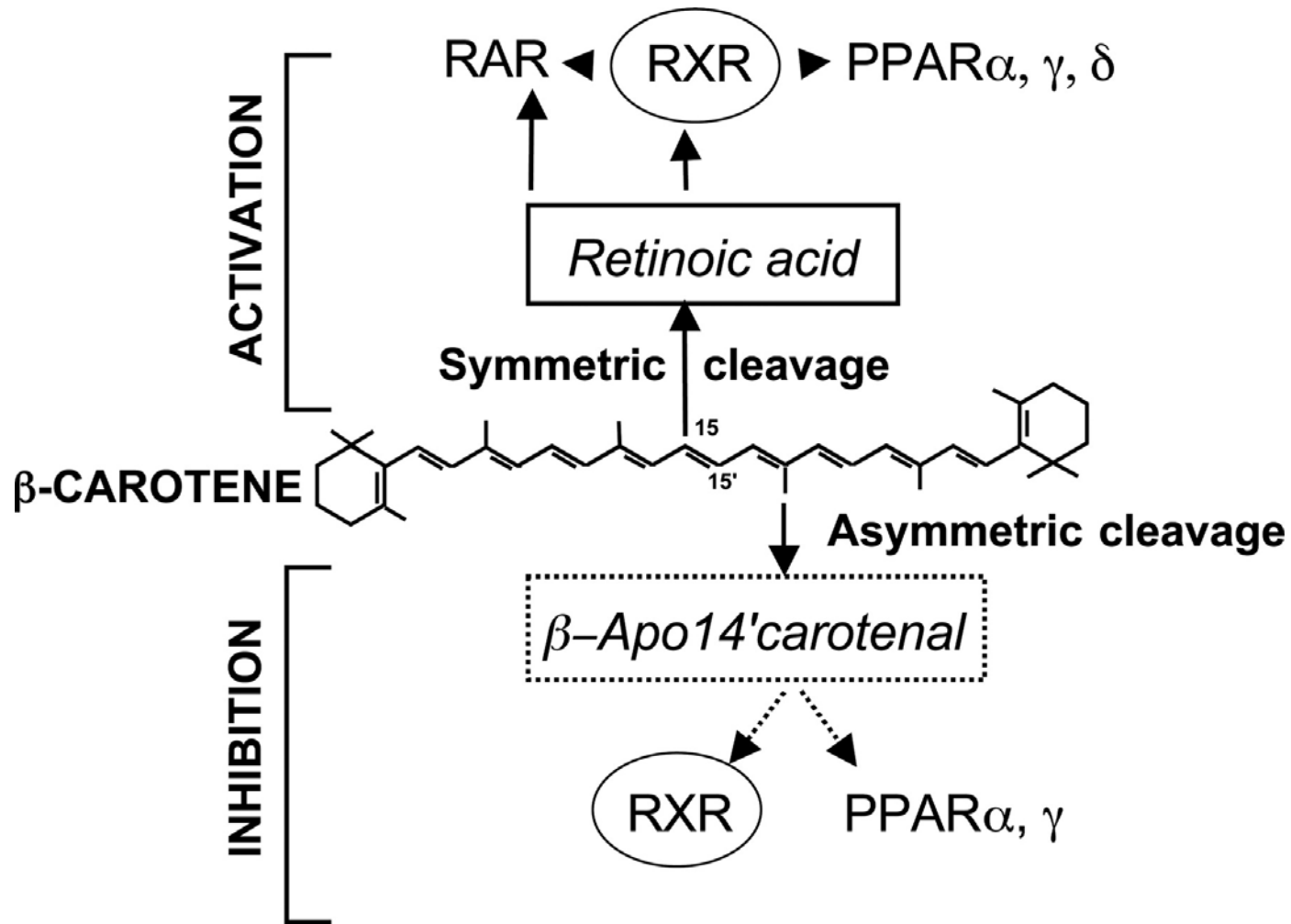


Retinol  
(vitamin A)

Retinaldehyde

Retinoic acid  
(all-trans RA)

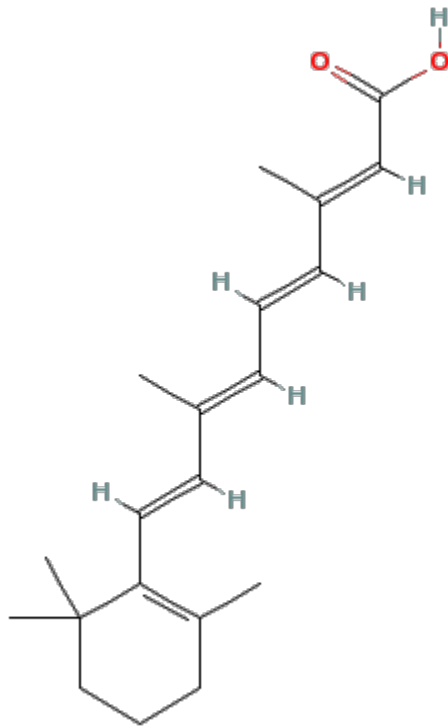
# Could asymmetric cleavage of beta-carotene produce product(s) that inhibit hepatic bile acid and lipid metabolism & transport?



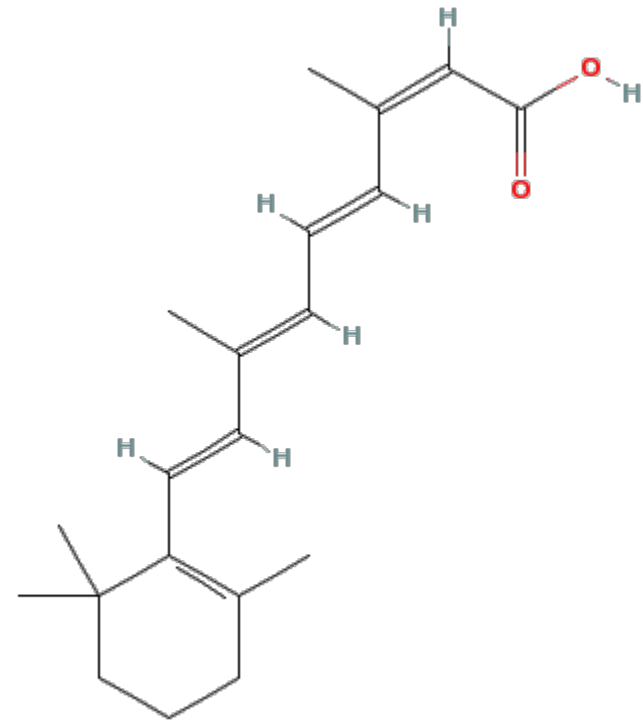
Ziouzenkova O, Orashanu G, Sukhova G, Lau E, Berger JP, Tang G, Krinsky NI, Dolnikowski GG, Plutzky J (2007) Asymmetric cleavage of beta-carotene yields a transcriptional repressor of RXR and PPAR responses. Mol. Endocrinol. 21: 77-88.

Reddy D, Siegel CA, Sands BE, Kane S (2006) Possible association between isotretinoin and inflammatory bowel disease. Am. J. Gastroenterol. 101: 1569-1573.

**“In a subgroup of patients, isotretinoin might serve as a trigger for IBD.”**



Retinoic acid  
(all-trans RA)



Isotretinoin (Accutane)  
(13-cis retinoic acid)

Gallego O, Ruiz FX, Ardevol A, Dominguez M, Alvarez R, de Lera AR, Rovira C, Farres J, Fita I, Pares X (2007) Structural basis for the high all-trans-retinaldehyde reductase activity of the tumor marker AKR1B10. Proc. Natl. Acad. Sci. U.S.A. 104: 20764-20769.

**Up-regulation of AKR1B10, resulting in retinoic acid depletion, may lead to cancer cell proliferation.**

