Metabolism of lipids

D'Eustachio, P., Gillespie, ME., Gopinathrao, G., Hannun, YA., Hansen, TV., Jassal, B., Joshi-Tope, G., Kersten, S., Luberto, C., May, B., Williams, MG.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

18/11/2022
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.

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Literature references


Reactome database release: 82

This document contains 11 pathways (see Table of Contents)

https://reactome.org
Lipids are hydrophobic but otherwise chemically diverse molecules that play a wide variety of roles in human biology. They include ketone bodies, fatty acids, triacylglycerols, phospholipids and sphingolipids, eicosanoids, cholesterol, bile salts, steroid hormones, and fat-soluble vitamins. They function as a major source of energy (fatty acids, triacylglycerols, and ketone bodies), are major constituents of cell membranes (cholesterol and phospholipids), play a major role in their own digestion and uptake (bile salts), and participate in numerous signaling and regulatory processes (steroid hormones, eicosanoids, phosphatidylinositols, and sphingolipids) (Vance & Vance 2008 - URL).

The central steroid in human biology is cholesterol, obtained from animal fats consumed in the diet or synthesized de novo from acetyl-coenzyme A. (Vegetable fats contain various sterols but no cholesterol.) Cholesterol is an essential constituent of lipid bilayer membranes and is the starting point for the biosyntheses of bile acids and salts, steroid hormones, and vitamin D. Bile acids and salts are mostly synthesized in the liver. They are released into the intestine and function as detergents to solubilize dietary fats. Steroid hormones are mostly synthesized in the adrenal gland and gonads. They regulate energy metabolism and stress responses (glucocorticoids), salt balance (mineralocorticoids), and sexual development and function (androgens and estrogens). At the same time, chronically elevated cholesterol levels in the body are associated with the formation of atherosclerotic lesions and hence increased risk of heart attacks and strokes. The human body lacks a mechanism for degrading excess cholesterol, although an appreciable amount is lost daily in the form of bile salts and acids that escape recycling.

Aspects of lipid metabolism currently annotated in Reactome include lipid digestion, mobilization, and transport; fatty acid, triacylglycerol, and ketone body metabolism; peroxisomal lipid metabolism; phospholipid and sphingolipid metabolism; cholesterol biosynthesis; bile acid and bile salt metabolism; and steroid hormone biosynthesis.

**Literature references**

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Peroxisome proliferator-activated receptor alpha (PPAR-alpha) is the major regulator of fatty acid oxidation in the liver. PPARalpha is also the target of fibrate drugs used to treat abnormal plasma lipid levels.

PPAR-alpha is a type II nuclear receptor (its subcellular location does not depend on ligand binding). PPAR-alpha forms heterodimers with Retinoid X receptor alpha (RXR-alpha), another type II nuclear receptor. PPAR-alpha is activated by binding fatty acid ligands, especially polyunsaturated fatty acids having 18-22 carbon groups and 2-6 double bonds.

The PPAR-alpha:RXR-alpha heterodimer binds peroxisome proliferator receptor elements (PPREs) in and around target genes. Binding of fatty acids and synthetic ligands causes a conformational change in PPAR-alpha such that it releases the corepressors and binds coactivators (CBP-SRC-HAT complex, ASC complex, and TRAP-Mediator complex) which initiate transcription of the target genes.

Target genes of PPAR-alpha participate in fatty acid transport, fatty acid oxidation, triglyceride clearance, lipoprotein production, and cholesterol homeostasis.

**Literature references**


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Lipid particle organization

Location: Metabolism of lipids

Stable identifier: R-HSA-8964572

Lipid droplets (LDs) are cytosolic structures found in cells of all eukaryotes, comprising a monolayer of phospholipids surrounding a core of uncharged lipids such as triglyceride (TAG) and sterol esters. CIDEA, CIDEB and CIDEC were first studied for their roles in promotion of apoptosis but they are also known to play a role in energy metabolism. CIDEA and C bind to lipid droplets and regulate their enlargement, thereby restricting lipolysis and favouring storage (by promoting net neutral lipid transfer from smaller to larger lipid droplets) (Gao & Goodman 2015). LD formation involves the partitioning of neutral lipids from their site of synthesis at the endoplasmic reticulum (ER) to the cytosol. The fat storage-inducing transmembrane proteins 1 and 2 (FITM1 and FITM2), associated with the ER membrane, mediate binding and partitioning of TAGs into LDs. The short-chain dehydrogenases/reductases (SDR) family is a large family of NAD- or NADP-dependent oxidoreductase enzymes. 17-beta-hydroxysteroid dehydrogenase 13 (HSD17B13) is a recently-discovered enzyme of unknown physiological function that is associated with lipid droplets and significantly upregulated in patients with nonalcoholic fatty liver disease. Hypoxia-inducible lipid droplet-associated protein (HILPDA) is a lipid droplet protein and stimulates intracellular lipid accumulation.

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The synthesis and breakdown of fatty acids are a central part of human energy metabolism, and the eicosanoid class of fatty acid derivatives regulate diverse processes in the body (Vance & Vance 2008 - URL). Processes annotated in this module include the synthesis of fatty acids from acetyl-CoA, mitochondrial and peroxisomal breakdown of fatty acids, and the metabolism of eicosanoids and related molecules.

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Fatty acids derived from the diet and synthesized de novo in the liver are assembled into triglycerides (triacylglycerols) for transport and storage. Synthesis proceeds in steps of conversion of fatty acyl-CoA to phosphatidic acid, conversion of phosphatidic acid to diacylglycerol, and conversion of diacylglycerol to triacylglycerol (Takeuchi & Reue 2009).

Hydrolysis of triacylglycerol to yield fatty acids and glycerol is a tightly regulated part of energy metabolism. A central part in this regulation is played by hormone-sensitive lipase (HSL), a neutral lipase abundant in adipocytes and skeletal and cardiac muscle, but also abundant in ovarian and adrenal tissue, where it mediates cholesterol ester hydrolysis, yielding cholesterol for steroid biosynthesis. The hormones to which it is sensitive include catecholamines (e.g., epinephrine), ACTH, and glucagon, all of which trigger signaling cascades that lead to its phosphorylation and activation, and insulin, which sets off events leading to its dephosphorylation and inactivation (Kraemer & Shen 2002).

The processes of triacylglycerol and cholesterol ester hydrolysis are also regulated by subcellular compartmentalization: these lipids are packaged in cytosolic particles and the enzymes responsible for their hydrolysis, and perhaps for additional steps in their metabolism, are organized at the surfaces of these particles (e.g., Brasaemle et al. 2004).

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Phospholipids contain a polar head group and two long-chain fatty acyl moieties, one of which is generally unsaturated. The head group is a glycerol or serine phosphate attached to a polar group such as choline. These molecules are a major constituent of cellular membranes, where their diverse structures and asymmetric distributions play major roles in determining membrane properties (Dowhan 1997). The four major classes of phospholipids in human plasma membranes are phosphatidylethanolamine, phosphatidylserine, phosphatidylcholine, and sphingomyelin. The first three are derivatives of glycerol while sphingomyelin is a derivative of serine.

Here, pathways for the metabolism of glycerophospholipids, phosphatidylinositol (PI), and sphingolipids are annotated.

**Literature references**


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Sphingolipid metabolism

Location: Metabolism of lipids

Stable identifier: R-HSA-428157

Sphingolipids are derivatives of long chain sphingoid bases such as sphingosine (trans-1,3-dihydroxy 2-amino-4-octadecene), an 18-carbon unsaturated amino alcohol which is the most abundant sphingoid base in mammals. Amide linkage of a fatty acid to sphingosine yields ceramides. Esterification of phosphocholine to ceramides yields sphingomyelin, and ceramide glycosylation yields glycosylceramides. Introduction of sialic acid residues yields gangliosides. These molecules appear to be essential components of cell membranes, and intermediates in the pathways of sphingolipid synthesis and breakdown modulate processes including apoptosis and T cell trafficking.

While sphingolipids are abundant in a wide variety of foodstuffs, these dietary molecules are mostly degraded by the intestinal flora and intestinal enzymes. The body primarily depends on de novo synthesis for its sphingolipid supply (Hannun and Obeid 2008; Merrill 2002). De novo synthesis proceeds in four steps: the condensation of palmitoyl-CoA and serine to form 3-ketosphinganine, the reduction of 3-ketosphinganine to sphinganine, the acylation of sphinganine with a long-chain fatty acyl CoA to form dihydroceramide, and the desaturation of dihydroceramide to form ceramide.

Other sphingolipids involved in signaling are derived from ceramide and its biosynthetic intermediates. These include sphinganine (dihydrosphingosine) 1-phosphate, phytoceramide, sphingosine, and sphingosine 1-phosphate.

Sphingomyelin is synthesized in a single step in the membrane of the Golgi apparatus from ceramides generated in the endoplasmic reticulum (ER) membrane and transferred to the Golgi by CERT (ceramide transfer protein), an isoform of COL4A3BP that is associated with the ER membrane as a complex with PPM1L (protein phosphatase 1-like) and VAPA or VAPB (VAMP-associated proteins A or B). Sphingomyelin synthesis appears to be regulated primarily at the level of this transport process through the revers-
ible phosphorylation of CERT (Saito et al. 2008).

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**Metabolism of steroids**

**Location:** Metabolism of lipids

**Stable identifier:** R-HSA-8957322

Steroids, defined by a four-ring cyclopenta[a]phenanthrene carbon skeleton, include cholesterol and bile acids and salts, steroid hormones, and vitamin D, three groups of molecules synthesized from it. In this module, pathways for the synthesis of cholesterol from HMG-CoA (hydroxymethylglutaryl-coenzyme A) (Russell 1992), and for its conversion to bile acids and salts (Russell 2003), steroid hormones (Payne & Hales 2004), and vitamin D (Dusso et al. 2005) are annotated, together with the SREBP-mediated regulatory process that normally links the rate of cholesterol synthesis to levels of cellular cholesterol (Brown & Goldstein 2009).

**Literature references**


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https://reactome.org
Waxes are esters of long chain fatty acids and long chain fatty alcohols that play an important role in protecting the skin surface from drying and abrasion (Cheng & Russell 2004a,b). Plasmalogens are an abundant subclass of phospholipids. While their functions are not well understood, defects in their metabolism are associated with serious human disease (de Vet et al. 1999; Nagan and Zoeller 2001). The biosynthesis of these two classes of molecules both start with the reduction of palmitoyl-CoA (PALM-CoA) to hexadecan-1-ol (HXOL) so it is convenient to group them here.

**Literature references**


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[https://reactome.org](https://reactome.org)
Ketone body metabolism

**Location:** Metabolism of lipids

**Stable identifier:** R-HSA-74182

**Compartments:** mitochondrial matrix

Acetoacetate, beta-hydroxybutyrate, and acetone collectively are called ketone bodies. The first two are synthesized from acetyl-CoA, in the mitochondria of liver cells; acetone is formed by spontaneous decarboxylation of acetoacetate. Ketone body synthesis in liver is effectively irreversible because the enzyme that catalyzes the conversion of acetoacetate to acetoacetyl-CoA is not present in liver cells.

Ketone bodies, unlike fatty acids and triglycerides, are water-soluble. They are exported from the liver, and are taken up by other tissues, notably brain and skeletal and cardiac muscle. There, they are broken down to acetyl-CoA which is oxidized via the TCA cycle to yield energy. In a normal person, this pathway of ketone body synthesis and utilization is most active during extended periods of fasting. Under these conditions, mobilization and breakdown of stored fatty acids generates abundant acetyl-CoA acetyl-CoA in liver cells for synthesis of ketone bodies, and their utilization in other tissues minimizes the demand of these tissues for glucose (Sass 2011).

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A host's normal protective response to tissue injury or pathogenic infection is acute inflammation. The condition of acute inflammation is created by the release of pro-inflammatory lipid mediators such as leukotrienes (LTs) and prostaglandins (PGs) that launch a series of signaling cascades to destroy invading pathogens and to repair damaged tissue (Libby 2007). The potent chemotactic agent leukotriene B4 (LTB4) promotes the recruitment of neutrophils (PMNs) to inflamed tissues, while the prostaglandins E2 and D2 (PGE2 and PGD2) further accelerate the inflammatory process. If left unchecked, the inflammatory response can initiate chronic systemic inflammatory disorders associated with cardiovascular disease, rheumatoid arthritis, periodontal disease, asthma, diabetes, inflammatory bowel disease (IBD), Alzheimer’s disease and age-related macular degeneration (AMD). The specific role by which inflammation contributes to their pathogenesis is not fully understood.

To prevent the onset of chronic inflammation, a lipid mediator class switch is thought to occur from the initial actions of pro-inflammatory lipid mediators to the anti-inflammatory and pro-resolving actions of lipoxins, resolvins, protectins and maresins (collectively called specialized proresolving mediators (SPMs)). Nanopicogram quantities of different lipid mediators are generated at different times during the evolution of the inflammatory response and these mediators coincide with distinct cellular events. The class switch activates leukocyte translational regulation of the enzymes required to produce pro-resolving lipid mediators (Levy et al. 2001). Each family of these PSMs exert specialized actions, including blocking neutrophil recruitment, promoting the recruitment and activation of monocytes, as well as mediating the nonphlogistic phagocytosis and lymphatic clearance of apoptotic neutrophils by activated macrophages (ie without inducing inflammation) and mediating tissue regeneration. Eventually, through the combined actions of these mediators, the resolution of inflammation is completed and homeostasis is reached (Serhan 2010, Bannenberg & Serhan 2010, Freire & Van Dyke 2013, Serhan et al. 2014).

SPMs are derived from polyunsaturated fatty acids (PUFAs) (Molfino et al. 2017). PUFAs of the ω-3 series are essential nutrients since they cannot be produced by humans (Duvall & Levy 2016) and are primarily found in dietary fish oils (Calder 2013) and in plants (Baker et al. 2016). The ω-3 PUFAs eicosapentaenoic
acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPAn-3) circulate in the bloodstream after dietary intake and are easily incorporated into cellular membranes in a time- and dose-dependent manner (Calder 2009), as well as being present in inflammatory exudates (Kasuga et al. 2008). They can be mobilised by phospholipase A2 from cellular membranes on injury or infection when they are converted to exudate SPMs (Serhan et al. 2002) to interact with local immune cells (Kasuga et al. 2008). EPA is the source for E-series resolvins while DHA is the source for D-series resolvins, protectins, maresins and sulfido conjugates in tissue regeneration mediators (Serhan et al. 2017). The ω-6 fatty acid arachidonic acid (AA) is the source for lipoxins. ω-3 or ω-6 PUFA docosapentaenoic acids (DPAn-3 and DPAn-6) are the sources of DPA-derived resolvins, protectins and maresins (Vik et al. 2017). Aspirin can also trigger the production of epimeric SPMs via acetylated PTGS2 (prostaglandin G/H synthase, COX2) (Serhan & Chiang 2002). Combinations of oxidation, reduction and hydrolysis can generate numerous SPMs. Electrophilic oxo-derivatives of ω-3 PUFAs are a class of oxidised derivatives that are generated in macrophages and neutrophils by the actions of 5-lipoxygenase, cyclooxygenase-2 and acetylated cyclooxygenase-2, followed by dehydrogenation. Being electrophilic, oxo-derivative SPMs reversibly bind to nucleophilic residues on target proteins, triggering the activation of cytoprotective pathways (Cipollina 2015). The pathways in this section describe the biosynthesis of these SPMs.

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