The retinoid cycle in cones (daylight vision)

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16/07/2019
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: 69

This document contains 1 pathway and 11 reactions (see Table of Contents)
The retinoid cycle in cones (daylight vision)

Stable identifier: R-HSA-2187335

Rods and cones share the same mechanism for the phototransduction process but perform functionally different roles. Although cone photoreceptors make up around 5% of all photoreceptor cells and are outnumbered 20 to 1 by rod photoreceptors, they mediate daylight vision in the human eye whereas rods mediate twilight vision. Also, cones are around 100-times less light-sensitive than rods thereby depriving us of colour vision in dark conditions in which cones cannot function. Rod function saturates in even moderate amounts of light whereas cones can adjust to even very bright light conditions, a process called light adaptation. In bright conditions, rods can take up to one hour to regain their sensitivity whereas cones can recover in a few minutes, a process called dark adaptation and which allows us to retain visual perception in changing light conditions.

Cone cells express three types of opsin which allow colour discrimination. Long Wavelength Sensitive Opsin (OPN1LW) detects red, Short Wavelength Sensitive Opsin (OPN1SW) detects blue, and Medium Wavelength Sensitive Opsin (OPN1MW) detects green regions of the light spectrum.

In the canonical retinoid (visual) cycle, the visual chromophore is regenerated in reactions involving the rod outer segments (ROS) and the retinal pigment epithelium (RPE). For cones, chromophore recycling is independent of the RPE and instead involves Muller cells in the retina which supply the chromophore selectively to cones. The molecular steps of the cone retinoid (visual) cycle are outlined in this section. The ability of cones to react to bright and differing light conditions means it has to regenerate the chromophore much quicker than rods. All-trans-retinol (atROL) released from cone outer segments is taken up by Muller cells where it is directly isomerized back to 11-cis-retinol (11cROL) then esterified by LRAT. When required, these 11-cis-retinyl esters can be hydrolysed by 11-cis-RE hydrolases back to 11cROL then oxidised in the cone photoreceptor cell to regenerate 11-cis-retinal (11cRAL), the visual chromophore (see reviews von Lintig 2012, Wang & Kefalov 2011, Kefalov 2012, Wolf 2004).

Literature references


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RBP3 regulates atROL taken up by Muller cells

Location: The retinoid cycle in cones (daylight vision)

Stable identifier: R-HSA-2465938

Type: omitted

Compartments: cytosol, extracellular region

All-trans-retinol (atROL), the product of the reduction of all-trans-retinal (atRAL) released from rod and cone opsinns, needs to be regenerated back to the visual chromophore 11-cis-retinal (11cRAL). For the regenerative steps, rods transports atROL back into the retinal pigment epithelium (RPE) while cones utilise Muller cells. Although interphotoreceptor retinoid-binding protein (RBP3, IRBP) (Fong & Bridges 1988, Fong et al. 1990) is not thought to be required to move all-trans-retinol (atROL) from photoreceptor cells to the retinal pigment epithelium (RPE) or Muller cells, 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 Muller cells and cone photoreceptor outer segments during the cone retinoid cycle.

Preceded by: atRAL is reduced to atROL

Followed by: RLBP1 binds atROL to form RLBP1:atROL

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RLBP1 binds atROL to form RLBP1:atROL

**Location:** The retinoid cycle in cones (daylight vision)

**Stable identifier:** R-HSA-2465971

**Type:** binding

**Compartments:** cytosol

Retinaldehyde-binding protein 1 (RLBP1, also called cellular retinaldehyde-binding protein, CRALBP) (Crabb et al. 1998) binds 11cROL (He et al. 2009) and is thought to enhance the activity of isomerase II and ARAT in experiments performed in cone-rich eyes from chickens (Mata et al. 2002, Mata et al. 2005).

**Preceded by:** RBP3 regulates atROL taken up by Muller cells

**Followed by:** An atROL isomerase isomerises atROL to 11cROL

**Literature references**


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An atROL isomerase isomerises atROL to 11cROL

**Location:** The retinoid cycle in cones (daylight vision)

**Stable identifier:** R-HSA-2465926

**Type:** omitted

**Compartments:** cytosol, endoplasmic reticulum membrane

**Inferred from:** Isomerase II isomerises atROL to 11cROL (Gallus gallus)

The canonical rod retinoid (visual) cycle is too slow to account for the photosensitivity of cones in bright light conditions. Novel enzyme activities demonstrated in ground-squirrel and chicken retinas produce a novel pathway of chromophore regeneration specific for cones. The first reaction in Muller cells, the isomerization of all-trans-retinol (atROL) to 11-cis-retinol (11cROL), is mediated by an as-yet-uncharacterised atROL isomerase (Mata et al. 2002, Mata et al. 2005). This reaction is proposed to take place in all vertebrates including humans (Wang & Kefalov 2009). Sphingolipid delta(4)-desaturase DES1 (DEGS1), an enzyme involved in sphingolipid de-novo biosynthesis, was recently found to possess retinoid isomerisation activity in chicken retinas but its physiological relevance in the synthesis of 11cROL remains inconclusive (Kaylor et al. 2013, Kiser et al. 2014).

**Preceded by:** RLBP1 binds atROL to form RLBP1:atROL

**Followed by:** AWAT2 transfers PALM to 11cROL forming 11cRPALM

**Literature references**


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AWAT2 transfers PALM to 11cROL forming 11cRPALM

**Location:** The retinoid cycle in cones (daylight vision)

**Stable identifier:** R-HSA-2465919

**Type:** transition

**Compartments:** cytosol, endoplasmic reticulum membrane

The esterification of alcohols with fatty acids is the favoured mechanism to form esterified forms of sterols, di- and triacylglycerols, and retinoids for storage. In the RPE and Muller cells of the eye, formation of retinyl esters is an essential step in the enzymatic regeneration of the visual chromophore 11-cis-retinal (11cRAL). Acyl-CoA wax alcohol acyltransferase 2 (AWAT2, aka Multifunctional O-acyltransferase, MFAT) (Yen et al. 2005) is an ER-membrane protein with a broad substrate specificity that can also esterify 11-cis retinol (11cROL) (Kaylor et al. 2014). The most common fatty acid is palmitate, forming retinyl palmitate (11cRPALM). Retinyl esters form into lipid droplets called retinosomes. In the previous step, retinol isomerase activity produces a mixture of retinol isomers (9-cis, 11-cis, 13-cis and all-trans-retinol) of which 11cROL only constitutes around 1% of the mixture. AWAT2’s preferential activity towards 11cROL has been proposed to be due to an allosteric modulation of AWAT2 by either bound (to RLBP1) or free 11cis-retinyl esters such as 11cRPALM. 11cRPALM impedes the acyl transfer onto 9-cis, 13-cis and all-trans retinols by making allosterically-induced changes in the active site of AWAT2 (Arne et al. 2017).

**Preceded by:** An atROL isomerase isomerises atROL to 11cROL

**Literature references**


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A REH hydrolyses 11cRE to 11cROL

Location: The retinoid cycle in cones (daylight vision)

Stable identifier: R-HSA-2465941

Type: omitted

Compartments: cytosol, lipid droplet, plasma membrane

Inferred from: An REH hydrolyses 11cRE to 11cROL (Gallus gallus)

This human event has been inferred from an as-yet-uncharacterised protein which has been demonstrated to possess retinyl ester hydrolase (REH) activity in chicken retina to hydrolyse 11-cis-retinyl palmitate (11cRPALM) to 11-cis-retinol (11cROL) (Bustamante et al. 1995).

Followed by: 11cROL translocates from Muller cells to cone photoreceptor cells

Literature references


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**11cROL translocates from Muller cells to cone photoreceptor cells**

**Location:** The retinoid cycle in cones (daylight vision)

**Stable identifier:** R-HSA-2465934

**Type:** omitted

**Compartments:** cytosol, extracellular region

The transfer of 11-cis-retinol (11cROL) from Muller cells to cone photoreceptor cells is thought to be mediated by interphotoreceptor retinoid-binding protein RBP3 (Liou et al. 1989, Fong & Bridges 1988) but the mechanism is poorly understood (Gonzalez-Fernandez & Ghosh 2008).

**Preceded by:** A REH hydrolyses 11cRE to 11cROL

**Followed by:** 11cRDH oxidises 11cROL to 11cRAL

**Literature references**


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11cRDH oxidises 11cROL to 11cRAL

**Location:** The retinoid cycle in cones (daylight vision)

**Stable identifier:** R-HSA-2465921

**Type:** omitted

**Compartments:** cytosol, endoplasmic reticulum membrane

11-cis-specific retinol dehydrogenase (11cRDH) activity found in chicken retina mediates the oxidation of 11-cis-retinol (11cROL) to 11-cis-retinal (11cRAL) using NADP+ as cofactor (Mata et al. 2002). The chicken protein that possesses this activity has not yet been identified. The actual enzyme responsible remains to be identified in human, even as evidence exists for this activity and for the alternative retinoid (visual) cycle in cones (Wang & Kefalov 2009). 11cRAL is the visual chromophore that is able to bind to opsins.

**Preceded by:** 11cROL translocates from Muller cells to cone photoreceptor cells

**Followed by:** OPN1SW, OPN1MW, OPN1LW bind 11cRAL

**Literature references**


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OPN1SW, OPN1MW, OPN1LW bind 11cRAL

**Location:** The retinoid cycle in cones (daylight vision)

**Stable identifier:** R-HSA-2465924

**Type:** transition

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

Human apo opsin proteins covalently bind the chromophore 11-cis-retinal (11cRAL) via a Schiff base linkage to a lysine residue in the seventh transmembrane alpha helix that is conserved in all known opsins (see review Shichida & Matsuyama 2009). The Schiff base linkage effectively results in an 11-cis-retinyl (11c-retinyl) group covalently linking to a lysine residue of opsins with subsequent loss of water. The three human cone opsins are Long Wavelength Sensitive Opsin (OPN1LW), Short Wavelength Sensitive Opsin (OPN1SW) and Middle Wavelength Sensitive Opsin (OPN1MW), sensing red, blue and green regions of the light spectrum, respectively (Nathans et al. 1986, Nathans et al. 1986b, Oprian et al. 1991).

**Preceded by:** 11cRDH oxidises 11cROL to 11cRAL

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

**Literature references**


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

Location: The retinoid cycle in cones (daylight vision)

Stable identifier: R-HSA-2465917

Type: transition

Compartments: photoreceptor outer segment membrane, extracellular region

Upon photon absorption, 11-cis-retinal (11cRAL) is isomerised to all-trans-retinal (atRAL). The structure of cone opsins which can ultimately activate G-proteins to initiate phototransduction is denoted as R* (Fan et al. 2002). R* is still bound to atRAL at this stage. The isomerisation is a very fast photochemical process (femtoseconds) (Schoenlein et al. 1991) followed by slower events described in the following reaction.

Preceded by: OPN1SW, OPN1MW, OPN1LW bind 11cRAL

Followed by: at-retinyl is hydrolysed from R* to release atRAL

Literature references


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https://reactome.org
at-retinyl is hydrolysed from R* to release atRAL

Location: The retinoid cycle in cones (daylight vision)

Stable identifier: R-HSA-2466085

Type: transition

Compartments: cytosol, photoreceptor outer segment membrane

After the very fast isomerisation of the 11-cis-retinyl (11c-retinyl) group to the all-trans-retinyl (at-retinyl) group attached to opsins by light stimulation, slower events lead to exposure of at-retinyl group to the aqueous environment, resulting in the hydrolysis of the Schiff base linkage. Although other intermediate products are formed, the ultimate result is the release of all-trans-retinal (atRAL) from opsins, with apo-opsins being reformed (Baumann & Bender 1973). These series of slow decay reactions are called light bleaching of opsin and ends when atRAL, which can diffuse across membranes to the cytosol, is reduced to all-trans-retinol (atROL)

Preceded by: Photons induce isomerisation of 11c-retinyl to at-retinyl

Followed by: atRAL is reduced to atROL

Literature references


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atRAL is reduced to atROL

**Location:** The retinoid cycle in cones (daylight vision)

**Stable identifier:** R-HSA-2465940

**Type:** transition

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

All-trans-retinal (atRAL) can diffuse across membranes to the cytosol and is reduced to all-trans-retinol (atROL) by the action of a short-chain dehydrogenase/reductase 3 using NADP+/NADPH as cofactor (Haeseleer et al. 1998).

**Preceded by:** at-retinyl is hydrolysed from R* to release atRAL

**Followed by:** RBP3 regulates atROL taken up by Muller cells

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