Retinoid metabolism and transport

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11/09/2019
**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: 70

This document contains 1 pathway and 28 reactions ([see Table of Contents](#))
Vitamin A (all-trans-retinol) must be taken up, either as carotenes from plants, or as retinyl esters from animal food. The most prominent carotenes are alpha-carotene, lycopene, lutein, beta-cryptoxanthine, and especially beta-carotene. After uptake they are mostly broken down to retinal. Retinyl esters are hydrolysed like other fats. In enterocytes, retinoids bind to retinol-binding protein (RBP). Transport from enterocytes to the liver happens via chylomicrons (Harrison & Hussain 2001, Harrison 2005).

**Literature references**


**Editions**

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PNLIP:CLPS hydrolyses RPALM to atROL and PALM

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-975593

Type: transition

Compartments: extracellular region, plasma membrane

Part of nutritional vitamin A is in the form of retinyl esters (REs). The main fatty acids which can form esters with retinol are palmitate, oleate, stearate and linoleate. REs are digested together with other lipids, and by the same enzymes. Pancreatic lipase catalyses the hydrolysis of RE to all-trans-retinol (atROL) and fatty acid which are then both taken up by enterocytic cell membranes (Bennekum et al. 2000).

Followed by: atROL binds to RBP2

Literature references


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**PLB1 hydrolyses RPALM to atROL**

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-975594

**Type:** transition

**Compartments:** extracellular region, plasma membrane

Part of retinol ester hydrolase activity in the small intestine is associated with the brush border membrane but the protein having it is not identified. It is thought to be phospholipase B (Rigtrup et al. 1994).

**Followed by:** atROL binds to RBP2

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atROL binds to RBP2

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-975633

**Type:** binding

**Compartments:** cytosol, plasma membrane

In enterocytes, the dominant retinol-binding protein is RBP2 (CRBPII) which is abundant and binds retinol faster than the cell membrane. So, even though lipophilic retinol can easily enter the cell membrane of bowel enterocytes, it is collected by the abundancy of RBP2 into the enterocyte cytosol where it is further processed (Inagami & Ong 1997).

**Preceded by:** PNLIP:CLPS hydrolyses RPALM to atROL and PALM, PLB1 hydrolyses RPALM to atROL

**Followed by:** LRAT esterifies RBP2:atROL and FACYLs to atREs

**Literature references**


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As long as vitamin A is needed, beta-carotene-monooxygenase (BCMO1) catalyses the cleavage of carotenes, resulting mainly in retinal (Fierce et al. 2008).

Followed by: atRAL binds to RBP2

Literature references

BCO2:Fe2+ cleaves betaC to APO10al and bION

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-5164399

**Type:** transition

**Compartments:** mitochondrial matrix

Beta,beta-carotene 9',10'-oxygenase (BCO2) is able to eccentrically cleave carotenoids to produce long chain (>C20) apocarotenoids (Amengual et al. 2011). This is in contrast to the other provitamin A-convert-ing enzyme, BCMO1 which is able to symmetrically cleave carotenoids to produce apocarotenoids of C20 length, such as all-trans-retinal (atRAL). BCMO1 is the main enzyme involved in retinoid homeostasis and resides in the cytosol whereas BCO2 resides in the mitochondrion, has broad substrate activity and is proposed to provide an alternative, minor route for retinoid production. How apocarotenoids produced by BCO2 cleavage are utilised is the subject of further investigation (Amengual et al. 2013). Being in the mitochondrion, BCO2 is able to degrade carotenoids which, if otherwise allowed to accumulate, are implicated in oxidative damage to the cell (Amengual et al. 2011). In this example, beta-carotene (betaC) is cleaved by BCO2 to produce beta-apo-10'-carotenal (APO10al) and beta-ionone (bION) in an enterocyte cell. Carotenoids, such as betaC, can also be metabolised in many other cell types including hepatocytes and stellate cells of the liver.

**Literature references**


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https://www.reactome.org
atRAL binds to RBP2

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-2399913

Type: binding

Compartments: cytosol

In enterocytes, all-trans-retinal (atRAL) binds to RBP2 (CRBPII) for stabilisation, metabolism and transport (Fierce et al. 2008).

Preceded by: BCMO1:Fe2+ cleaves betaC to atRAL

Followed by: RDH11 reduces RBP2:atRAL to RBP2:atROL, AKRs reduce RBP2:atRAL to RBP2:atROL

Literature references


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RDH11 reduces RBP2:atRAL to RBP2:atROL

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-975629

**Type:** transition

**Compartments:** cytosol, endoplasmic reticulum membrane

Although the enzyme catalysing retinal reduction in human enterocytes is not identified, the best candidate is retinol dehydrogenase 11 (RDH11, RalR1). It is expressed in the intestine, has a basic pH optimum, and localises to the ER membrane where LRAT catalyses the next step in the pathway. However, RDH11 catalyses retinal reduction to retinol *in vitro* and uses NADPH as cofactor (Fierce et al. 2008).

**Preceded by:** atRAL binds to RBP2

**Followed by:** LRAT esterifies RBP2:atROL and FACYLs to atREs

**Literature references**

AKRs reduce RBP2:atRAL to RBP2:atROL

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2855252

**Type:** transition

**Compartments:** cytosol

RDH11 is the best-characterised enzyme that reduces all-trans-retinal (atRAL) to all-trans-retinol (atROL). In addition, several aldo-keto reductase (AKR) enzymes from subfamilies 1B and 1C also show all-trans-retinal (atRAL) reductase activity. AKR1B10 shows high reductase activity towards atRAL (Gallego et al. 2007, Ruiz et al. 2009) whereas AKR1C1, 1C3 and 1C4 all show much lower reductase activity towards arRAL (Ruiz et al. 2011).

**Preceded by:** atRAL binds to RBP2

**Followed by:** LRAT esterifies RBP2:atROL and FACYLs to atREs

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LRAT esterifies RBP2:atROL and FACYLs to atREs

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-975608

**Type:** transition

**Compartments:** cytosol, endoplasmic reticulum membrane, plasma membrane

Transfer of fatty acyl residues (FACYLs) from lecithin is the main way to esterify all-trans-retinol (atROL). Lecithin is a generic name for the yellowy-brown fatty substances in animals and tissues. It can be composed of phosphatidylcholines, phosphatidylethanolamines, and phosphatidylinositol. Fatty acyl transfer is catalyzed by Lecithin retinol acyltransferase (LRAT) and takes place near the endoplasmic reticulum membrane. The main fatty acyl moieties that are substrates for LRAT are palmitoyl, oleoyl, stearoyl and linoleoyl groups present in the A1 position of membrane phosphatidylcholine molecules. LRAT esterifies atROL with these acyl groups to form all-trans-retinyl esters (atREs). The aim is not storage but transport via chylomicrons (Ruiz et al. 1999).

**Preceded by:** atROL binds to RBP2, RDH11 reduces RBP2:atRAL to RBP2:atROL, AKRs reduce RBP2:atRAL to RBP2:atROL

**Followed by:** atREs binds to nascent CM

**Literature references**


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atREs binds to nascent CM

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2395764

**Type:** binding

**Compartments:** cytosol

Chylomicrons (CM) are large (75–450 nm), spherical lipoprotein particles secreted by intestinal cells postprandially and transport dietary fat and fat-soluble vitamins in the lymphatic system (Nayak et al. 2001, During & Harrison 2007). All-trans-retinyl esters (atREs) are packaged into nascent chylomicrons.

**Preceded by:** LRAT esterifies RBP2:atROL and FACYLs to atREs

**Followed by:** Cytosolic CMs translocate to extracellular region

**Literature references**


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Cytosolic CMs translocate to extracellular region

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-2187332

Type: transition

Compartments: cytosol, extracellular region

Nascent chylomicrons (CM) containing all-trans-retinyl esters (atREs) are secreted from intestinal cells and transported to the liver via the lymphatic system (Nayak et al. 2001, During & Harrison 2007).

Preceded by: atREs binds to nascent CM

Followed by: Nascent CMs transform into mature CMs

Literature references


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Nascent CMs transform into mature CMs

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-2395784

Type: transition

Compartments: extracellular region

Nascent chylomicrons (CMs) acquire copies of apolipoproteins C-II, C-III, and E from circulating spherical (mature) high-density lipoprotein particles, becoming mature chylomicrons (Havel et al. 1973, Bisgaier & Glickman 1983). Here, this interaction is annotated to involve the transfer of a single copy of each lipoprotein, but a mature chylomicron in fact contains approximately 25 copies of apolipoprotein E and 180 copies of C apolipoproteins (Bhattacharya & Redgrave 1981).

Preceded by: Cytosolic CMs translocate to extracellular region

Followed by: LPL hydrolyses TGs from mature CMs

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LPL hydrolyses TGs from mature CMs

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2395768

**Type:** transition

**Compartments:** extracellular region, plasma membrane

Lipoprotein lipase dimers (LPL:LPL) are tethered to heparan sulfate proteoglycans (HSPG) at endothelial cell surfaces (Fernandez-Borja et al. 1996; Peterson et al. 1992). Both syndecan 1 (Rosenberg et al. 1997) and perlecan (Goldberg 1996) HSPG molecules are capable of tethering LPL. The LPL enzyme catalyzes the hydrolysis and release of triacylglycerols (TG) associated with circulating chylomicrons to leave a CM remnant (CR). This reaction is annotated here as causing the hydrolysis and release of 50 molecules of TG. In vivo, the number is much larger, and TG depletion probably occurs in the course of multiple encounters between a chylomicron and endothelial LPL. This reaction is strongly activated by chylomicron-associated apo C-II protein both in vivo and in vitro (Jackson et al. 1986). Chylomicron-associated apoC-II protein inhibits LPL activity in vitro (Brown and Baginsky 1972), and recent studies have indicated a positive regulatory role for apoA-5 protein, though its molecular mechanism of action remains unclear (Marcais et al. 2005; Merkel and Heeren 2005). CRs can then be taken up by liver parenchymal cells in two ways; 1) directly by the LDL receptor or 2) apoE/HSPG-directed uptake by LDL receptor-related proteins.

**Preceded by:** Nascent CMs transform into mature CMs

**Followed by:** CR:atREs binds apoE and HSPG, LDLR transports extracellular CR:atREs to cytosol

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LDLR transports extracellular CR:atREs to cytosol

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2424254

**Type:** transition

**Compartments:** extracellular region, plasma membrane, early endosome

**Inferred from:** Extracellular CR:atREs are transported to cytosol by Ldlr (Mus musculus)

Chylomicron remnants (CRs) are "sieved" when they arrive at the liver by size, the appropriate sized remnants passing through the space of Disse. Once inside, CRs containing all-trans-retinyl esters (atREs) can be directly and rapidly taken up by liver parenchymal cells via the low-density lipoprotein receptor (LDLR) using apolipoprotein E (apoE) as a ligand. Internalization of remnants occur via endocytosis (see review D'Ambrosio et al. 2011). This reaction is inferred from uptake studies in mice (Yu et al. 2000). Defects in LDLR cause familial hypercholesterolemia (FH, MIM:143890), a common autosomal disease that affects about 1 in 500 people in most countries. Abnormal LDLR doesn't remove LDL from circulation resulting in high levels of LDL in blood, leading to early cardiovascular disease via atherosclerosis. The defect was first described by Brown and Goldstein (1974).

**Preceded by:** LPL hydrolyses TGs from mature CMs

**Followed by:** NREH hydrolyses atREs to atROL and FAs

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Jassal, B.

Blaner, WS.
CR:atREs binds apoE and HSPG

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-2423785

Type: binding

Compartments: extracellular region, plasma membrane

When the low-density lipoprotein receptor (LDLR) is missing, saturated or inhibited, chylomicron remnants (CRs) containing all-trans-retinyl esters (atREs) bind apolipoprotein E (apoE). ApoE, secreted by hepatocytes, acts as a high-affinity ligand for the LDL-related receptor protein (LRP) family. CR:atREs:apoE then binds to cell-surface heparan sulfate proteoglycan (HSPG), abundant in the space of Disse. HSPG/apoE binding plays a critical role in the capture of CR:atREs, ready for internalization via LRPs (Futamura et al. 2005, Yamauchi et al. 2008).

Preceded by: LPL hydrolyses TGs from mature CMs

Followed by: LRPs transport extracellular CR:atREs:HSPG:apoE to cytosol

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LRPs transport extracellular CR:atREs:HSPG:apoE to cytosol

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-2404131

Type: transition

Compartments: plasma membrane, early endosome

When the low-density lipoprotein receptor (LDLR) is missing, saturated or inhibited, chylomicron remnants (CRs) containing all-trans-retinyl esters (atREs) can be cleared from circulation by interaction with cell-surface heparan sulfate proteoglycan (HSPG) and secreted apolipoprotein E (apoE). This complex is then presented to LDL receptor-related proteins (LRPs; reviews May et al. 2007, Li et al. 2001, Hussain 2001) for internalization (Ji et al. 1993).

Preceded by: CR:atREs binds apoE and HSPG

Followed by: NREH hydrolyses atREs (HSPG:apoE) to atROL and FAs

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NREH hydrolyses atREs to atROL and FAs

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2404140

**Type:** transition

**Compartments:** early endosome, cytosol

Once inside liver parenchymal cells, all-trans-retinyl esters (atREs), are hydrolysed to all-trans-retinol (at-tROL) and fatty acids (FAs) by a neutral, all-trans-retinyl ester hydrolase (NREH). No NREH has been characterised yet although both acidic and neutral REH activity has been shown to be associated with endosomes and plasma membrane preparations from rodent livers (Harrison & Gad 1989, Gad & Harrison 1991, Hagen et al. 1999). As the acidity increases, early endosomes change to late endosomes and further hydrolysis of atREs is mediated by acid retinyl ester hydrolase (AREH). Like NREH, AREH has not yet been characterised (see refs above). The translocation mechanism of atROL to cytosol is unknown.

**Preceded by:** LDLR transports extracellular CR:atREs to cytosol

**Followed by:** RETSAT reduces atROL to at-13,14-dhROL, atROL binds RBP1 (parenchymal cell)

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NREH hydrolyses atREs (HSPG:apoE) to atROL and FAs

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2429643

**Type:** transition

**Compartments:** early endosome, plasma membrane, cytosol

Once inside liver parenchymal cells, all-trans-retinyl esters (atREs), are hydrolysed to all-trans-retinol (atROL) and fatty acids (FAs) by a neutral, all-trans-retinyl ester hydrolase (NREH). No NREH has been characterised yet although both acidic and neutral REH activity has been shown to be associated with endosomes and plasma membrane preparations from rodent livers (Harrison & Gad 1989, Gad & Harrison 1991, Hagen et al. 1999). As the acidity increases, early endosomes change to late endosomes and further hydrolysis of atREs is mediated by acid retinyl ester hydrolase (AREH). Like NREH, AREH has not yet been characterised (see refs above). The translocation mechanism of atROL to cytosol is unknown.

**Preceded by:** LRPs transport extracellular CR:atREs:HSPG:apoE to cytosol

**Followed by:** RETSAT reduces atROL to at-13,14-dhROL, atROL binds RBP1 (parenchymal cell)

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RETSAT reduces atROL to at-13,14-dhROL

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-8956427

Type: transition

Compartments: cytosol, endoplasmic reticulum membrane

Inferred from: Retsat reduces atROL to at-13,14-dhROL (Mus musculus)

All-trans-retinol 13,14-reductase (RETSAT) is an ER membrane-associated protein that mediates the saturation of the 13-14 double bond of all-trans-retinol (atROL) to produce all-trans-13,14-dihydroretinol (at-13,14-dhROL). The product formed is a metabolite of unknown biological function. The human activity of RETSAT is inferred from mouse Retsat enzyme assays (Moise et al. 2004). In human and mouse, RETSAT is induced during adipogenesis and is directly regulated by the transcription factor peroxisome proliferator activated receptor gamma (PPAR-gamma). Ablation of RETSAT inhibits adipogenesis but this block was not overcome by the product of RETSAT enzymatic activity. In adipose tissue, RETSAT is expressed in adipocytes but is downregulated in obesity. RETSAT could be a novel target for therapeutic intervention in metabolic disease (Schupp et al. 2009).

Preceded by: NREH hydrolyses atREs (HSPG:apoE) to atROL and FAs, NREH hydrolyses atREs to atROL and FAs

Literature references


Editions

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https://www.reactome.org
atROL binds RBP1 (parenchymal cell)

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2855259

**Type:** binding

**Compartments:** cytosol

All-trans-retinol (atROL) binds to cellular retinol-binding protein 1 (RBP1) (Folli et al. 2001). RBP1 is thought to be required for intracellular transport of atROL in the liver.

**Preceded by:** NREH hydrolys atREs (HSPG:apoE) to atROL and FAs, NREH hydrolys atREs to atROL and FAs

**Followed by:** Parenchymal atROL translocates to HSCs

**Literature references**


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https://www.reactome.org
Parenchymal atROL translocates to HSCs

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2404144

**Type:** omitted

**Compartments:** cytosol

When the body is in a retinoid-sufficient state, all-trans-retinol (atROL) is transferred to hepatic stellate cells (HSCs) for storage. The transfer was established in rat experiments (Blomhoff et al. 1982, Blomhoff et al. 1984). The mechanism of transport is as yet unknown.

**Preceded by:** atROL binds RBP1 (parenchymal cell)

**Followed by:** atROL binds RBP1

**Literature references**


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atROL binds RBP1

*Location:* Retinoid metabolism and transport

*Stable identifier:* R-HSA-2404142

*Type:* binding

*Compartments:* cytosol

All-trans-retinol (atROL) is stored in hepatic stellate cells (HSCs) in its esterified form. 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. It is thought the binding of RBP1 serves to translocate atROL to the endoplasmic reticulum where LRAT is located.

**Preceded by:** Parenchymal atROL translocates to HSCs

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

**Literature references**


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

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2404137

**Type:** transition

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

All-trans-retinyl esters (atREs) are the main storage form of retinol in hepatic stellate cells (HSCs). Lecithin retinol acyltransferase (LRAT) mediates the esterification of all-trans-retinol (atROL) with a variety of fatty acyl groups (FACYLs) to form REs which are stored in lipid droplets in the cytosol. Cellular retinol-binding protein 1 (RBP1) is an effective donor of atROL for LRAT (Ruiz et al. 1999).

**Preceded by:** atROL binds RBP1

**Followed by:** A REH hydrolses atREs to atROL and FAs

**Literature references**


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Retinyl esters (REs) are stored in lipid droplets (LDs) in hepatic stellate cells (HSCs) until there is a demand for retinoid by the body. Mobilization of atREs stores require lipases with retinyl ester hydrolase (REH) activity. At present, the identity of the REH mediating atRE mobilization is unknown (see reviews Shirakami et al. 2012, Schreiber et al. 2012). In studies performed with rat livers, Mello et al. found that the carboxylesterases ES4 and ES10 possessed REH activity and were localised to HSCs (Mello et al. 2008) but it’s not confirmed that these are the actual REHs involved in retinoid mobilization. The human orthologue to these rat enzymes is presently unknown.

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

**Followed by:** HSC cytosolic atROL translocates to extracellular region

**Literature references**


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HSC cytosolic atROL translocates to extracellular region

Location: Retinoid metabolism and transport

Stable identifier: R-HSA-2404139

Type: transition

Compartments: cytosol, extracellular region

Once hydrolysed from all-trans-retinyl esters (atREs), all-trans-retinol (atROL) can either be esterified for storage or secreted into the bloodstream for transport to target tissues/organs (Kanai et al. 1968). The mechanism of secretion/efflux is currently unknown.

Preceded by: A REH hydrolses atREs to atROL and FAs

Followed by: RBP4 binds atROL

Literature references


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APOM binds retinoids

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-5246478

**Type:** binding

**Compartments:** extracellular region

Apolipoprotein M (APOM) is a plasma protein usually associated with HDLs and to a lesser extent, with LDLs. APOM could be classed as a lipocalin (LCN) because it shares the structurally conserved beta-barrel, which in many LCNs, binds hydrophobic ligands. Mature APOM retains its signal peptide, which serves as a lipid anchor to attach it to lipoproteins, thereby keeping it in the circulation (Christoffersen et al. 2008). APOM is able to bind retinoids such as retinol, all-trans-retinoate and 9-cis-retinoate with low affinity although they may not be the natural ligands (Ahnstrom et al. 2007, Dahlback & Nielsen 2009). APOM does not bind cholesterol, vitamin K or arachidonate (Ahnstrom et al. 2007).

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At the stellate cell surface, all-trans-retinol (atROL) binds to retinol binding protein 4 (RBP4, holo-RBP) (Kanai et al. 1968). atROL is insoluble in aqueous conditions and it's thought RBP4 picks up atROL from the outer leaflet of the plasma membrane. RBP4 is a 21 kDa protein secreted into the bloodstream by the liver in an atROL-dependent manner. Defects in RBP4 cause retinol-binding protein deficiency (RBP deficiency, MIM:180250), causing night vision problems and progressive atrophy of the retinal pigment epithelium (RPE) (Seeliger et al. 1999).

Preceded by: HSC cytosolic atROL translocates to extracellular region

Followed by: RBP4:atROL binds TTR

Literature references


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https://www.reactome.org
**RBP4:atROL binds TTR**

**Location:** Retinoid metabolism and transport

**Stable identifier:** R-HSA-2404134

**Type:** binding

**Compartments:** extracellular region

In the bloodstream, circulating retinol binding protein 4 (RBP4, in complex with atROL), binds transthyretin (TTR, a 51 kDa protein) in a 1:1 molar complex (Naylor & Newcomer, 1999). The resultant TTR:RBP4:atROL complex is larger and therefore less susceptible to glomerular filtration, maintaining normal levels of retinoid and RBP4 in the circulation. In TTR-deficient mice, plasma levels of atROL and RBP4 were observed to be 5% of wild type levels, highlighting the importance of TTR binding to RBP4:atROL (Episkopou et al. 1993). TTR is also a transporter for thyroxine in the brain (not shown here) (Herbert et al. 1986).

**Preceded by:** RBP4 binds atROL

**Literature references**

Naylor, HM., Newcomer, ME. (1999). The structure of human retinol-binding protein (RBP) with its carrier protein transthyretin reveals an interaction with the carboxy terminus of RBP. *Biochemistry, 38, 2647-53.*


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LRPs transport extracellular CR:atREs:HSPG:apoE to cytosol

NREH hydrolyses atREs to atROL and FAs

NREH hydrolyses atREs (HSPG:apoE) to atROL and FAs

RETSAT reduces atROL to at-13,14-dhROL

atROL binds RBP1 (parenchymal cell)

Parenchymal atROL translocates to HSCs

atROL binds RBP1

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