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Editorial

# The retinoid cycle and retina disease

Rhodopsin, the best studied G protein-coupled receptor, occupies center stage between two physiological pathways: phototransduction/recovery from bleaching (return of activated components to the dark state) and the retinoid cycle (production of 11-*cis*-retinal) (see Fig. 1). The retinoid cycle has recently gained much attention owing to the fact that multiple genes encoding components with prominent roles in this cycle have been identified, cloned and linked to retina diseases. The intent of the meeting in Ft. Lauderdale (Florida), May 2–3, 2003, was to present a broad overview on the biochemical mechanisms of visual pigment bleaching in light, chromophore recycling, and visual pigment regeneration in the dark. Emphasis was also directed toward retina diseases arising from defects in genes encoding components of the retinoid cycle. These events were thoroughly discussed in eight sessions (see http://www.visres-interactivemeeting.com/oral.htm) before an audience of over 200 students, researchers and clinicians.

Vertebrate phototransduction is initiated by a photochemical reaction whereby 11-*cis*-retinal bound to its opsin moiety (rhodopsin = opsin + 11-*cis*-retinal) undergoes isomerization to all-*trans*-retinal producing conformation changes in opsin. The initial events of rhodopsin isomerization, researched intensively for many decades, are the focus of several contributions in this Special Issue (e.g., Janz and Farrens, Pepperberg, Ramon et al.). In vertebrates, restoration of a photosensitive receptor conformation (return to the dark state) requires the formation of 11-*cis*-retinal from all-*trans*-retinal via the retinoid cycle. The entire cycle of isomerization and pigment regeneration in humans occurs on a time scale of minutes for rhodopsin, and significantly faster for cone pigments. Reduction of all-*trans*-retinal to all-*trans*-retinol takes place in photoreceptor outer segments whereas all other reactions, including isomerization, occur within retinal pigment epithelial cells (RPE) (shown schematically in Fig. 2). The all-*trans*-retinylidene Schiff base hydrolyzes and all-*trans*-retinal dissociates from the binding pocket of opsin, yet the molecular steps leading to its release from the opsin-binding pocket remain not fully explained. Removal of all-*trans*-retinal from the disks may be facilitated by an ATP-binding cassette transporter (ABCR), mutations in which are causative of an array of retina diseases including Stargardt's disease, retinitis pigmentosa and possibly macular degeneration.

Further, all-*trans*-retinal is reduced to all-*trans*-retinol by NADPH-dependent all-*trans*-retinol dehydrogenase, a membrane-associated enzyme that belongs to large gene family of short-chain alcohol dehydrogenases (SCAD). all-*trans*-Retinol translocates to the RPE via a poorly defined process, perhaps involving components like IRBP and RBP present in the interphotoreceptor matrix (IPM), or passive diffusion driven by trapping retinoids (e.g., insoluble fatty acid retinyl esters) in RPE. Interphotoreceptor (interstitial) retinoid-binding protein (IRBP), an extracellular protein residing in the IPM is the subject of two contributions in this issue (Gonzales-Fernandez, Semenova and Converse). Esterification in the RPE involves the transfer of an acyl group from lecithin to retinol and is catalyzed by lecithin:retinol acyltransferase (LRAT). These esters may be substrates for an as yet unknown enzyme termed isomerohydrolase, which would use the energy of retinyl ester hydrolysis to isomerase all-*trans*-retinol to 11-*cis*-retinol and thus, drive the reaction forward. Alternatively, these two reactions may proceed separately, i.e., the ester may be first hydrolyzed by a retinyl ester hydrolase and then isomerized to 11-*cis*-retinol through a carbocation intermediate. 11-*cis*-Retinol would then be oxidized to 11-*cis*-retinal in a reaction catalyzed by NAD- and NADP-dependent 11-*cis*-retinol dehydrogenases, which are other short chain dehydrogenase family members. One of these, 11-*cis*-RDH, has been thoroughly characterized and its mutant forms are associated with the human condition, *fundus albipunctatus*. Finally,

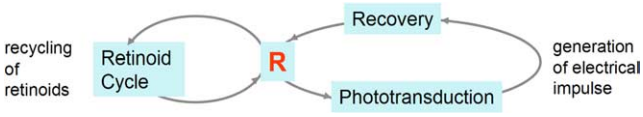


Fig. 1. Rhodopsin (R) is situated at the intersection of two major pathways, phototransduction/recovery and the retinoid cycle.

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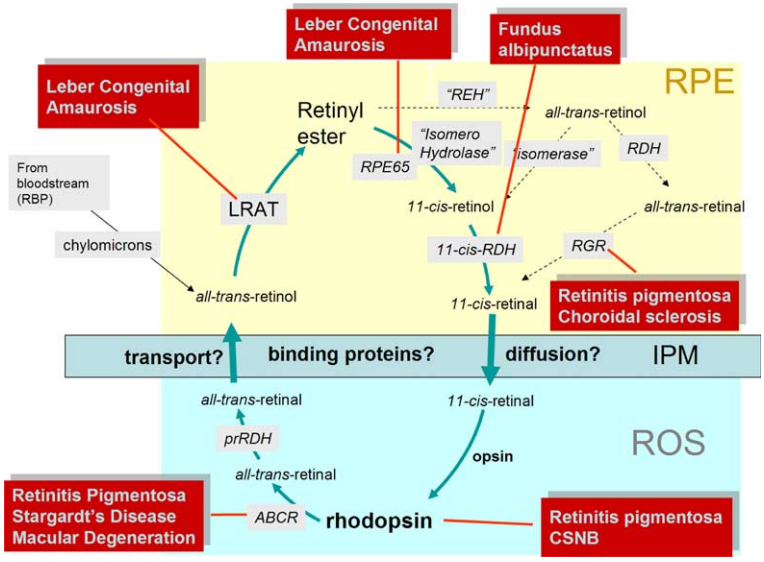


Fig. 2. Schematic diagram of the retinoid cycle. All-*trans*-retinol (Vitamin A) is taken up by the RPE from the bloodstream, converted to retinyl ester by LRAT and stored. Rhodopsin receives its supply of 11-*cis*-retinal from the RPE, and the isomerized chromophore, all-*trans*-retinal, is recycled along the pathway shown. Defects in genes encoding essential components of the retinoid cycle may lead to severe retinal dystrophies.

11-*cis*-retinal moves back to the rod photoreceptors, either in IRBP-dependent or -independent fashion, where it joins with opsin to regenerate visual pigment.

Importance of the visual cycle for sustaining vision derives from several retina diseases that have been linked to defects in visual cycle genes. Null alleles commonly lead to deficiency in visual pigment function and disruption of the retinoid cycle. An exception is a laboratory generated knockout of 11-*cis*-RDH in which another RDH isozyme appears to substitute for lost function.

We thank all speaker-contributors for their enthusiastic participation during the meeting, their timely submissions, and their patience during the process of manuscript revision. After months of preparation, the organizers were rewarded by a meeting of new and high quality presentations, stimulating and engaging discussions, a strong poster session and the introduction of numerous students to the field.

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