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Keeping an "eye" on the structure and role of visual cycle proteins

Opsins are ocular proteins in photoreceptors that transform light energy to initiate signals for vision. Each opsin contains an 11-*cis*-retinal chromophore which is converted into all-*trans*-retinal when activated by a photon. The all-*trans*-retinal must be recycled back into its 11-*cis* form before it can accept another signal. This recycling process is known as the visual cycle, of which there are two: classic and intraretinal.

The classic visual cycle takes place in two different types of cells, photoreceptors, which are rod or cone cells, and retinal pigment epithelium (RPE) cells. The all-*trans*-retinal from the photoreceptor's opsin is transferred to the RPE cells where it undergoes several chemical reactions until it is converted to 11-*cis*-retinal and returned to the photoreceptor. In the recently uncovered intraretinal visual cycle, only cone photoreceptors are involved, along with Müller glial cells. Instead of being converted back to the 11-*cis*-retinal form in Müller cells, it is returned as 11-*cis*-retinol to cone photoreceptors, which convert it to 11-*cis*-retinal with a dehydrogenase enzyme.

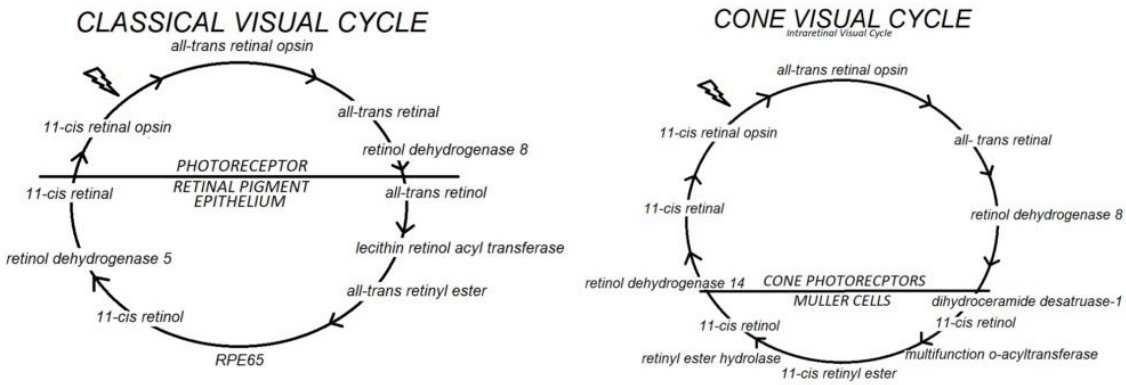

Fig. 1. Classic (rod and cone photoreceptor) and the cone (cone photoreceptor) visual cycles.

A well-studied protein of the classic visual cycle is RPE65, which is bound to endoplasmic reticulum in the retinal pigment epithelium. Studies have shown that RPE65 catalyzes the hydrolysis of all-*trans*-retinyl ester as well as the isomerization of all-*trans*-retinol to 11-*cis*-retinol. Mutations in this enzyme are linked to many retinal diseases.

Another important protein is interphotoreceptor retinoid binding protein (IRBP). IRBP protects all-*trans*– and 11-*cis*-retinol from photodegradation. It also plays a role in retinoid exchange between rods and RPE as a carrier protein. Recent studies have shown that IRBP may function in the intraretinal cycle as a protective protein for transfer of retinol and retinal between cones and Müller cells.

Chromosome	Mutations	Example of a disease with the mutated protein and gene mutation ID
1	28	Recessive Leber's congenital amaurosis; RPE65; candidate gene for LCA
2	22	Recessive retinitis pigmentosa; zinc finger protein; linkage mapping
3	17	Dominant retinitis pigmentosa; rhodopsin; linkage mapping
4	21	Recessive retinitis pigmentosa; LRAT; candidate gene
5	9	Dominant Wagner disease; versican; linkage mapping
6	20	Age-related macular degeneration; complement component 2; association study
7	9	Dominant tritanopia; blue cone opsin; candidate gene
8	12	Recessive Jobert syndrome; centrosome--spindle pole protein; whole-exome sequencing
9	11	Age-related macular degeneration; Toll-like receptor 4; link mapping; association study
10	22	Recessive retinitis pigmentosa; IRBP; homozygosity mapping; candidate gene
11	19	Recessive Usher syndrome; myosin VIIA; linkage mapping
12	13	Recessive fundus albipunctatus; RDH5; candidate gene
13	5	Somatic retinoblastoma; RB1; deletion mapping; candidate gene
14	13	Recessive Leber's congenital amaurosis; RDH 12; homozygosity mapping; linkage mapping
15	9	Recessive Usher syndrome; calcium- and integrin-binding protein; linkage mapping
16	16	Recessive Leber's congenital amaurosis; clusterin-associated protein 1; whole exome sequence
17	16	Dominant retinitis pigmentosa; carbonic anhydrase IV; linkage mapping
18	3	Recessive retinal dystrophy; α1-laminin; homozygosity mapping
19	10	Age-related macular degeneration; complement component 3; association study
20	8	Recessive retinitis pigmentosa; Kizuna centrosomal protein; whole-exome sequencing
21	2	Recessive cone-red dystrophy; chromosome 21 open reading frame 2; homozygosity Ma
22	5	Dominant Sorsby's fundus dystrophy; tissue inhibitor of MP3; linkage mapping
X	24	Protanopia; red cone opsin; candidate gene
Mitochondria	7	Leber's hereditary optic neuropathy; complex I, II or V; sequencing
Total	321	

Tab. 1. Genes and mapped loci causing retinal diseases
The data were accessed at https://sph.uth.edu/retnet/disease.htm on March 28, 2018. Please note that the JBC is not responsible for the long-term archiving and maintenance of this site or any other third party hosted site.

There are a number of diseases that result from genetic mutations in visual cycle proteins. One such disease, and the most common, is retinitis pigmentosa (RP). RP impacts rod photoreceptors first and then cones, so patients first experience vision difficulty in dim light and peripheral vision, and eventually most are unable to read.

Another genetic retinal disease is Leber's congenital amaurosis (LCA). Those with LCA have drastically reduced vision at birth, though their retinas appear normal in fundoscopic exams. By adolescence, the retinal arterioles are constricted, and pigment changes occur, making the condition more evident. The cause is unclear, but autosomal recessive mutations in RPE65 are attributed to approximately 6-16% of cases.

Stargardt disease (STGD) is the most common hereditary juvenile macular disease. In contrast with RP, STGD leads to loss of central vision and peripheral vision is retained. It is attributed to various recessive mutations of the ABCA4 gene that leads to an accumulation of all-*trans*-retinol.

Diabetic retinopathy (DR) is the leading cause of blindness in adults. It is a diabetic complication, which includes visual cycle proteins, that results from damage to retinal capillaries. The capillary damage can lead to proliferative DR and eventually retinal detachment and blindness.

Further research is necessary to discover novel mechanisms and to evaluate effective treatments to successfully treat for various eye disorders from visual cycle proteins. β-cyclodextrins are being tested to enhance photoreceptor survival in LCA or STGD and minocycline as an anti-inflammatory to counteract DR. In 2017, the FDA approved a gene therapy protocol that utilizes injection-based techniques to treat RPE65 conditions such as LCA, and there is research currently being conducted on rAAV vector possibilities to deliver human RPE65 cDNA. Stem cell therapy is also being explored. Researchers have successfully derived

functional RPE that can uptake all-*trans*-retinol and secrete 11-*cis*-retinal, opening the gate for transplantation research.

Current and future research on the role of visual cycle proteins is important to protect human vision and to prevent blindness.

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