Arachidonic acid metabolism

D'Eustachio, P., Jassal, B., Jupe, S., Le Novere, N., Rush, MG., 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.

14/11/2022
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.

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 9 pathways and 5 reactions (see Table of Contents)
Arachidonic acid metabolism

Stable identifier: R-HSA-2142753

Eicosanoids, oxygenated, 20-carbon fatty acids, are autocrine and paracrine signaling molecules that modulate physiological processes including pain, fever, inflammation, blood clot formation, smooth muscle contraction and relaxation, and the release of gastric acid. Eicosanoids are synthesized in humans primarily from arachidonic acid (all-cis 5,8,11,14-eicosatetraenoic acid) that is released from membrane phospholipids. Once released, arachidonic acid is acted on by prostaglandin G/H synthases (PTGS, also known as cyclooxygenases (COX)) to form prostaglandins and thromboxanes, by arachidonate lipoxygenases (ALOX) to form leukotrienes, epoxygenases (cytochrome P450s and epoxide hydrolase) to form epoxides such as 15-eicosatetraenoic acids, and omega-hydrolases (cytochrome P450s) to form hydroxyeicosatetraenoic acids (Buczynski et al. 2009, Vance & Vance 2008).

Levels of free arachidonic acid in the cell are normally very low so the rate of synthesis of eicosanoids is determined primarily by the activity of phospholipase A2, which mediates phospholipid cleavage to generate free arachidonic acid. The enzymes involved in arachidonic acid metabolism are typically constitutively expressed so the subset of these enzymes expressed by a cell determines the range of eicosanoids it can synthesize.

Eicosanoids are unstable, undergoing conversion to inactive forms with half-times under physiological conditions of seconds or minutes. Many of these reactions appear to be spontaneous.

Literature references


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Once bound to the membrane, cPLA2 hydrolyzes phosphatidylcholine to produce arachidonic acid (AA), a precursor to inflammatory mediators. While several phospholipases can catalyze this reaction in cells overexpressing the enzymes, PLA2G4A is the major enzyme that catalyzes this reaction in vivo (Reed et al. 2011). At the same time, possible physiological roles have been described for soluble phospholipases (sPLA) in the mobilization of arachidonic acid in some cell types or under some physiological conditions (Murakami et al. 2011). Here, the major role of PLA2G4A has been annotated.

Followed by: Arachidonate diffuses across the ER membrane

**Literature references**


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**Arachidonate diffuses across the ER membrane**

**Location:** Arachidonic acid metabolism

**Stable identifier:** R-HSA-428990

**Type:** transition

**Compartments:** endoplasmic reticulum lumen, cytosol

Arachidonate released by phospholipases diffuses within the membrane and out of the membrane into the ER lumen and cytosol. The relatively low level of arachidonate in the cytoplasm is probably due to reesterification into complex lipids by acyl transferases.

**Preceded by:** Hydrolysis of phosphatidylcholine

**Literature references**

Irvine, RF. (1982). How is the level of free arachidonic acid controlled in mammalian cells?. *Biochem J*, 204, 3-16.

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AWAT1 transfers acyl group from acyl-CoA to ARACOH, forming wax esters

**Location:** Arachidonic acid metabolism

**Stable identifier:** R-HSA-5696424

**Type:** transition

**Compartment:** endoplasmic reticulum membrane, endoplasmic reticulum lumen

Arachidyl alcohol (ARACOH) is a straight-chain fatty alcohol of C20 length used as an emollient in cosmetics. Esterification of alcohols with fatty acids represents the formation of both storage and cytoprotective molecules in the body. Overproduction of these esters is associated with several disease pathologies, including atherosclerosis and obesity. The ER membrane-associated acyl-CoA wax alcohol acyltransferase 1 (AWAT1) mediates the esterification of its preferred substrate ARACOH (Turkish et al. 2005).

**Literature references**


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Fatty acid amides are a class of lipid transmitters that include the endogenous cannabinoid anandamide (AEA) and the sleep-inducing chemical oleamide. The magnitude and duration of their signalling are controlled by enzymatic hydrolysis mediated by fatty-acid amide hydrolases 1 and 2 (FAAH, H2). Hydrolysis of AEA is described here (Wei et al. 2006). FAAH is localised to the ER membrane whereas FAAH2 is localised to lipid droplets (Kaczocha et al. 2010).

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[https://reactome.org](https://reactome.org)
Synthesis of Prostaglandins (PG) and Thromboxanes (TX)

**Location:** Arachidonic acid metabolism

**Stable identifier:** R-HSA-2162123

The bioactive prostaglandin (PG) signalling molecules, including PGA2, PGE2, PGF2a, and PGI2 (prostacyclin) are synthesised from arachidonic acid and its products by various prostaglandin synthase type enzymes. Prostaglandin H2 (PGH2) is the starting point for the synthesis of Thromboxanes (TXs) (Buczynski et al. 2009, Vance & Vance 2008). PGs and TXs are collectively known as the prostanoids.

Two enzymes, PTGS1 and 2 (COX1 and 2) both catalyze the two-step conversion of arachidonic acid to PGH2. PTGS1 is constitutively expressed in many cell types while PTGS2 is induced in response to stress and mediates the syntheses of prostaglandins associated with pain, fever, and inflammation. Aspirin irreversibly inactivates both enzymes (though it acts more efficiently on PTGS1), explaining both its antiinflammatory effects and side effects like perturbed gastric acid secretion. Drugs like celecoxib, by specifically inhibiting PTGS2, have a strong anti-inflammatory effect with fewer side effects. These PTGS2-specific drugs, however, probably because of their effects on the balance of prostaglandin synthesis in platelets and endothelial cells, can also promote blood clot formation (Buczynski et al. 2009; Stables & Gilroy 2011).

**Literature references**


Leukotrienes (LTs) are biologically active molecules formed in response to inflammatory stimuli. They cause contraction of bronchial smooth muscles, stimulation of vascular permeability, and attraction and activation of leukocytes. LTs were discovered in 1938 and were termed the "slow release substance" (SRS) until their structures were determined in 1979 and they were then renamed to leukotrienes. LTs are derived from arachidonic acid through action by arachidonate 5-lipoxygenase (ALOX5). Cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are generated as products derived from leukotriene A4 (LTA4). Eoxins are generated from leukotrienes (LTs) and resemble cysteinyl leukotrienes but have a different three-dimensional structure (Murphy & Gijon 2007, Hammarstrom 1983, MA.Claesson 2009, Vance & Vance 2008, Buczynski et al. 2009).

**Literature references**


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5-hydroperoxy-eicosatetraenoic acid (5-HpETE), 5-hydroxyeicosatetraenoic acid (5S-HETE) and 5-oxo-eicosatetraenoic acid (5-oxoETE) are formed after the initial step of arachidonic acid oxidation by arachidonate 5-lipoxygenase (ALOX5) (Buczynski et al. 2009, Vance & Vance 2008).

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Synthesis of 15-eicosatetraenoic acid derivatives

Location: Arachidonic acid metabolism

Stable identifier: R-HSA-2142770

The 15-eicosatetraenoic acids: 15-hydroperoxy-eicosatetraenoic acid (15-HpETE), 15-hydroxyeicosatetraenoic acid (15-HETE) and 15-oxo-eicosatetraenoic acid (15-oxoETE) are formed after the initial step of arachidonic acid oxidation by the arachidonate 15-lipoxygenases (ALOX15 and ALOX15B) (Buczynski et al. 2009, Vance & Vance 2008).

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The 12-eicosatetraenoic acids: 12-hydroperoxy-eicosatetraenoic acid (12-HpETE), 12-hydroxyeicosatetraenoic acid (12-HETE) and 12-oxo-eicosatetraenoic acid (12-oxoETE) are formed after the initial step of arachidonic acid oxidation by the arachidonate 12 and 15 lipoxygenases (ALOX12, ALOX12B and ALOX15 respectively). This part of the pathway is bifurcated at the level of 12S-hydroperoxy-eicosatetraenoic acid (12S-HpETE), which can either be reduced to 12S-hydro-eicosatetraenoic acid (12S-HETE) or converted to hepopxilins (Buczynski et al. 2009, Vance & Vance 2008).

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Hepoxilins are biologically relevant signalling molecules produced by certain arachidonate 12-lipoxygenase (ALOX12s). Hepoxilin A3 (HXA3) and B3 (HXB3) have been identified, both of which incorporate an epoxide across the C-11 and C-12 double bond, as well as an additional hydroxyl moiety. HXA3 has a C-8 hydroxyl, whereas the HXB3 hydroxyl occurs at C-10. The epoxy moiety is labile and can be hydrolyzed either by a hepoxilin specific epoxide hydrolase (HXEH) or in acidic aqueous solution to form the corresponding diol metabolites trioxilin A3 (TrXA3) and B3 (TrXB3) (Buczynski et al. 2009, Vance & Vance 2008).

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Similar to the lipoxygenases, cytochrome P450 (CYP) enzymes catalyse the hydroxylation and epoxygenation of arachidonic acid. However, whereas lipoxygenases use an active non-heme iron to abstract hydrogen directly from arachidonic acid, CYPs contain a heme-iron active site that oxidizes its substrate by a different mechanism. They hydroxylate arachidonic acid between C-5 and C-15 to produce lipoxygenase-like hydroxyeicosatetraenoic acids (HETEs) and add a hydroxyl moiety to the sp3-hybridized omega-carbons to form a unique class of HETEs. The transfer of oxygen to the unstable arachidonic acid intermediate terminates the reaction by forming HETE or epoxy-eicosatrienoic acid (EETs), respectively (Capdevila et al. 2000, Buczynski et al. 2009, Vance & Vance 2008).

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https://reactome.org
Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET)

Location: Arachidonic acid metabolism

Stable identifier: R-HSA-2142670

The epoxidation of arachidonic acid by cytochrome P450s (CYPs) results in the formation of unique bioactive lipid mediators termed epoxyeicosatrienoic acids (EETs). Each double bond has been shown to be susceptible to oxidation, resulting in 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET. The majority of the EET biological activities are diminished by the hydrolysis to the corresponding dihydroxyeicosatrienoic acids (DHET) (Capdevila et al. 2000, Buczynski et al. 2009, Vance & Vance 2008).

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