The canonical retinoid cycle in rods (twilight vision)

Blaner, WS., Carleton, KL., D'Eustachio, P., Jassal, B., Schmidt, EE.
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 82

This document contains 2 pathways and 20 reactions (see Table of Contents)
The canonical retinoid cycle in rods (twilight vision)

Stable identifier: R-HSA-2453902

The retinoid cycle (also referred to as the visual cycle) is the process by which the visual chromophore 11-cis-retinal (11cRAL) is released from light-activated opsins in the form all-trans-retinal and isomerized back to its 11-cis isomer ready for another photoisomerization reaction. This process involves oxidation, reduction and isomerization reactions and take place in the retinal pigment epithelium (RPE) and photoreceptor segments of the eye (von Lintig 2012, Blomhoff & Blomhoff 2006, von Lintig et al. 2010, D’Ambrosio et al. 2011). This section describes the retinoid cycle in rods during dark/twilight conditions.

Literature references


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TTR:RBP:atROL binds to STRA6 receptor

Location: The canonical retinoid cycle in rods (twilight vision)

Stable identifier: R-HSA-2453876

Type: binding

Compartments: plasma membrane, extracellular region

All-trans-retinol (atROL) circulates in the bloodstream in complex with transthyretin (TTR) and retinol-binding protein 4 (RBP4). The receptor Stimulated by retinoic acid gene 6 protein homologue (STRA6) acts as a high-affinity cell-surface receptor for the complex (Berry et al. 2012), removing atROL and transporting it into tissues expressing STRA6, including the eyes (Kawaguchi et al. 2007).

Followed by: STRA6 transports atROL from extracellular region to cytosol

Literature references


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STRA6 transports atROL from extracellular region to cytosol

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2453863

**Type:** dissociation

**Compartments:** plasma membrane, extracellular region, cytosol

Stimulated by retinoic acid gene 6 protein homologue (STRA6) acts as a high-affinity cell-surface receptor for the TTR:RBP4:atROL complex (Berry et al. 2012). Once bound, STRA6 removes atROL and transports it into cells expressing STRA6 receptors, including eye (Kawaguchi et al. 2007). Defects in STRA6 cause microphthalmia syndromic type 9 (MCOPS9, Matthew-Wood syndrome or Spear syndrome; MIM:601186) (Chassaing et al. 2009). The uptake of atROL is driven by the conversion of atROL to retinyl ester (RE) by LRAT (Kawaguchi et al. 2011).

**Preceded by:** TTR:RBP:atROL binds to STRA6 receptor

**Followed by:** atROL binds RBP1 to form RBP1:atROL

**Literature references**


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atROL binds RBP1 to form RBP1:atROL

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-74843

**Type:** binding

**Compartments:** cytosol

Once all-trans-retinol (atROL) enters the retinal pigment epithelium (RPE) and before esterification takes place, atROL binds to cellular retinol-binding protein 1 (RBP1) (Folli et al. 2001). The resultant complex (RBP1:atROL) serves as a substrate for lecithin retinol acyltransferase (LRAT), the main enzyme responsible for the esterification of atROL.

**Preceded by:** RBP3 regulates the transport of atROL from ROS to RPE, STRA6 transports atROL from extracellular region to cytosol

**Followed by:** LRAT esterifies RBP1:atROL and FACYLs to atREs

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LRAT esterifies RBP1:atROL and FACYLs to atREs

Location: The canonical retinoid cycle in rods (twilight vision)

Stable identifier: R-HSA-2453855

Type: transition

Compartments: endoplasmic reticulum membrane, plasma membrane, lipid droplet, cytosol

Lecithin retinol acyltransferase (LRAT) mediates the esterification of all-trans-retinol (atROL) to form all-trans-retinyl esters (atREs). atREs are stored in lipid droplet form called retinosomes (Imanishi et al. 2004). Cellular retinol-binding protein 1 (RBP1) is an effective donor of atROL for LRAT (Ruiz et al. 1999). LRAT is an important enzyme required for the clearance of atROL as it drives the uptake of atROL from the bloodstream through the receptor STRA6 (Kawaguchi et al. 2011) and clearance of atROL from rod outer segments (ROS). In addition, the esterified form of atROL serves as substrate for RPE65.

Preceded by: atROL binds RBP1 to form RBP1:atROL

Followed by: RPE65 isomero-hydrolyses atREs to 11cROL

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https://reactome.org
All-trans-retinol esters (atREs) serve as substrates for retinoid isomerohydrolase (RPE65), located in retinal pigment epithelium (RPE) cells. RPE65 hydrolyses atREs to 11-cis-retinol (11cROL), thus performing an isomerase activity as well as hydrolysis. RPE65 is membrane-bound, this being dependent on the palmitylation of the residue Cys-112 (Takahashi et al. 2009). RPE65 normally undergoes a light-dependent translocation to become more concentrated in the central region of RPE cells. This translocation requires Unconventional myosin-VIIa (MYO7A or USH1B) (Lopes et al. 2011).

Preceded by: LRAT esterifies RBP1:atROL and FACYLs to atREs

Followed by: 11cROL binds to RLBP1 to form RLBP1:11cROL

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11cROL binds to RLBP1 to form RLBP1:11cROL

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2454264

**Type:** binding

**Compartments:** cytosol

Cellular retinaldehyde-binding protein (RLBP1, CRALBP) (Intres et al. 1994) is abundant in retinal pigment epithelium (RPE) and Muller cells of the retina where it plays a role in sequestering 11-cis retinoids produced during the retinoid cycle. The natural ligands are 11-cis-retinol (11cROL) and 11-cis-retinal (11cRAL) (Crabb et al. 1998).

**Preceded by:** RPE65 isomero-hydrolyses atREs to 11cROL

**Followed by:** RDH10,11 oxidise 11cROL to 11cRAL, RDH5 oxidises 11cROL to 11cRAL

**Literature references**


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RDH10,11 oxidise 11cROL to 11cRAL

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-74872

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, cytosol

Using NADP+ as cofactor, several members of the short-chain dehydrogenases/reductases (SDR) family can (reversibly) catalyse the oxidation of 11-cis-retinol (11cROL) to 11-cis-retinal (11cRAL) in retinal pigment epithelium (RPE) cells. Retinol dehydrogenases 10 and 11 (RDH10 and 11) are two such members utilizing the cofactor NADP+ (Wu et al. 2002, Kedishvili et al. 2002 respectively). Cellular retinaldehyde-binding protein (RLBP1), the protein bound to 11cRAL in RPE, is not present in photoreceptor cells.

**Preceded by:** 11cROL binds to RLBP1 to form RLBP1:11cROL

**Followed by:** RLBP1:11cRAL dissociates

**Literature references**


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https://reactome.org
RDH5 oxidises 11cROL to 11cRAL

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2454081

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, cytosol

Another member of the short-chain dehydrogenases/reductases (SDR) family, RDH5, can (reversibly) catalyse the oxidation of 11-cis-retinol (11cROL) to 11-cis-retinal (11cRAL) in retinal pigment epithelium (RPE) cells using NAD+ as cofactor (Simon et al. 1996, Gonzalez-Fernandez et al. 1999). Cellular retinaldehyde-binding protein (RLBP1), the protein bound to 11cRAL in RPE, is not present in photoreceptor cells.

**Preceded by:** 11cROL binds to RLBP1 to form RLBP1:11cROL

**Followed by:** RLBP1:11cRAL dissociates

**Literature references**


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[https://reactome.org](https://reactome.org)
Interphotoreceptor retinoid-binding protein (RBP3) is the major soluble protein in the interphotoreceptor matrix (IPM) (Liou et al. 1989, Fong & Bridges 1988). It is thought to shuttle 11-cis-retinal (11cRAL) between retinal pigment epithelium (RPE) and photoreceptor outer segments during the visual cycle but the mechanism is poorly understood (Gonzalez-Fernandez & Ghosh 2008). It is assumed cellular retinaldehyde-binding protein (RLBP1) must dissociate from 11cRAL before 11cRAL is transported as RLBP1 is not present in photoreceptor cells.

**Preceded by:** RDH10,11 oxidise 11cROL to 11cRAL, RDH5 oxidises 11cROL to 11cRAL

**Followed by:** RBP3 transports 11cRAL to rod photoreceptor outer segment

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RBP3 transports 11cRAL to rod photoreceptor outer segment

Location: The canonical retinoid cycle in rods (twilight vision)

Stable identifier: R-HSA-2454113

Type: uncertain

Compartments: extracellular region, cytosol

Interphotoreceptor retinoid-binding protein (RBP3) is the major soluble protein in the interphotoreceptor matrix (IPM) (Liou et al. 1989, Fong & Bridges 1988). It is thought to shuttle 11-cis-retinal (11cRAL) between retinal pigment epithelium (RPE) and photoreceptor outer segments during the visual cycle but the mechanism is poorly understood (Gonzalez-Fernandez & Ghosh 2008).

Preceded by: RLBP1:11cRAL dissociates

Followed by: 11cRAL binds to opsin to form 11c-retinyl:RHO

Literature references


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11cRAL binds to opsin to form 11c-retinyl:RHO

Location: The canonical retinoid cycle in rods (twilight vision)

Stable identifier: R-HSA-2454118

Type: transition

Compartments: cytosol, photoreceptor outer segment membrane

Human opsin-2 is a G-protein coupled photoreceptor found in the disc membranes of rod outer segments (ROS) (Nathans & Hogness 1984). It is an integral membrane protein and covalently binds the chromophore 11-cis-retinal (11cRAL) to form rhodopsin (RHO). Binding occurs via a protonated Schiff base linkage at Lys-296 (Fan et al. 2002) with Glu-113 at helix 3 serving as the counterion of the protonated Schiff base (Han et al. 1993). The resultant 11-cis-retinyl (11c-retinyl) group attached to lysine is completely embedded within the RHO structure. Opsins found in cone outer segments which bind 11cRAL are described in the cone visual cycle. Unlike other GPCRs in which direct ligand binding activates the receptor, rhodopsin is in an inactive state when bound to 11c-retinyl (which acts as an inverse agonist).

Preceded by: RBP3 transports 11cRAL to rod photoreceptor outer segment

Followed by: Photons induce isomerization of 11c-retinyl to at-retinyl

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Photons induce isomerization of 11c-retinyl to at-retinyl

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-74101

**Type:** transition

**Compartments:** photoreceptor disc membrane, extracellular region

The visual pigment rhodopsin consists of a seven transmembrane helix protein, opsin (RHO), to which an 11-cis-retinal (11cRAL) chromophore is bound as a protonated Schiff base (Hargrave et al. 1983, Nathans & Hogness 1984, Ovchinnikov et al. 1983). The covalent bond between opsin and its 11-cis-retinyl (11c-retinyl) ligand, which is unique among G protein coupled receptors, helps to confer extraordinary stability in darkness (Baylor et al. 1984). 11cRAL is an inverse agonist, that quenches the weak ability of opsin to activate transducin G protein (Gt). Upon photon absorption, the bound 11c-retinyl group isomerizes in a few hundred femtoseconds (Schoenlein et al. 1991) and with a high quantum efficiency of 0.7 (Dartnall 1968) to the bound all-trans-retinyl (at-retinyl) isomer. Then in the next few milliseconds, opsin undergoes a rearrangement in structure that renders it catalytically active (MII aka metarhodopsin II or R*) (Emeis et al. 1982). The isomerisation is a very fast photochemical process (femtoseconds) followed by slower events (Smith 2010).

Mutations in RHO can give rise to autosomal dominant or recessive forms of retinitis pigmentosa or autosomal dominant congenital stationary night blindness (https://sph.uth.edu/retnet/). Retinitis pigmentosa is a progressive form of blindness marked by an initial degeneration of rods, followed by the secondary loss of cones.

**Preceded by:** 11cRAL binds to opsin to form 11c-retinyl:RHO

**Literature references**


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**ABCA4 mediates atRAL transport**

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-1467466

**Type:** transition

**Compartments:** cytosol, photoreceptor outer segment membrane

Rhodopsin (RHO) is localised to both the disc membrane and the plasma membrane of rod outer segments (ROS). All-trans-retinal (atRAL) released from rhodopsin during the bleaching process, needs to translocate to the cytosol for reduction to all-trans-retinol (atROL) via all-trans-retinol dehydrogenases. Although atRAL can diffuse through membranes unaided, there exists an ABC transporter on disc membranes which may facilitate the transport of excess atRAL. Retinal-specific ATP-binding cassette transporter (ABCA4, ABCR) is the only ABC transporter which mediates the transport of retinoids (Biswas & Biswas 2000). Studies using bovine ABCA4 demonstrates atRAL transport (Sun et al. 1999). Human ABCR was found to be identical to the ABC transporter linked to Stargardt's disease type 1 (STGD1, MIM:248200), a cause of macular degeneration in childhood (Nasonkin et al. 1998).

**Followed by:** RDH12 reduces atRAL to atROL, RDH8 reduces atRAL to atROL

**Literature references**


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https://reactome.org
ABCA4 transports NRPE from photoreceptor outer segment membrane to cytosol

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2466749

**Type:** transition

**Compartments:** photoreceptor disc membrane, cytosol, photoreceptor outer segment membrane

**Inferred from:** NRPE is a substrate for Abca4 (Bos taurus)

Bovine studies (Beharry et al. 2004) have indicated NRPE to be the preferred substrate for ABCA4 (ABCR, rim protein, RmP) (Azarian et al. 1998), which acts as an inward-directed retinoid flippase and facilitates the transfer of NRPE to the cytoplasmic side of the disc membrane. This transfer is essential to avoid build up of potentially toxic retinoid intermediates which are implicated in many retinal degenerative diseases (see review Tsybovsky et al. 2010). Defective ABCA4 cannot perform this function leading to impaired vision and blindness disorders such as Stargardt disease (MIM:248200).

**Followed by:** NRPE dissociates to atRAL and PE

**Literature references**


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NRPE dissociates to atRAL and PE

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2466718

**Type:** transition

**Compartments:** cytosol, photoreceptor outer segment membrane

Once NRPE is "flipped" to the cytoplasmic side of disc membranes by the ABC transporter ABCA4, it can dissociate to all-trans-retinal (atRAL) and phosphatidylethanolamine (PE). atRAL is thus released to re-enter the retinoid cycle to reform the visual chromophore 11-cis-retinal (11cRAL) (Tsybovsky et al. 2010).

**Preceded by:** ABCA4 transports NRPE from photoreceptor outer segment membrane to cytosol

**Followed by:** RDH12 reduces atRAL to atROL

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Biosynthesis of A2E, implicated in retinal degradation

Location: The canonical retinoid cycle in rods (twilight vision)

Stable identifier: R-HSA-2466712

Diseases: dystrophies primarily involving the retinal pigment epithelium

Lipofuscin is a yellow-brown pigment grain composed mainly of lipids but also sugars and certain metals. Accumulation of lipofuscin is associated with degenerative diseases such as Alzheimer's disease, Parkinson's disease, chronic obstructive pulmonary disease and retinal macular degeneration.

A prominent component of lipofuscin in retinal pigment epithelial (RPE) cells is the bisretinoid A2E (di-retinoid-pyridinium-ethanolamine), the end-product of the condensation of 2 molecules of all-trans-retinal (atRAL) and phosphatidylethanolamine (PE) in photoreceptor outer disc membranes. Once formed, A2E is phagocytosed, together with outer segments (Kevany & Palczewski 2010), to RPE where it accumulates. There is no evidence as yet to indicate that A2E can be catabolised (Sparrow et al. 2012, Sparrow et al. 2010). A simplified biosynthetic pathway for A2E is described here.

Literature references


Editions

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https://reactome.org
atRAL(membrane) diffuses to atRAL(cytosol)

Location: The canonical retinoid cycle in rods (twilight vision)

Stable identifier: R-HSA-2464810

Type: transition

Compartments: cytosol, photoreceptor outer segment membrane

The majority of all-trans-retinal (atRAL) simply diffuses across membranes into the cytosol. Experiments performed with mice rods demonstrate that atRAL diffusion is independent of assisted transport by ABCA4 (Mata et al. 2000, Blakeley et al. 2011).

Followed by: RDH12 reduces atRAL to atROL, RDH8 reduces atRAL to atROL

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https://reactome.org
**RDH12 reduces atRAL to atROL**

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2464822

**Type:** transition

**Compartments:** photoreceptor inner segment membrane, cytosol

The reversible, NADP(H)-dependent reduction of all-trans-retinal (atRAL) to all-trans-retinol (atROL) occurs in both rod and cone photoreceptor cells where multiple retinol dehydrogenases (RHDs) are located. RHDs belong to the short-chain dehydrogenase/reductase (SDR) superfamily. RDH12 (located in photoreceptor inner segments) is partially responsible, together with other RDHs, for mediating this reaction (Belyaeva et al. 2005).

**Preceded by:** atRAL(membrane) diffuses to atRAL(cytosol), ABCA4 mediates atRAL transport, NRPE dissociates to atRAL and PE

**Followed by:** RBP3 regulates the transport of atROL from ROS to RPE

**Literature references**


**Editions**

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RDH8 reduces atRAL to atROL

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2464803

**Type:** transition

**Compartments:** cytosol, photoreceptor outer segment membrane

**Inferred from:** Rdh8 reduces atRAL to atROL (Bos taurus)

The reversible, NADP(H)-dependent reduction of all-trans-retinal (atRAL) to all-trans-retinol (atROL) occurs in both rod and cone photoreceptor cells where multiple retinol dehydrogenases (RHDs) are located. RHDs belong to the short-chain dehydrogenase/reductase (SDR) superfamily. RDH8 (located in photoreceptor outer segments) is partially responsible, together with other RHDs, for mediating this reaction. The activity for human RDH8 is inferred from a bovine experiment (Rattner et al. 2000).

**Preceded by:** atRAL(membrane) diffuses to atRAL(cytosol), ABCA4 mediates atRAL transport

**Followed by:** RBP3 regulates the transport of atROL from ROS to RPE

**Literature references**


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[https://reactome.org](https://reactome.org)
**RBP3 regulates the transport of atROL from ROS to RPE**

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-2464809

**Type:** uncertain

**Compartments:** extracellular region, cytosol

Although interphotoreceptor retinoid-binding protein (RBP3, IRBP) (Fong & Bridges 1988, Fong et al. 1990) is not required to move all-trans-retinol (atROL) from photoreceptor cells to the retinal pigment epithelium (RPE), it may function to regulate retinoid trafficking and possibly protect retinoids from biochemical damage. RBP3 is secreted by photoreceptor cells into the interphotoreceptor matrix (IPM), where, being a larger protein (135kDa) than the IPM space, becomes trapped (see mini-review Gonzalez-Fernandez & Ghosh 2008). It is through this space that retinoids move between the RPE and photoreceptor or outer segments during the retinoid cycle. Once atROL enters the RPE, it binds with RBP1.

**Preceded by:** RDH8 reduces atRAL to atROL, RDH12 reduces atRAL to atROL

**Followed by:** atROL binds RBP1 to form RBP1:atROL

**Literature references**


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CYP4V2 omega-hydroxylates DHA to HDoHE

**Location:** The canonical retinoid cycle in rods (twilight vision)

**Stable identifier:** R-HSA-6786239

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, cytosol

The main physiological function of normal retinal photoreceptor epithelial (RPE) cells is to import polyunsaturated fatty acids (PUFAs) from the bloodstream and to recycle them to maintain lipid homeostasis in photoreceptors. CYP4 enzymes are microsomal fatty acid omega-hydroxylases that function to degrade cellular lipids. CYP4V2 is present in epithelial cells of the retina and cornea, localised to the endoplasmic reticulum membrane and can hydroxylate PUFAs to their respective omega-hydroxylated products. Docosahexaenoic acid (DHA), which is found at high concentrations in the eye, is a C22 PUFAs which is hydroxylated to omega-hydroxy-DHA (Nakano et al. 2009, 2012). Defects in CYP4V2 can cause Bietti crystalline corneoretinal dystrophy (BCD; MIM:210370), an ocular disease characterised by retinal degeneration and marginal corneal dystrophy resulting in progressive night blindness and constriction of the visual field. A typical feature is multiple glistening intraretinal crystals scattered over the fundus (Li et al. 2004, Nakano et al. 2012).

**Literature references**


**Editions**

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