commentary

# Acyl-CoA wax alcohol acyltransferase 2: its regulation and actions in support of color vision[1]

**William S. Blaner, *Editorial Board*[2]**

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The enzyme acyl-CoA wax alcohol acyltransferase 2 (AWAT2), which is also commonly referred to as multifunctional *O*-acyltransferase (MFAT), was first identified more than a decade ago by several groups as an enzyme responsible for wax monoester biosynthesis in the skin (1–3). These early investigations established that AWAT2 is highly expressed in both human and rodent skin, primarily in mature sebocytes of the sebaceous gland (4). Although AWAT2 was reported to be expressed predominantly in skin, low levels of expression were also reported for human testis, lung, brain, and adipose tissue suggesting a broad role of this enzyme in the body (3). Substrate specificity studies by Yen et al. (3), employing recombinant human AWAT2, established that AWAT2 can catalyze esterification reactions that use monoacylglycerols, long-chain alcohols, and all-*trans*-retinol as acyl acceptors, respectively, resulting in the synthesis of diacylglycerols, wax monoesters, and all-*trans*-retinyl esters. This work convincingly established that human AWAT2 possessed an acyl-CoA:retinol acyltransferase (ARAT) activity that converts retinol to retinyl ester. Yen et al. (3) did not provide insight into whether the ARAT activity of AWAT2 had a physiologically significant role in the body in mediating the known metabolism or actions of retinoids (vitamin A, its metabolites and synthetic analogs). However, this insight was provided a few years later by Kaylor et al. (5), who compellingly demonstrated that AWAT2 has a role in catalyzing 11-*cis*-specific retinyl ester synthesis in retinal Müller cells. These authors showed that the ARAT activity of AWAT2 helped sustain cone (color) vision in daylight by driving production of 11-*cis*-retinoids utilized for the synthesis of visual chromophore within cone photoreceptors. The findings of Golczak and colleagues (6) that are published in this issue of the *Journal of Lipid Research* provide biochemical understanding of how an enzyme like AWAT2, which has a broad substrate specificity, acquires stronger specificity directed toward a retinoid substrate. The authors of this present work provide evidence for allosteric modulation of the ARAT activity of AWAT2 that occurs upon binding to 11-*cis*-retinoids that then preferentially drives AWAT2 catalyzed synthesis of 11-*cis*-retinyl esters.

The studies being reported by Golczak et al. (6) considerably extend biochemical understanding of what has been referred to as the cone-specific retinoid (visual) cycle [*see* **Fig. 1** and (7)]. The cone-specific retinoid cycle is distinct, both with regards to its cellular location and its metabolic steps, from the rod-specific retinoid cycle that was first elucidated through the Nobel Prize-winning work of George Wald (8). The cone-specific cycle involves metabolic interactions between cone and Müller cells in the retina; unlike the rod-specific cycle, which involves interactions between rod and retinal pigmented epithelial (RPE) cells (7). In the cone-specific cycle, all-*trans*-retinol is thought to undergo enzyme-catalyzed isomerization to 11-*cis*-retinol in the Müller cells via the actions of dihydroceramide desaturase-1 (DES-1) (9). This 11-*cis*-retinol can be transferred to cones where it is oxidized to 11-*cis*-retinaldehyde, which then complexes with one of several cone visual opsins forming the cone visual pigments (10). Alternatively, the 11-*cis*-retinol can undergo AWAT2 catalyzed esterification to 11-*cis*-retinyl ester, which is stored in the Müller cells (5, 7). This is mechanistically different from the rod-specific cycle where lecithin:retinol acyltransferase (LRAT), located within the RPE cells, catalyzes the formation of all-*trans*-retinyl esters (7). These all-*trans*-retinyl esters are either stored in the RPE or converted to 11-*cis*-retinol through the actions of the isomerohydrolase RPE65 (7). This metabolic distinction is functionally significant for color vision. Because cones both dark-adapt faster than rods and can operate in bright light without saturating, this suggests that the rate of visual chromophore delivery to cones is necessarily much greater than that to rods (7). This further suggests that within Müller cells there must exist a mechanism allowing for the accumulation of 11-*cis*-retinoids during dark adaptation and the rapid mobilization of 11-*cis*-retinoids to cones upon exposure to bright light. The new data reported by Golczak and colleagues (6) provide a basis for understanding how 11-*cis*-retinol present in Müller cells becomes alternatively shunted toward retinyl ester formation or transferred immediately to cones to support color vision.

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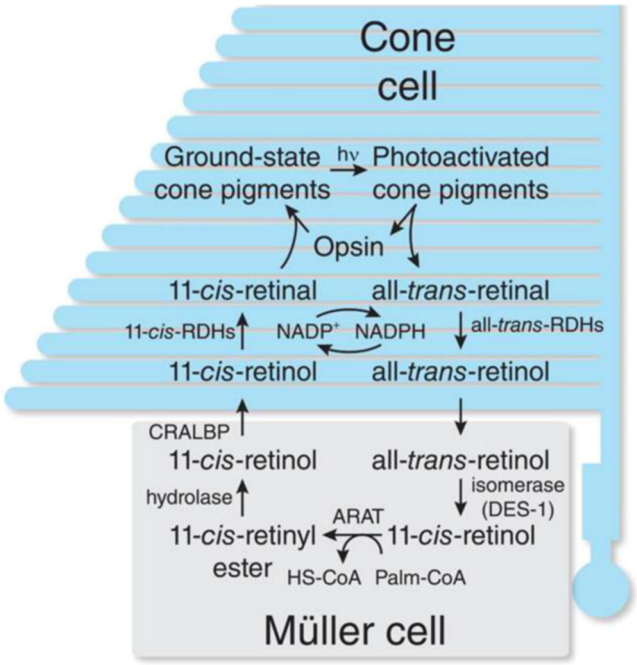


**Fig. 1.** Depiction of the cone-specific retinoid (visual) cycle as it is presently understood. The pathway involves the actions of enzymes and other proteins present in Müller cells and cone photoreceptors within the retina. The metabolic role and location of AWAT2 in this pathway is designated with the label "ARAT". All-*trans*-retinol within the Müller cells is thought to undergo enzyme-catalyzed isomerization to 11-*cis*-retinol through the actions of dihydroceramide desaturase-1 (DES-1). 11-C*is*-retinol after its translocation to the cone photoreceptors undergoes oxidation catalyzed by an 11-*cis*-retinol retinol dehydrogenase (11-*cis*-RDH) forming 11-*cis*-retinaldehyde, which binds to cone opsins forming visual pigment. The figure was taken directly from Reference 7.

Golczak and colleagues (6) propose that the binding of 11-*cis*-retinoids to AWAT2 in Müller cells causes a ligand-induced structural change that makes the enzyme more efficient in catalyzing 11-*cis*-retinol esterification. This increased efficiency is specific for 11-*cis*-retinol esterification, at the expense of the 9-*cis*, 13-*cis*-, and all-*trans*-retinol isomers that may be present in the cell, thus driving 11-*cis*-retinyl ester accumulation and flux. This is important because visual pigment regeneration in cones relies on the accumulation of 11-*cis*-retinyl esters facilitated by AWAT2. Moreover, these findings provide a basis for understanding how an enzyme like AWAT2, one which has a broad substrate specificity and is broadly expressed in many tissues, can play a key role in the cone-specific visual cycle that is localized specifically to the retina. It would appear based on this work that in tissues lacking 11-*cis*-retinol, the function of AWAT2 would reflect its catalytic activity toward long chain alcohols or mono- and diacylglycerols (6). Because 11-*cis*-retinoids are found only in ocular tissue, one would surmise that the ARAT activity of AWAT2 is physiologically significant solely in this tissue. However, given the high level of AWAT2 expression in skin and the importance of retinoids for maintaining the health of skin (11), this speculation will need to be experimentally verified if one is to preclude a role for AWAT2 in retinoid biology in skin or other tissues.

AWAT2 is one of three enzymes that are known to be important in vivo for catalyzing retinyl ester formation. Owing to the work of Golczak and colleagues (6), there is now molecular understanding of mechanisms that modulate the ARAT activity of this relatively nonspecific enzyme. Diacylglycerol acyl-CoA acyltransferase 1 (DGAT1), which plays a central role in catalyzing triglyceride formation, is also known to possess an ARAT activity. Based on in vivo studies, DGAT1 is proposed to play a role in retinyl ester formation in the skin and intestine but not in other tissues (12, 13). Although DGAT1 is widely expressed in many tissues; i.e., in the liver where relatively high levels of retinyl esters are found, there is no evidence that DGAT1 plays a role in catalyzing retinyl ester formation in these tissues. This observation has been puzzling. Possibly, DGAT1 substrate specificity is in some way affected by allosteric modifiers like the situation reported by the Golczak group for AWAT2. LRAT, the third enzyme in the body that catalyzes retinyl ester formation, accounts for most retinol esterification in the body, including in the RPE, liver, intestine, lung, and in most other tissues (14). Unlike AWAT2 and DGAT1, there is no biochemical or in vivo evidence that LRAT catalyzes any reaction other than the esterification of retinoids.

What needs to be learned regarding AWAT2 and its actions to extend the findings of Golczak and colleagues now being published in the *JLR*? One obvious biochemical question raised by this work is whether the other known AWAT2 substrates, monoacylglycerols and long-chain alcohols, may have similar allosteric effects on AWAT2 directing enzymatic activity toward these lipids. In order to gain a better understanding of AWAT2 and its role in the cone-specific visual cycle, it will be necessary to determine at the molecular level the identity of the hydrolase within Müller cells that cleaves 11-*cis*-retinyl esters, allowing for the mass action driven movement of 11-*cis*-retinol to cone cells. Are AWAT2 and this hydrolase coordinately regulated and, if so, how? Finally, it will be necessary to gain a better understanding of the global actions of AWAT2 within the body, including its role in mono- and diacylglycerol synthesis and in wax ester synthesis. This would best be undertaken through genetic manipulation of AWAT2 expression in the entire body and in specific tissues. A genetic approach will likely provide the ultimate validation of the biochemical findings reported by Golczak and colleagues (6).

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