commentary

Bringing retinoid metabolism into the 21st century[1]

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The requirement of vitamin A (retinoids) for normal growth has been recognized for almost a century (1, 2). It plays an important role in a number of physiological processes including vision, cell differentiation, reproduction, and immunity. Vitamin A is a fat-soluble organic compound that cannot be synthesized endogenously by humans and thus, it is an essential nutrient. The main sources of vitamin A in the diet are provitamin A carotenoids from vegetables and retinyl esters from animal tissues [mainly the liver (3)]. All of the retinyl esters are enzymatically converted to retinol in the intestinal lumen before absorption by intestinal enterocytes (see **Fig. 1**). Subsequently, retinol is esterified with long-chain fatty acids to form retinyl esters, which are then incorporated into chylomicrons.

Chylomicrons are secreted into intestinal lymph and then move into the blood. Triglycerides in chylomicrons are extrahepatically hydrolyzed by LPL and fatty acids are taken up by muscle and adipose tissues (4). Cholesteryl esters and retinyl esters in chylomicron-remnants are simultaneously taken up by the liver parenchymal cells [hepatocytes (5)] through the remnant receptor, of which the molecular structure is still under active discussion (6, 7). Intracellularly, both cholesteryl esters and retinyl esters are hydrolyzed either at the plasma membrane or in early endosomes (5).

The majority of the formed cholesterol appears in the bile, mainly as bile acids (5), whereas the retinol is associated with retinol-binding protein 4 for secretion from the cells. Most of the retinol that is derived from chylomicron retinyl esters is transferred from hepatocytes to hepatic perisinusoidal stellate cells [fat-storing cells, Ito cells (3)]. In animals, about 50 to 80% of the total body Vitamin A is stored in liver stellate cells as retinyl esters (3).

The outline of the mechanism of absorption, transport, and cellular fate of retinyl esters has been intensively studied in the 1980s and 1990s of the 20th century with mostly rats as experimental animals. In this issue, Schreiber et al. (8) revitalize this field by an attempt to characterize the enzyme(s) responsible for the hydrolysis of retinoids in the liver. It is no surprise that from the 47 references in this paper, there are no citations of publications in the last 4 years and only four citations to relevant publications in the 21st century (see **Fig. 2**). Actually, only the group of Blaner et al. (9, 10) from Columbia University brought transgenic mouse studies into this field. Historically, the Department of Medicine at the College of Physicians and Surgeons, Columbia University, headed by DeWitt S. Goodman, played a major role in establishing the pathway of vitamin A metabolism (11). This work was often accomplished in collaboration with outside laboratories (12–15), including such illustrious coworkers as O. Stein, Y. Stein, N. Fidge, K. Norum, and D. Steinberg, and developed classic technologies like thin-layer chromatography of sterols and steroids (16).

In work reported in this issue, the group of Rudi Zechner (8) report important new information on the mechanisms by which retinyl esters are hydrolyzed in the liver. They cloned 12 separate carboxyl esterases into a mammalian expression vector and expressed these recombinant His-tagged proteins in COS-7 cells. Using retinyl palmitate emulsified with cholate as substrate, they showed that esterase 22 was the most likely candidate responsible for physiological hydrolytic activity. It appears that esterase 22 specifically hydrolyzes retinyl esters and that esterase 22 overexpression attenuates accumulation of retinol esters in COS-7 cells.

Esterase 22 can form a complex with β-glucuronidase and the β-glucuronidase exhibits hydrolyzing activity toward retinoyl β-glucuronide, a naturally occurring metabolite of vitamin A. These data make it likely that esterase 22 and β-glucuronidase act in concert in mobilizing retinol from retinol esters and retinoyl β-glucuronide. Both of these enzymes colocalize in the endoplasmic reticulum in hepatocytes.

Although the present publication does not provide definitive proof for the exclusive role of esterase 22 and β-glucuronidase in hydrolyzing retinoids in mouse liver, it does bring up-to-date 21st century technology into the field of retinoid metabolism. Recently, the group of Zechner has provided definitive proof for the role of adipose triglyceride lipase in lipolysis and energy metabolism (17,

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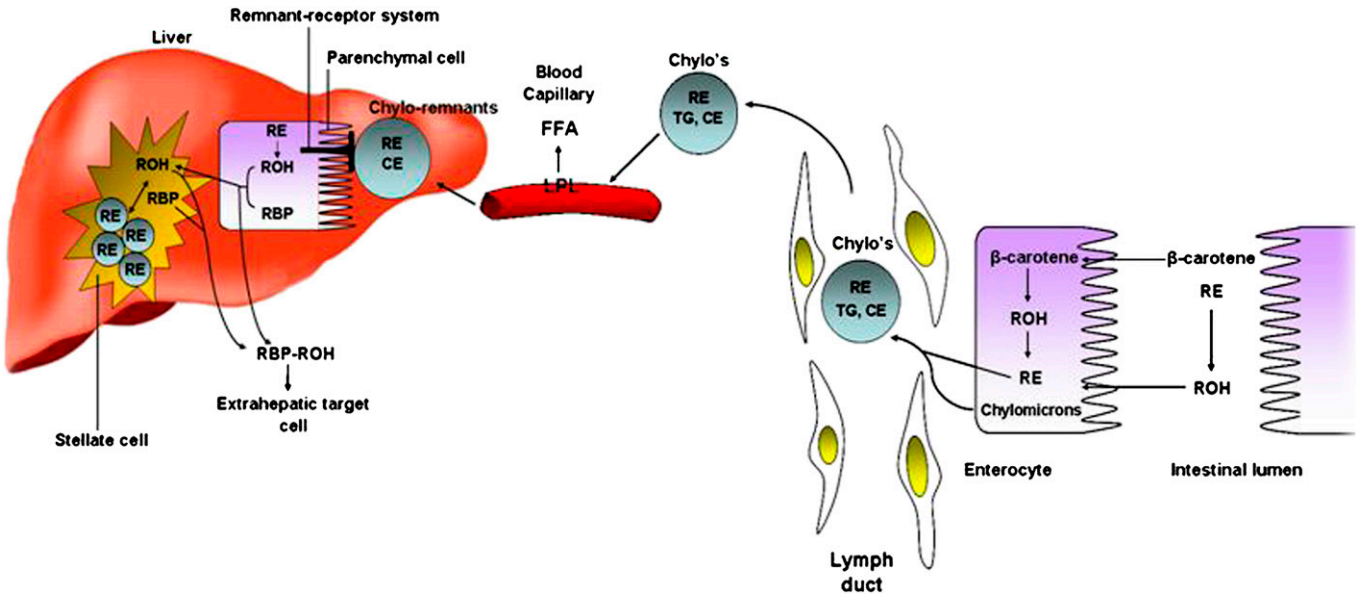

Fig. 1. Retinoid transport in the body. See first three paragraphs for explanation. RE, retinol ester; ROH, retinol; TG, triglycerides; CE, cholesterol ester; LPL, lipoprotein lipase; RBP, retinol binding protein.

18). Haemmerle et al. (17) used genetic inactivation of adipose triglyceride lipase to prove the crucial and rate-limiting role of this enzyme in the catabolism of cellular fat depots and energy homeostasis. It can be anticipated that a similar approach will be used to provide more definitive data on the role of esterase 22 and β-glucuronidase in retinoid metabolism and the present manuscript thus forms an important first step in defining this pathway.

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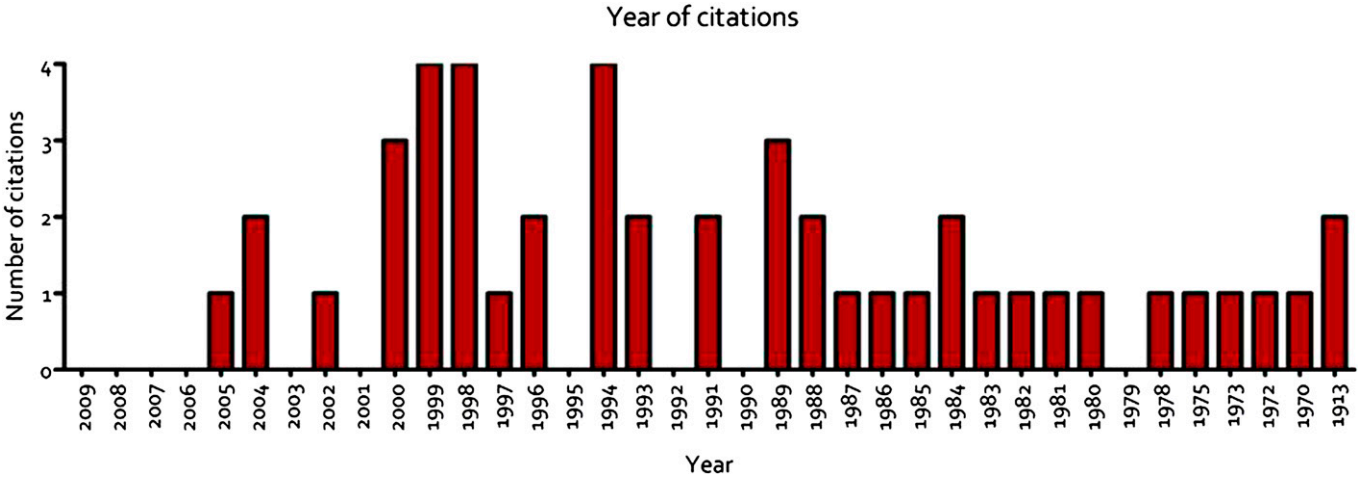

Fig. 2. Number of citations per year in the article of Schreiber et al. (8)

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