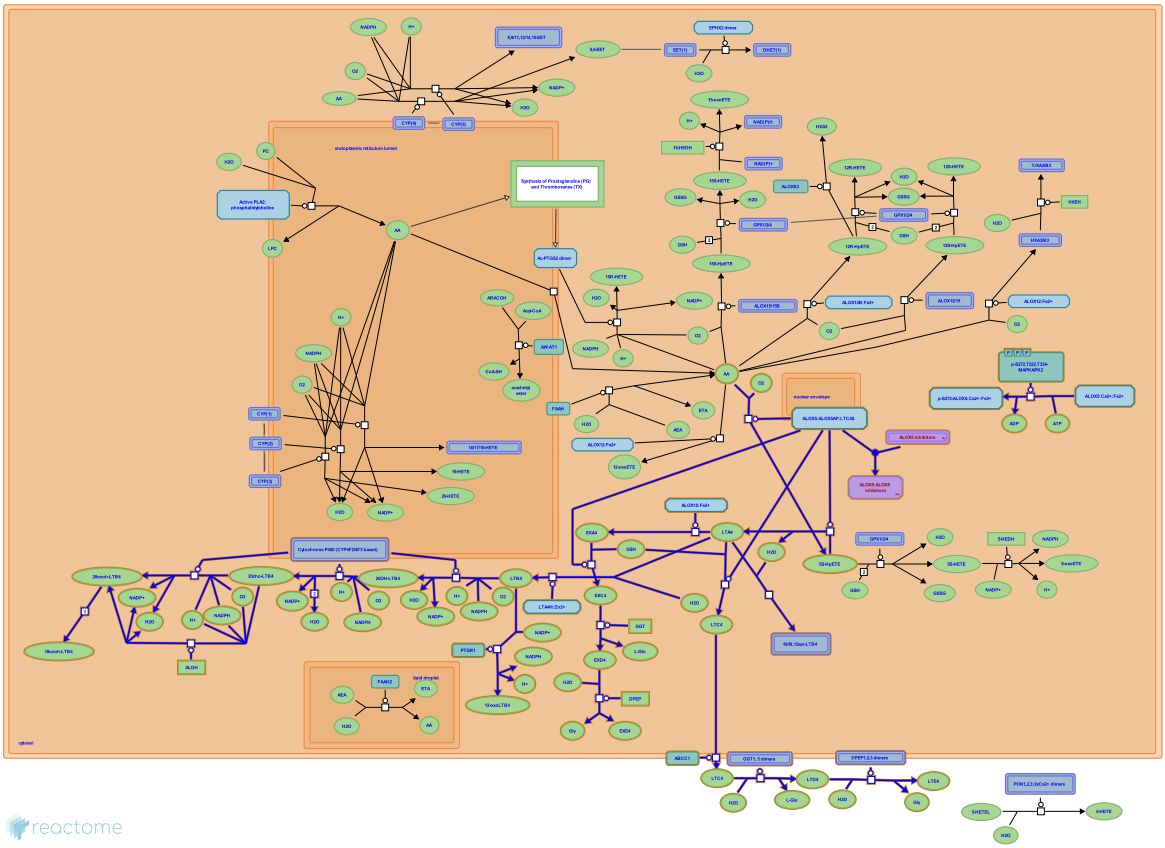
Synthesis of Leukotrienes (LT) and Eoxins (EX)



Hansen, TV., Huddart, R., Jassal, B., Jupe, S., Matthews, L., Rush, MG., Williams, MG.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

17/05/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

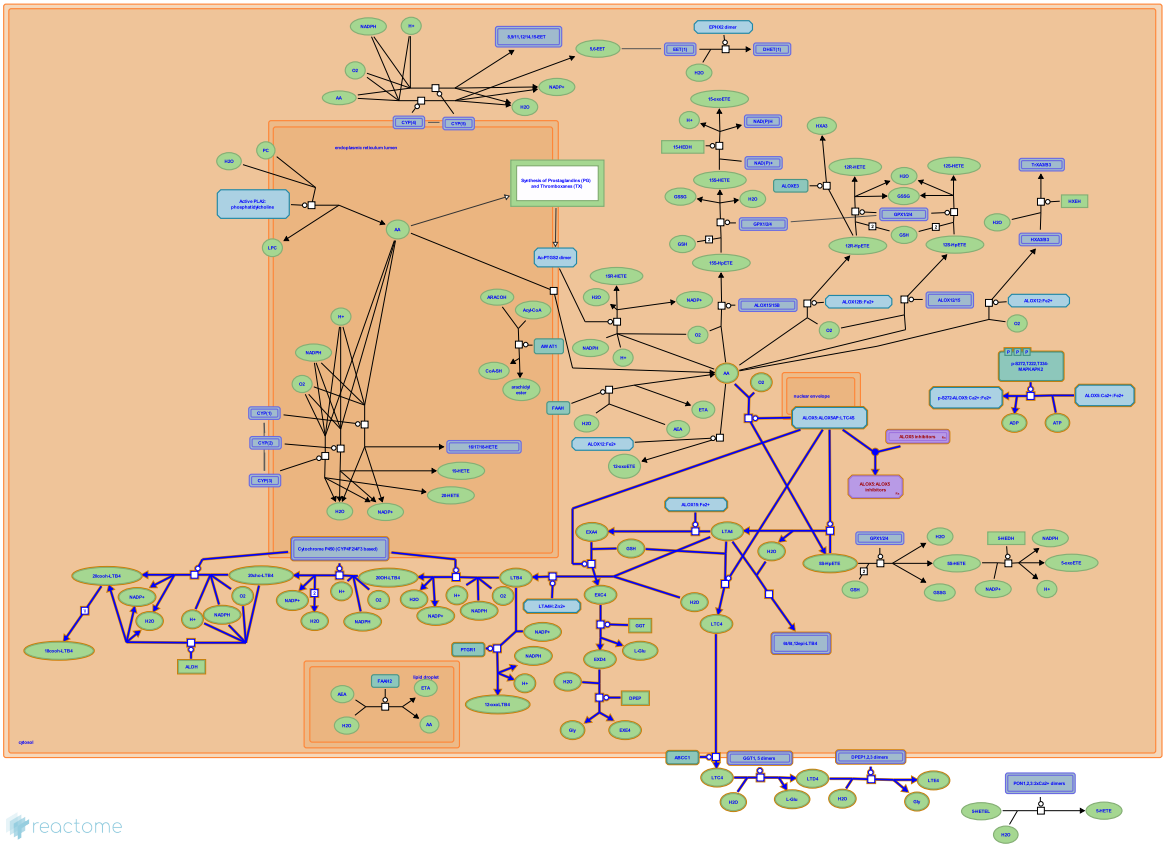
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Synthesis of Leukotrienes (LT) and Eoxins (EX) ↗

Stable identifier: R-HSA-2142691



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

Hammarström, S. (1983). Leukotrienes. *Annu Rev Biochem, 52*, 355-77. ↗

Gijon, MA., Murphy, RC. (2007). Biosynthesis and metabolism of leukotrienes. *Biochem J, 405*, 379-95. ↗

Claesson, HE. (2009). On the biosynthesis and biological role of eoxins and 15-lipoxygenase-1 in airway inflammation and Hodgkin lymphoma. *Prostaglandins Other Lipid Mediat, 89*, 120-5. ↗

Vance, JE., Vance, DE. (2008). The eicosanoids: cyclooxygenase, lipoxygenase, and epoxygenase pathways, Biochemistry of Lipids, Lipoproteins and Membranes, 5th Edition. *Elsevier Science*, 331-362.

Dumlao, DS., Buczynski, MW., Dennis, EA. (2009). Thematic Review Series: Proteomics. An integrated omics analysis of eicosanoid biology. *J Lipid Res, 50*, 1015-38. ↗

Editions

2012-02-24	Authored, Edited	Williams, MG.
2012-11-10	Reviewed	Rush, MG.

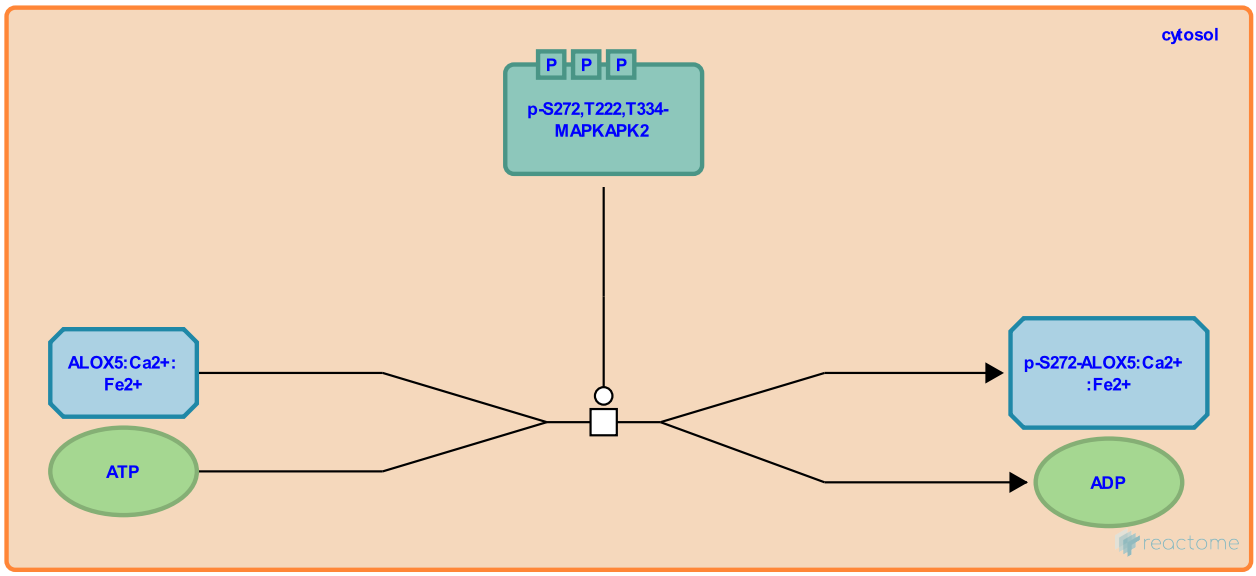
ALOX5 is phosphorylated by MAPKAP2

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-429016

Type: transition

Compartments: cytosol



Arachidonate 5-lipoxygenase (ALOX5) catalyzes the first step in leukotriene biosynthesis and has a key role in inflammatory processes. ALOX5 is phosphorylated by MAPKAPK2; MAPKAPK2 is stimulated by arachidonic acid.

Followed by: Arachidonic acid is oxidised to 5S-HpETE by ALOX5

Literature references

Steinhilber, D., Rådmark, O., Werz, O., Szellas, D. (2002). Arachidonic acid promotes phosphorylation of 5-lipoxygenase at Ser-271 by MAPK-activated protein kinase 2 (MK2). *J Biol Chem, 277*, 14793-800.

Rådmark, O., Klemm, J., Werz, O., Samuelsson, B. (2000). 5-lipoxygenase is phosphorylated by p38 kinase-dependent MAPKAP kinases. *Proc Natl Acad Sci U S A, 97*, 5261-6.

Editions

2009-07-14	Authored	Jupe, S.
2010-05-06	Edited	Jupe, S.
2012-11-10	Reviewed	Rush, MG.

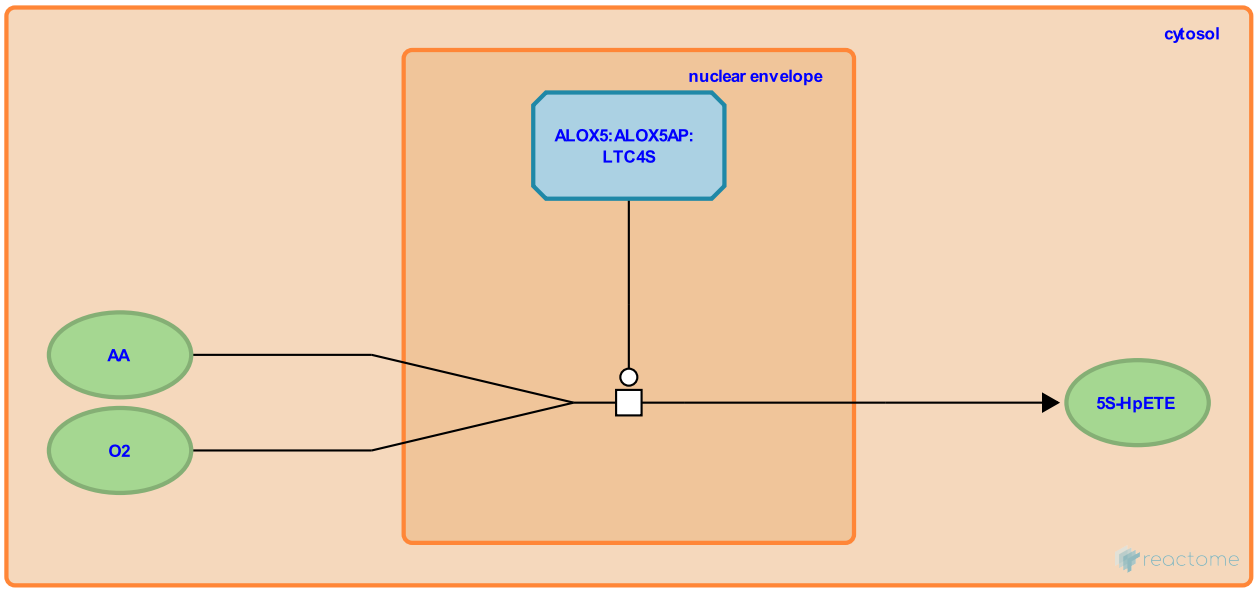
Arachidonic acid is oxidised to 5S-HpETE by ALOX5 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-265296

Type: transition

Compartments: nuclear envelope, cytosol



Arachidonate 5-lipoxygenase (ALOX5) catalyzes the formation of leukotriene A4 (LTA4) from arachidonic acid in a two-step process. First, arachidonic acid AA is oxidized to form 5S-hydroperoxyeicosatetranoic acid (5S-HpETE) (Rouzer et al. 1988, Rouzer & Samuelsson 1987, Rouzer et al. 1986).

Preceded by: ALOX5 is phosphorylated by MAPKAP2

Followed by: 5S-HpETE is dehydrated to LTA4 by ALOX5

Literature references

Rouzer, CA., Samuelsson, B. (1987). Reversible, calcium-dependent membrane association of human leukocyte 5-lipoxygenase. *Proc Natl Acad Sci U S A, 84*, 7393-7. ↗

Matsumoto, T., Rouzer, CA., Samuelsson, B. (1986). Single protein from human leukocytes possesses 5-lipoxygenase and leukotriene A4 synthase activities. *Proc Natl Acad Sci U S A, 83*, 857-61. ↗

Register, RB., Jones, RE., Kargman, S., Dixon, RA., Rouzer, CA., Rands, E. (1988). Characterization of cloned human leukocyte 5-lipoxygenase expressed in mammalian cells. *J Biol Chem, 263*, 10135-40. ↗

Editions

2008-04-21	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.
2012-11-10	Reviewed	Rush, MG.

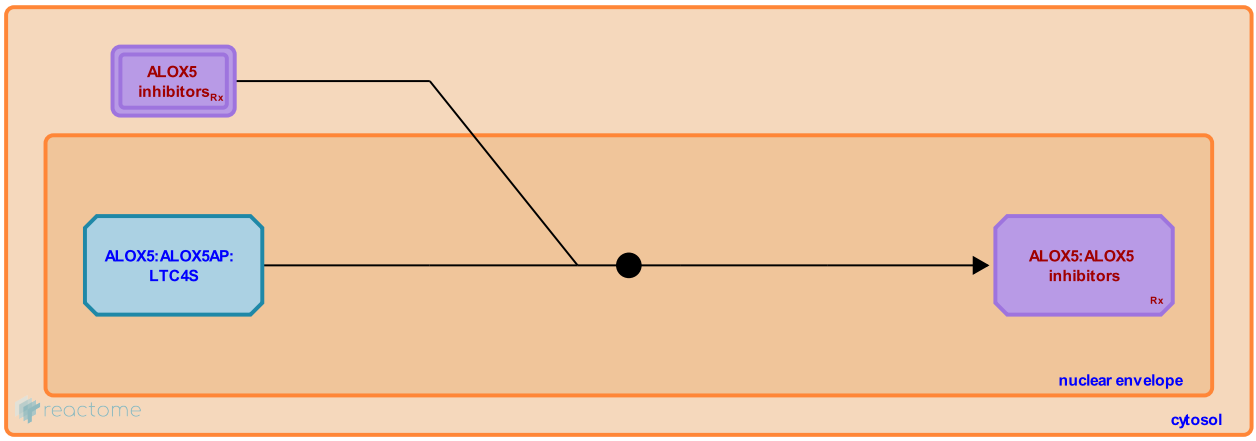
ALOX5 binds ALOX5 inhibitors ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-9707186

Type: binding

Compartments: nuclear envelope, cytosol



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 (AA) that is released from membrane phospholipids. Once released, AA can be acted on by various enzymes to form different eicosanoids. Arachidonate lipoxygenase 5 (ALOX)5 form leukotrienes (LTs) and eicosatetraenoic acids (ETEs) from AA. LTs and ETEs 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. When produced in excess, these molecules may contribute to a wide range of pathological inflammatory responses.

ALOX5 inhibitors are compounds that slow or stop the action of the ALOX5 enzyme, which is responsible for the production of inflammatory LTs and ETEs. Zileuton blocks the activity of ALOX5 (Carter et al. 1991). Zileuton is used in the treatment of acne vulgaris (Zouboulis 2005, Zouboulis et al. 2009) and for the prophylaxis and chronic treatment of allergic asthma (Bruno et al. 2018, Morina et al. 2016). Meclofenamic acid is a non-steroidal anti-inflammatory drug (NSAID) used for the relief of mild to moderate pain, for the treatment of primary dysmenorrhea and for the treatment of idiopathic heavy menstrual blood loss. It is also used for relief of the signs and symptoms of acute and chronic rheumatoid arthritis and osteoarthritis. In vitro meclofenamic acid was found to be an inhibitor of human ALOX5 activity (Boctor et al. 1986). Balsalazide, olsalazine and sulfasalazine are all pro-drugs that are enzymatically cleaved in the colon to produce the anti-inflammatory agent mesalazine (5-aminosalicylic acid, 5-ASA, mesalazine (Klotz 1985, Selby et al. 1985, Sharon et al. 1978, Hawkey et al. 1985, Neilsen et al. 1987). Once metabolised, 5-ASA acts locally in the colon to reduce inflammation in conditions such as inflammatory bowel disease and ulcerative colitis (Wiggins & Rajapakse 2009, Rask-Madsen et al. 1992, Singer et al. 2006, Hoult 1986, Feagan & Macdonald 2012).

Literature references

Spaziano, G., Nabavi, SM., D'Agostino, B., Sureda, A., Liparulo, A., Filosa, R. et al. (2018). Recent advances in the search for novel 5-lipoxygenase inhibitors for the treatment of asthma. *Eur J Med Chem, 153*, 65-72. ↗

Sharon, P., Zor, U., Rachmilewitz, D., Ligumsky, M. (1978). Role of prostaglandins in ulcerative colitis. Enhanced production during active disease and inhibition by sulfasalazine. *Gastroenterology, 75*, 638-40. ↗

Schmausser, H., Singer, MV., Schönfeld, G. (2006). Efficacy and tolerability of olsalazine (dipentum) in the treatment of patients with ulcerative colitis--results of a field study. *Hepatogastroenterology, 53*, 317-21. ↗

Jewell, DP., Mason, CH., Ireland, A., Barr, GD., Selby, WS. (1985). Olsalazine in active ulcerative colitis. *Br Med J (Clin Res Ed), 291*, 1373-5. ↗

Hawkey, CJ., Boughton-Smith, NK., Whittle, BJ. (1985). Modulation of human colonic arachidonic acid metabolism by sulfasalazine. *Dig Dis Sci, 30*, 1161-5. ↗

Editions

2021-03-25	Authored	Jassal, B.
2021-10-27	Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

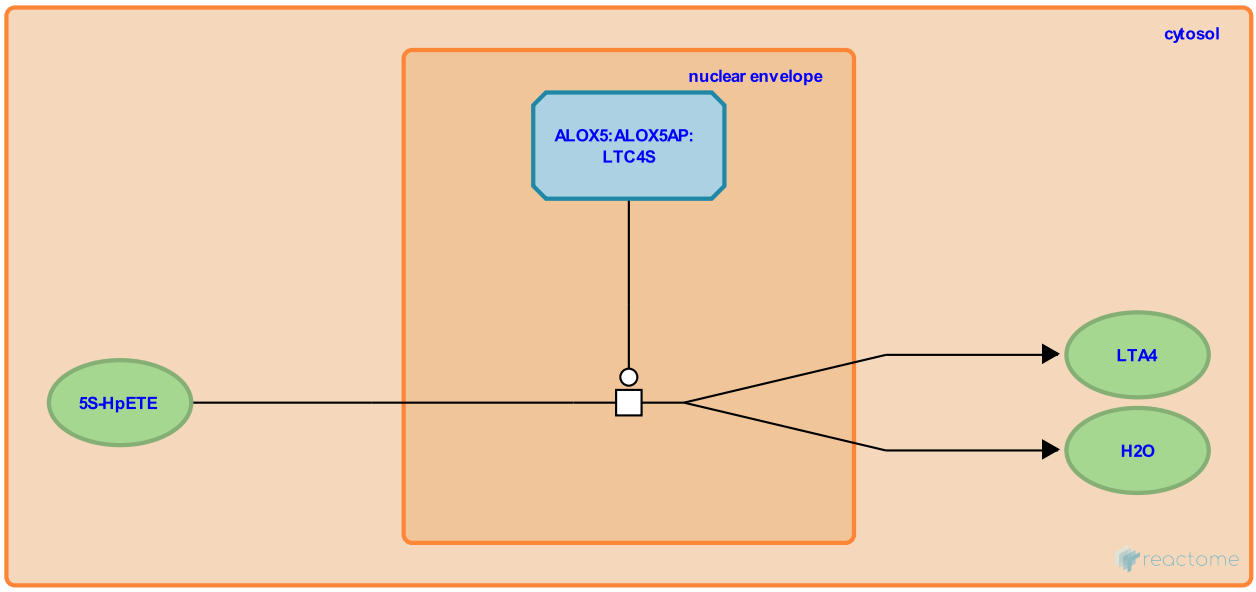
5S-HpETE is dehydrated to LTA4 by ALOX5 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-266051

Type: transition

Compartments: nuclear envelope, cytosol



In the second step of the formation of leukotriene A4 (LTA4) from arachidonic acid, arachidonate 5-lipoxygenase (ALOX5) converts 5S-hydroperoxyeicosatetranoic acid (5S-HpETE) to an allylic epoxide, leukotriene A4 (LTA4) (Rouzer et al. 1988, Rouzer & Samuelsson 1987, Rouzer et al. 1986).

Preceded by: Arachidonic acid is oxidised to 5S-HpETE by ALOX5

Followed by: LTA4 is hydrolysed to 6t-/6t,12epi-LTB4, LTA4 is converted to EXA4 by ALOX15, LTA4 is hydolysed to LTB4 by LTA4H, LTA4 is converted to LTC4 by LTC4S

Literature references

Rouzer, CA., Samuelsson, B. (1987). Reversible, calcium-dependent membrane association of human leukocyte 5-lipoxygenase. *Proc Natl Acad Sci U S A, 84*, 7393-7. ↗

Matsumoto, T., Rouzer, CA., Samuelsson, B. (1986). Single protein from human leukocytes possesses 5-lipoxygenase and leukotriene A4 synthase activities. *Proc Natl Acad Sci U S A, 83*, 857-61. ↗

Register, RB., Jones, RE., Kargman, S., Dixon, RA., Rouzer, CA., Rands, E. (1988). Characterization of cloned human leukocyte 5-lipoxygenase expressed in mammalian cells. *J Biol Chem, 263*, 10135-40. ↗

Editions

2008-04-21	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.
2012-11-10	Reviewed	Rush, MG.
2018-02-21	Reviewed	Hansen, TV.

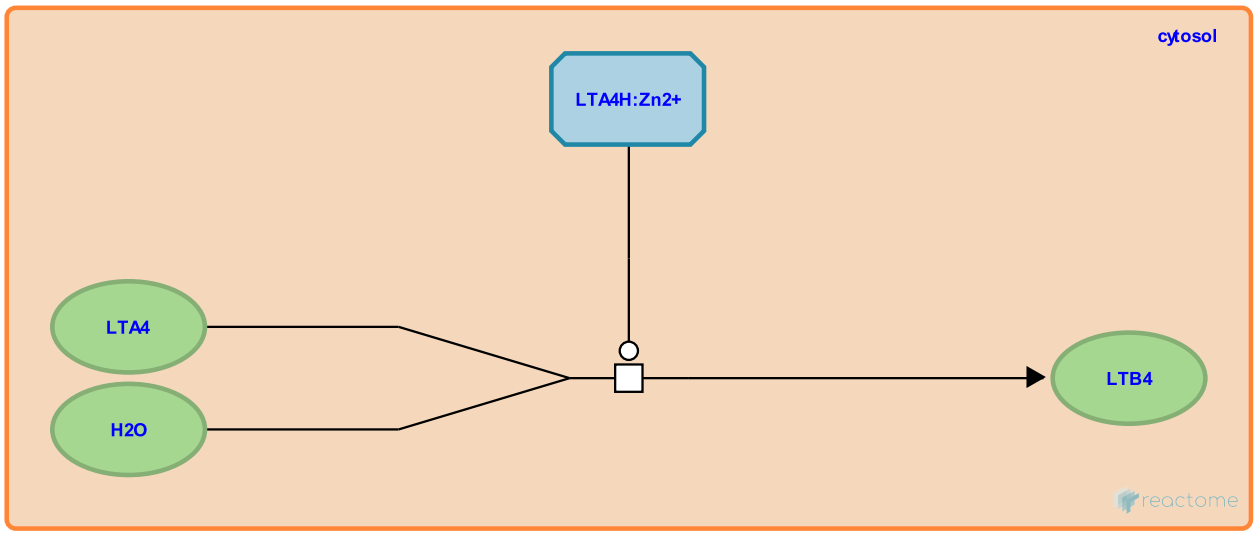
LTA4 is hydolysed to LTB4 by LTA4H ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-266072

Type: transition

Compartments: cytosol



Leukotriene A4 hydrolase (LTA4H) is a monomeric, soluble enzyme that catalyzes the hydrolysis of the allylic epoxide leukotriene A4 (LTA4) to the dihydroxy acid leukotriene B4 (LTB4) (Radmark et al. 1984, McGee & Fitzpatrick 1985).

Preceded by: 5S-HpETE is dehydrated to LTA4 by ALOX5

Followed by: LTB4 is oxidised to 12-oxoLTB4 by PTGR1, CYP4F2, 4F3 20-hydroxylate LTB4

Literature references

Jörnvall, H., Rådmark, O., Shimizu, T., Samuelsson, B. (1984). Leukotriene A4 hydrolase in human leukocytes. Purification and properties. *J Biol Chem, 259,* 12339-45. ↗

McGee, J., Fitzpatrick, F. (1985). Enzymatic hydration of leukotriene A4. Purification and characterization of a novel epoxide hydrolase from human erythrocytes. *J Biol Chem, 260,* 12832-7. ↗

Editions

2008-04-21	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.
2012-11-10	Reviewed	Rush, MG.

LTB4 is oxidised to 12-oxoLTB4 by PTGR1 ↗

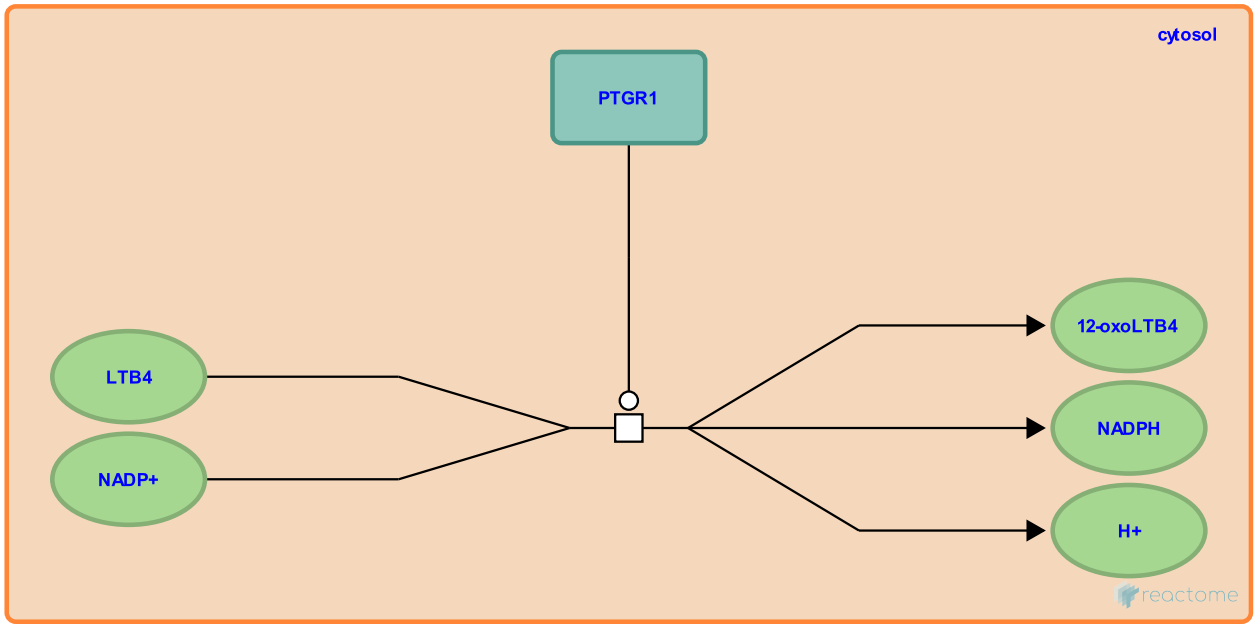
Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161567

Type: transition

Compartments: cytosol

Inferred from: LTB4 is oxidised to 12-oxoLTB4 by PTGR1 (Sus scrofa)



Prostaglandin reductase 1 (PTGR1) aka LTB4DH metabolizes eicosanoids by catalysing the oxidation of leukotriene B4 (LTB4) to form 12-oxo-Leukotriene B4 (12-oxoLTB4) aka 12-Keto-LTB4. The gene was originally cloned as leukotriene B4 12-hydroxydehydrogenase (LTB4DH) but was later discovered to have dual functionality as a prostaglandin reductase (Yokomizo et al. 1996). This reaction has been inferred from a reaction in pigs (Yokomizo et al. 1993, Ensor et al. 1998).

Preceded by: LTA4 is hydolysed to LTB4 by LTA4H

Literature references

Tai, HH., Zhang, H., Ensor, CM. (1998). Purification, cDNA cloning and expression of 15-oxoprostaglandin 13-reductase from pig lung. *Biochem J, 330*, 103-8. ↗

Takahashi, T., Kasama, T., Yokomizo, T., Sato, F., Kobayashi, Y., Taketani, Y. et al. (1993). Enzymatic inactivation of leukotriene B4 by a novel enzyme found in the porcine kidney. Purification and properties of leukotriene B4 12-hydroxydehydrogenase. *J Biol Chem, 268*, 18128-35. ↗

Kume, K., Uozumi, N., Ogawa, Y., Yokomizo, T., Izumi, T., Shimizu, T. (1996). cDNA cloning, expression, and mutagenesis study of leukotriene B4 12-hydroxydehydrogenase. *J Biol Chem, 271*, 2844-50. ↗

Editions

2012-02-24	Authored, Edited	Williams, MG.
2012-11-10	Reviewed	Rush, MG.

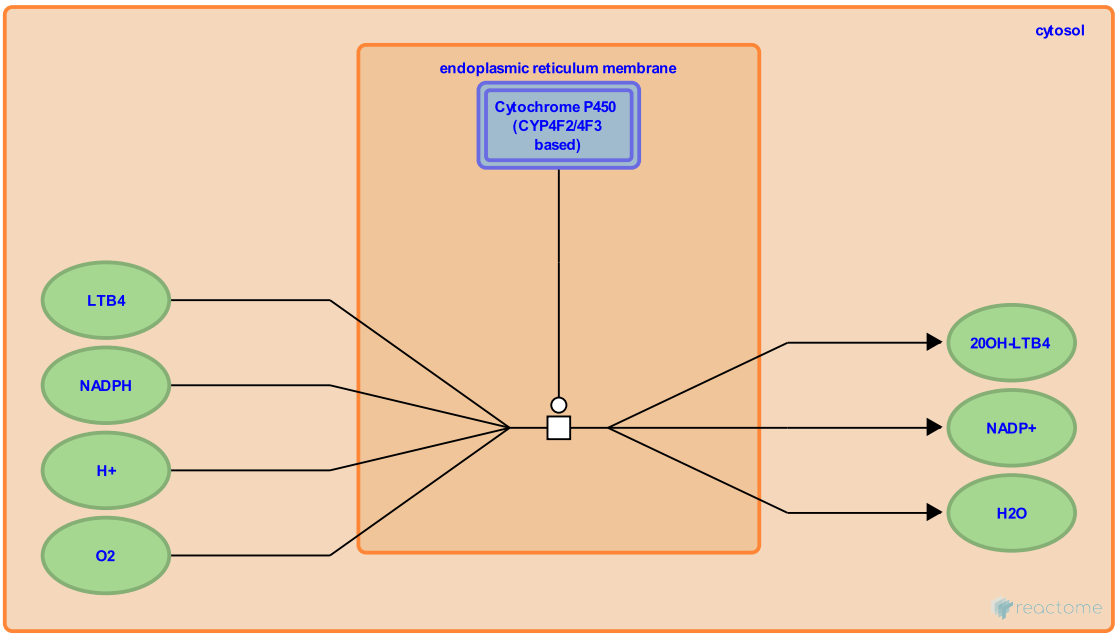
CYP4F2, 4F3 20-hydroxylate LTB4 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-211873

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Leukotriene B4 (LTB4) is formed from arachidonic acid and is a potent inflammatory mediator. LTB4's activity is terminated by formation of its omega hydroxylated metabolite, 20-hydroxyleukotriene B4 (20OH-LTB4), catalysed by CYP4F2 primarily in human liver (Jin et al. 1998) and also by CYP4F3 (Kikuta et al. 1998).

Preceded by: LTA4 is hydolysed to LTB4 by LTA4H

Followed by: 20oh-LTB4 is oxidised to 20cho-LTB4 by CYP4F2/4F3

Literature references

Jin, R., Lasker, JM., Koop, DR., Raucy, JL. (1998). Role of human CYP4F2 in hepatic catabolism of the proinflammatory agent leukotriene B4. *Arch Biochem Biophys, 359*, 89-98. ↗

Kikuta, Y., Tanaka, K., Kusunose, M., Kamada, N., Kato, M., Miyauchi, Y. et al. (1998). Human leukotriene B4 omega-hydroxylase (CYP4F3) gene: molecular cloning and chromosomal localization. *DNA Cell Biol, 17*, 221-30. ↗

Editions

2008-05-19	Authored, Edited	Jassal, B.
2012-11-10	Reviewed	Rush, MG.
2014-06-23	Revised	Jassal, B.

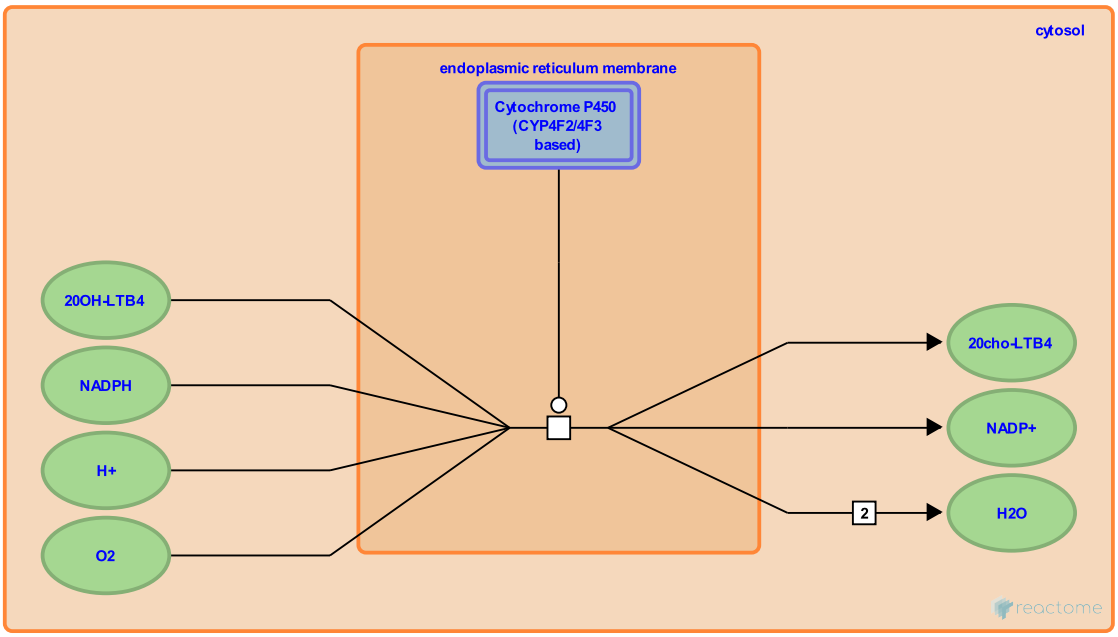
20oh-LTB4 is oxidised to 20cho-LTB4 by CYP4F2/4F3 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161745

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



The cytochrome P450s 4F2 (CYP4F2) and F3 (CYP4F3) oxidise the omega hydroxylated metabolite, 20-hydroxyleukotriene B4 (20oh-LTB4) to form 20-aldehyde leukotriene B4 (20cho-LTB4) (Soberman et al. 1988).

Preceded by: CYP4F2, 4F3 20-hydroxylate LTB4

Followed by: 20cho-LTB4 is oxidised to 20cooh-LTB4 by ALDH, 20cho-LTB4 is oxidised to 20cooh-LTB4 by CYP4F2/4F3

Literature references

Sutyak, JP., Soberman, RJ., Okita, RT., Roberts LJ, 2nd., Wendelborn, DF., Austen, KF. (1988). The identification and formation of 20-aldehyde leukotriene B4. *J Biol Chem, 263*, 7996-8002. ↗

Editions

2012-02-24	Authored, Edited	Williams, MG.
2012-11-10	Reviewed	Rush, MG.

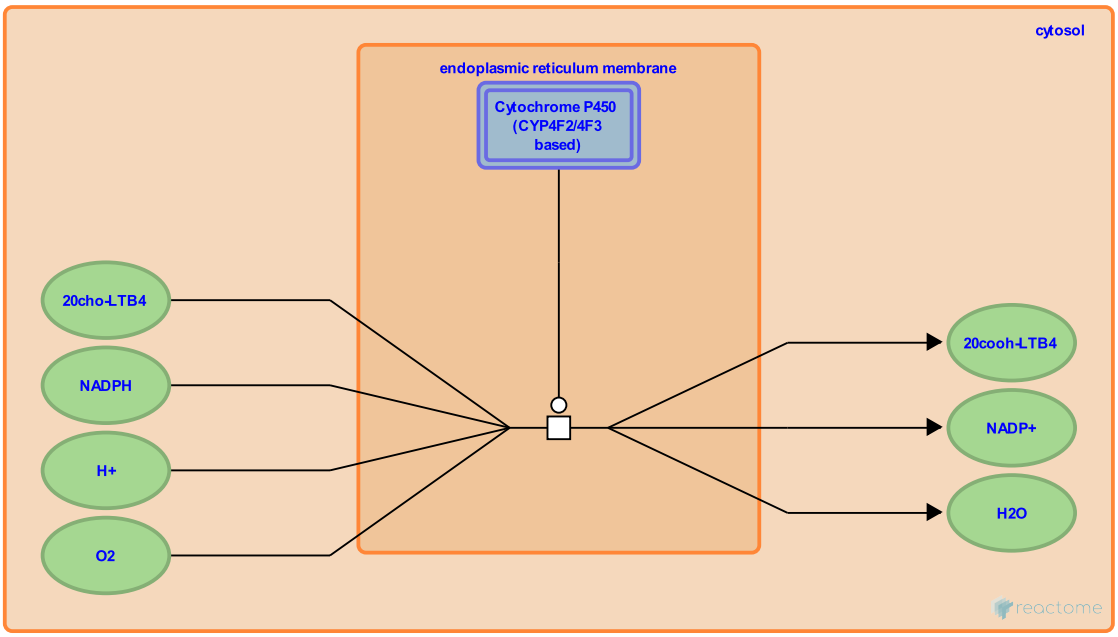
20cho-LTB4 is oxidised to 20cooh-LTB4 by CYP4F2/4F3 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161792

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



The cytochrome P450s 4F2 (CYP4F2) and F3 (CYP4F3) oxidise 20-aldehyde leukotriene B4 (20cho-LTB4) to form 20-carboxy leukotriene B4 (20cooh-LTB4) (Soberman et al. 1988).

Preceded by: 20oh-LTB4 is oxidised to 20cho-LTB4 by CYP4F2/4F3

Followed by: 20cooh-LTB4 is converted to 18cooh-LTB4

Literature references

Sutyak, JP., Soberman, RJ., Okita, RT., Roberts LJ, 2nd., Wendelborn, DF., Austen, KF. (1988). The identification and formation of 20-aldehyde leukotriene B4. *J Biol Chem, 263*, 7996-8002. ↗

Editions

2012-02-24	Authored, Edited	Williams, MG.
2012-11-10	Reviewed	Rush, MG.

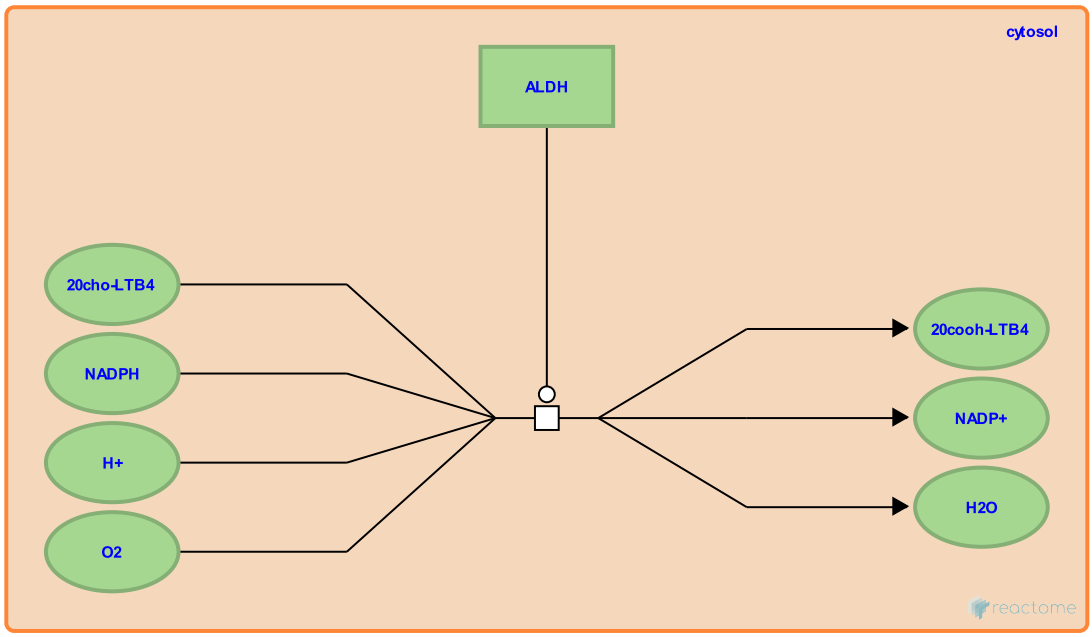
20cho-LTB4 is oxidised to 20cooh-LTB4 by ALDH ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161979

Type: transition

Compartments: cytosol



An aldehyde dehydrogenase (ALDH) yet to be cloned in humans has been observed to oxidise 20-aldehyde leukotriene B4 (20cho-LTB4) to form 20-carboxy leukotriene B4 (20cooh-LTB4) (Sutyak et al. 1989).

Preceded by: 20oh-LTB4 is oxidised to 20cho-LTB4 by CYP4F2/4F3

Followed by: 20cooh-LTB4 is converted to 18cooh-LTB4

Literature references

Soberman, RJ., Sutyak, J., Austen, KF. (1989). Identification of an aldehyde dehydrogenase in the microsomes of human polymorphonuclear leukocytes that metabolizes 20-aldehyde leukotriene B4. *J Biol Chem, 264*, 14818-23. ↗

Editions

2012-02-24	Authored, Edited	Williams, MG.
2012-11-10	Reviewed	Rush, MG.

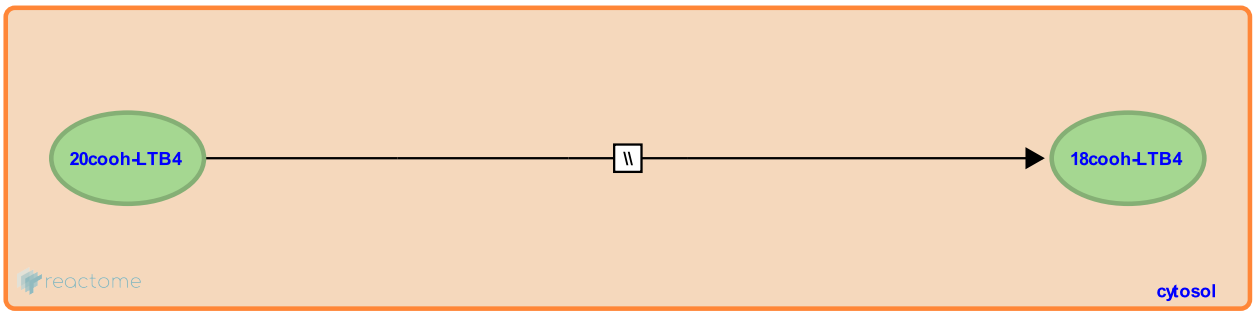
20cooh-LTB4 is converted to 18cooh-LTB4 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161790

Type: omitted

Compartments: cytosol



Once omega-oxidation has occurred, 20-carboxy leukotriene B4 (20cooh-LTB4) can be further metabolized by beta-oxidation at its omega end into 18-carboxy-LTB4 (18cooh-LTB4) (Berry et al. 2003, Wheelan et al. 1999). The actual human enzyme or enzymes involved have yet to be identified.

Preceded by: 20cho-LTB4 is oxidised to 20cooh-LTB4 by ALDH, 20cho-LTB4 is oxidised to 20cooh-LTB4 by CYP4F2/4F3

Literature references

Hankin, JA., Bilir, B., Murphy, RC., Wheelan, P., Guenette, D. (1999). Metabolic transformations of leukotriene B4 in primary cultures of human hepatocytes. *J Pharmacol Exp Ther, 288*, 326-34. ↗

Berry, KA., Gosselin, J., Flamand, L., Murphy, RC., Borgeat, P. (2003). Urinary metabolites of leukotriene B4 in the human subject. *J Biol Chem, 278*, 24449-60. ↗

Editions

2012-02-24	Authored, Edited	Williams, MG.
2012-11-10	Reviewed	Rush, MG.

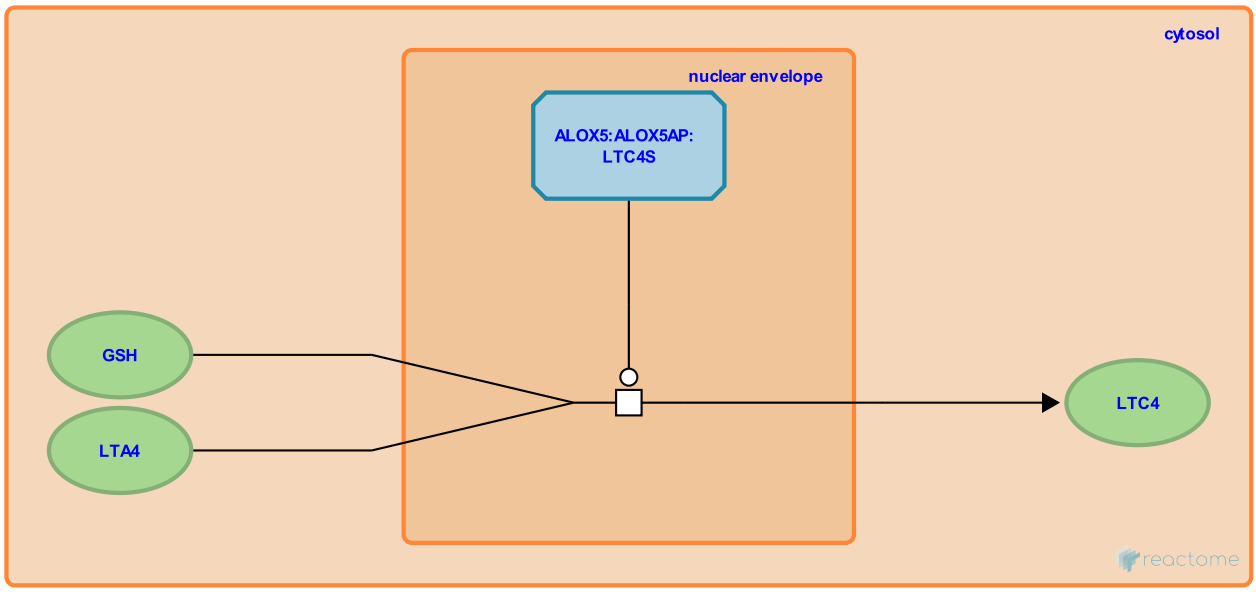
LTA4 is converted to LTC4 by LTC4S ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-266050

Type: transition

Compartments: nuclear envelope, cytosol



Leukotriene A4 conjugates with reduced glutathione (GSH) to produce leukotriene C4 (LTC4). This conjugation is mediated by the homodimeric, perinuclear membrane-bound enzyme leukotriene C4 synthase (LTC4S) (Lam et al. 1994, Welsch et al. 1994). LTC4S differs from cytosolic and microsomal GSH-S-transferases by having a very narrow substrate specificity and the inability to conjugate xenobiotics.

Preceded by: 5S-HpETE is dehydrated to LTA4 by ALOX5

Followed by: LTC4 is exported from the cytosol by ABCC1

Literature references

Hauser, SD., Isakson, PC., Mathis, KJ., Welsch, DJ., Creely, DP., Krivi, GG. (1994). Molecular cloning and expression of human leukotriene-C4 synthase. *Proc Natl Acad Sci U S A, 91*, 9745-9. ↗

Freeman, GJ., Lam, BK., Austen, KF., Penrose, JF. (1994). Expression cloning of a cDNA for human leukotriene C4 synthase, an integral membrane protein conjugating reduced glutathione to leukotriene A4. *Proc Natl Acad Sci U S A, 91*, 7663-7. ↗

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2008-04-21	Edited	Jassal, B.
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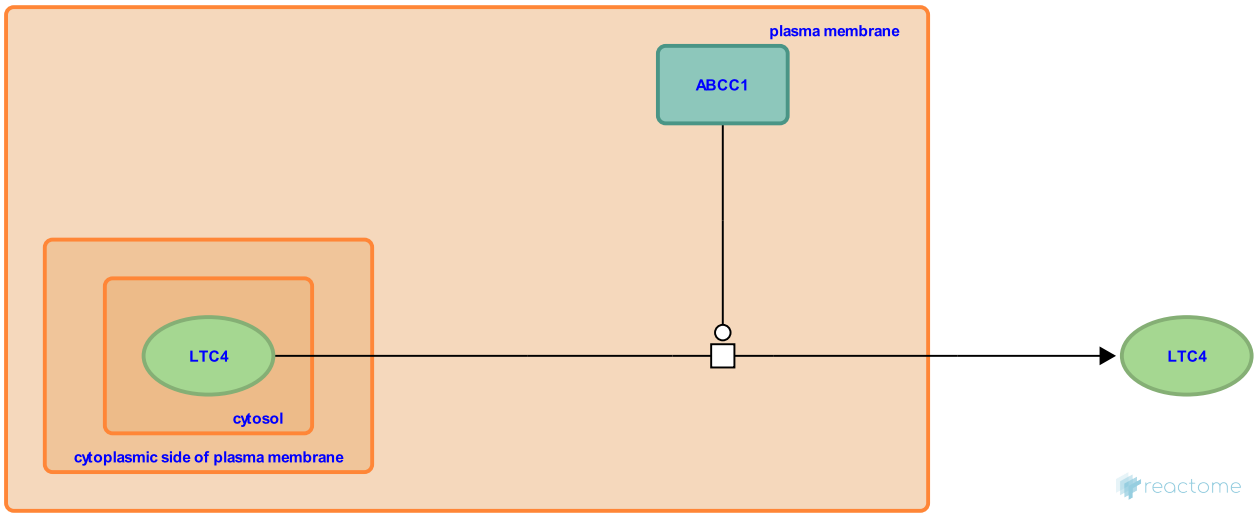
LTC4 is exported from the cytosol by ABCC1 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-266070

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



On formation, leukotriene C4 (LTC4) is exported to the extracellular region by the ABCC1 transporter (Sjolinder et al. 1999, Lam et al. 1989) and processed further by cleavage reactions.

Preceded by: LTA4 is converted to LTC4 by LTC4S

Followed by: GGT1, 5 dimers hydrolyse LTC4 to LTD4

Literature references

Soberman, RJ., Owen WF, Jr., Lam, BK., Austen, KF. (1989). The identification of a distinct export step following the biosynthesis of leukotriene C4 by human eosinophils. *J Biol Chem, 264*, 12885-9. ↗

Hydman, J., Sjölinder, M., Tornhamre, S., Claesson, HE., Lindgren, J. (1999). Characterization of a leukotriene C4 export mechanism in human platelets: possible involvement of multidrug resistance-associated protein 1. *J Lipid Res, 40*, 439-46. ↗

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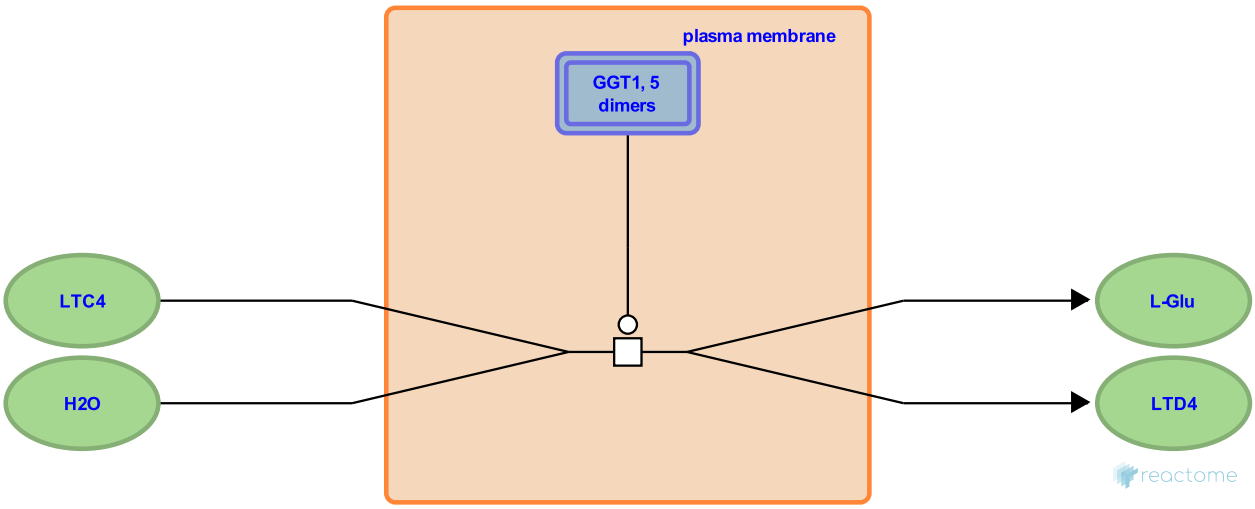
GGT1, 5 dimers hydrolyse LTC4 to LTD4 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-266046

Type: transition

Compartments: plasma membrane, extracellular region



The reversible conversion of leukotriene C4 (LTC4) to leukotriene D4 (LTD4) is catalysed by gamma-glutamyl transferases 1 (GGT1) and 5 (GGT5). GGTs are present on the outer surface of plasma membranes and are a heterodimer of a heavy and a light chain. Its action involves the hydrolysis of the gamma-glutamyl peptide bond of glutathione and glutathione conjugates, releasing glutamate. In this example, LTC4 is a glutathione conjugate that is hydrolysed to LTD4 (Anderson et al. 1982, Wickham et al. 2011).

Preceded by: LTC4 is exported from the cytosol by ABCC1

Literature references

Allison, RD., Meister, A., Anderson, ME. (1982). Interconversion of leukotrienes catalyzed by purified gamma-glutamyl transpeptidase: concomitant formation of leukotriene D4 and gamma-glutamyl amino acids. *Proc Natl Acad Sci U S A, 79*, 1088-91. ↗

West, MB., Cook, PF., Hanigan, MH., Wickham, S. (2011). Gamma-glutamyl compounds: substrate specificity of gamma-glutamyl transpeptidase enzymes. *Anal Biochem, 414*, 208-14. ↗

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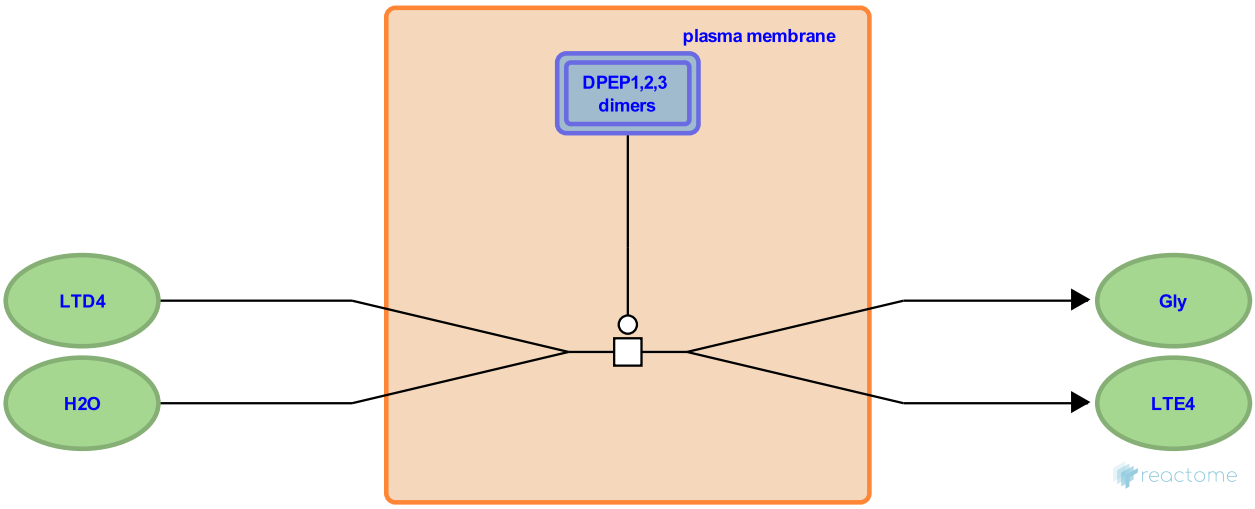
LTD4 is converted to LTE4 by DPEP1/2

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-266012

Type: transition

Compartments: plasma membrane, extracellular region



Another outer surface membrane-bound, homodimeric enzyme, dipeptidase, existing in two forms DPEP1 (Adachi et al. 1989) and DPEP2 (Lee et al. 1983, Raulf et al. 1987), further hydrolyses leukotriene D4 (LTD4) to leukotriene E4 (LTE4), cleaving a glycine residue in the process.

Literature references

Lee, CW., Lewis, RA., Corey, EJ., Austen, KF. (1983). Conversion of leukotriene D4 to leukotriene E4 by a dipeptidase released from the specific granule of human polymorphonuclear leucocytes. *Immunology, 48*, 27-35.

Stüning, M., Köller, M., König, W., Raulf, M. (1987). Release and functional characterization of the leukotriene D4-metabolizing enzyme (dipeptidase) from human polymorphonuclear leucocytes. *Scand J Immunol, 25*, 305-13.

Noguchi, T., Tsujimoto, M., Okamura, N., Iwata, H., Kubota, I., Nakazato, H. et al. (1989). Purification and characterization of human microsomal dipeptidase. *J Biochem, 105*, 957-61.

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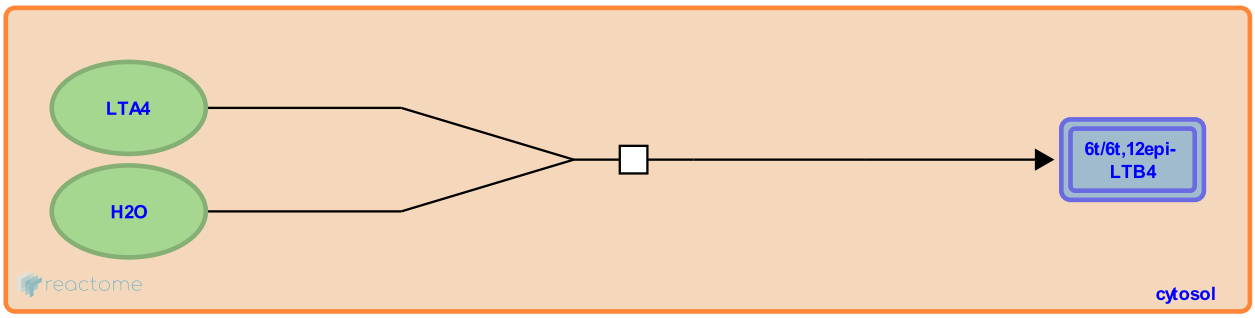
LTA4 is hydrolysed to 6t-/6t,12epi-LTB4 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161962

Type: transition

Compartments: cytosol



Non-enzymatic hydrolysis of the leukotriene A4 (LTA4) epoxide bond creates 6-trans leukotriene B4 (6t-LTB4) and 6-trans,12-epi leukotriene B4 (6t,12epi-LTB4) stereoisomers (Mansour & Agha 1999, Sirois et al. 1985).

Preceded by: 5S-HpETE is dehydrated to LTA4 by ALOX5

Literature references

Chagnon, M., Sirois, P., Borgeat, P., Gentile, J., Gladu, M., Salari, H. et al. (1985). Metabolism of leukotrienes by adult and fetal human lungs. *Exp Lung Res, 9*, 17-30. ↗

Mansour, M., Agha, A. (1999). Inhibition of calcium ionophore-stimulated leukotriene generation from intact human neutrophils by captopril. *Res Commun Mol Pathol Pharmacol, 104*, 345-60. ↗

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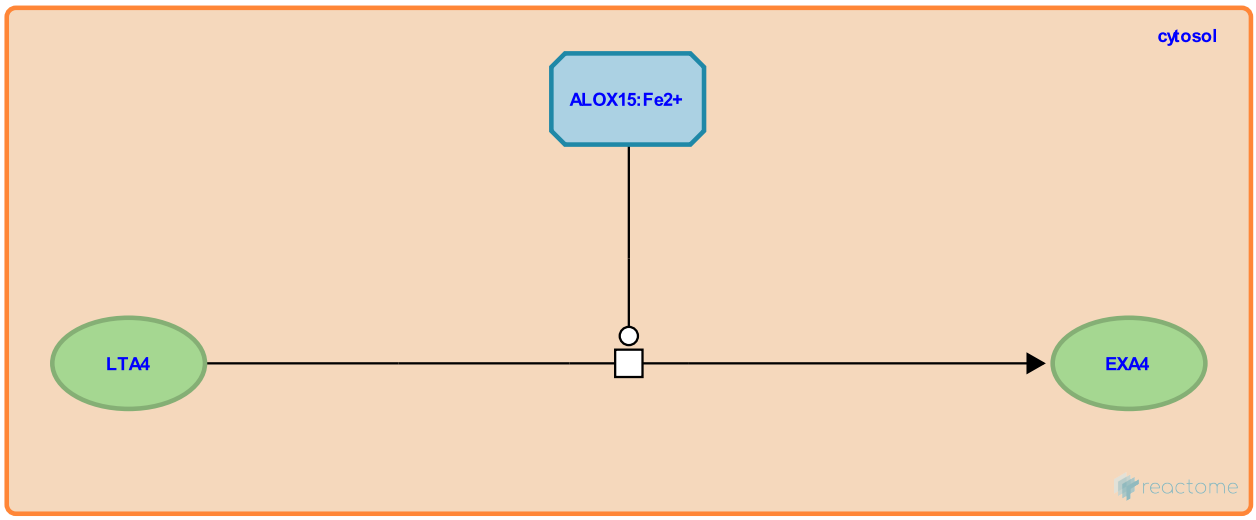
LTA4 is converted to EXA4 by ALOX15 ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2162019

Type: transition

Compartments: cytosol



Analogous to arachidonate 5-lipoxygenase (ALOX5) biosynthesis of leukotriene A4 (LTA4), arachidonate 15-lipoxygenase (ALOX15) can form an epoxide across C-14 and C-15 to form 14,15-LTA4 aka eoxin A4 (EXA4) (Feltenmark et al. 2008, Claesson et al. 2008).

Preceded by: 5S-HpETE is dehydrated to LTA4 by ALOX5

Followed by: EXA4 is converted to EXC4 by LTC4S

Literature references

Griffiths, W., Brunnström, A., Edenius, C., Backman, L., Björkholm, M., Gautam, N. et al. (2008). Eoxins are proinflammatory arachidonic acid metabolites produced via the 15-lipoxygenase-1 pathway in human eosinophils and mast cells. *Proc Natl Acad Sci U S A, 105*, 680-5. ↗

Brunnström, A., Björkholm, M., Johnson, HA., Griffiths, WJ., Sjöberg, J., Porwit, A. et al. (2008). Hodgkin Reed-Sternberg cells express 15-lipoxygenase-1 and are putative producers of eoxins in vivo: novel insight into the inflammatory features of classical Hodgkin lymphoma. *FEBS J, 275*, 4222-34. ↗

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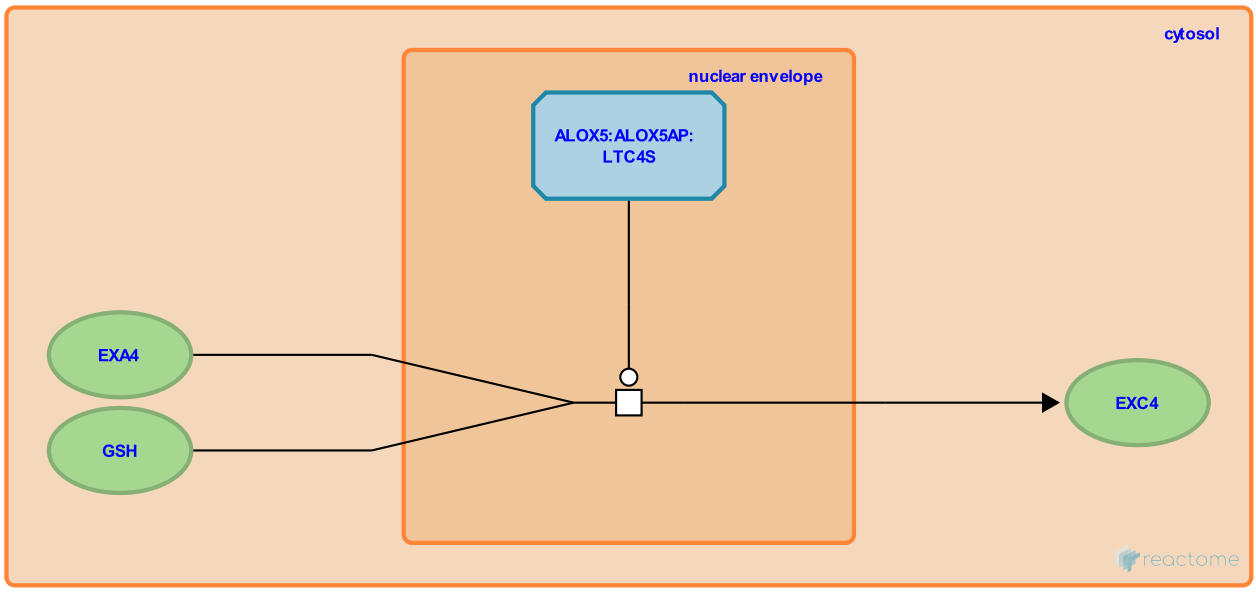
EXA4 is converted to EXC4 by LTC4S ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161768

Type: transition

Compartments: nuclear envelope, cytosol



In addition to its role converting leukotriene A4 (LTA4) into leukotriene C4 (LTC4), the enzyme leukotriene C4 synthase (LTC4S) analogously converts eoxin A4 (EXA4), with reduced glutathione (GSH), to eoxin C4 (EXC4) (Feltenmark et al. 2008, Claesson et al. 2008).

Preceded by: LTA4 is converted to EXA4 by ALOX15

Followed by: EXC4 is converted to EXD4 by GGT

Literature references

Griffiths, W., Brunnström, A., Edenius, C., Backman, L., Björkholm, M., Gautam, N. et al. (2008). Eoxins are proinflammatory arachidonic acid metabolites produced via the 15-lipoxygenase-1 pathway in human eosinophils and mast cells. *Proc Natl Acad Sci U S A, 105*, 680-5. ↗

Brunnström, A., Björkholm, M., Johnson, HA., Griffiths, WJ., Sjöberg, J., Porwit, A. et al. (2008). Hodgkin Reed-Sternberg cells express 15-lipoxygenase-1 and are putative producers of eoxins in vivo: novel insight into the inflammatory features of classical Hodgkin lymphoma. *FEBS J, 275*, 4222-34. ↗

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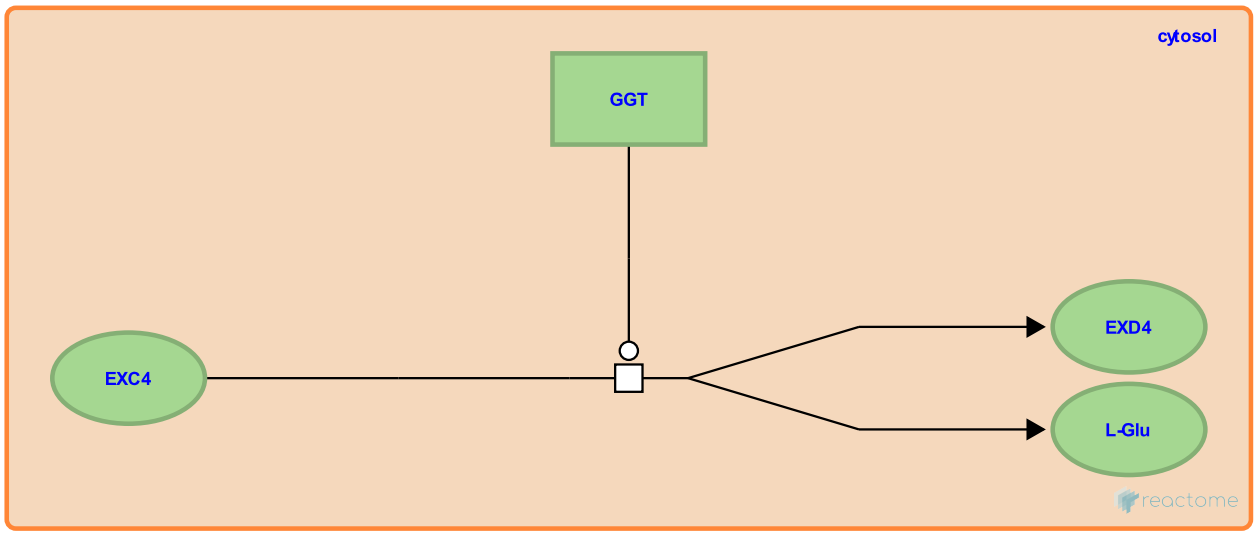
EXC4 is converted to EXD4 by GGT ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161945

Type: transition

Compartments: cytosol



In an analogous reaction to the formation of leukotriene D4 (LTD4), eoxin C4 (EXC4) is converted to eoxin D4 (EXD4) by a class of gamma-glutamyltransferase (GGT) (Feltenmark et al. 2008, Claesson et al. 2008) which has not yet been identified.

Preceded by: EXA4 is converted to EXC4 by LTC4S

Followed by: EXD4 is converted to EXE4 by DPEP

Literature references

Griffiths, W., Brunnström, A., Edenius, C., Backman, L., Björkholm, M., Gautam, N. et al. (2008). Eoxins are proinflammatory arachidonic acid metabolites produced via the 15-lipoxygenase-1 pathway in human eosinophils and mast cells. *Proc Natl Acad Sci U S A, 105*, 680-5. ↗

Brunnström, A., Björkholm, M., Johnson, HA., Griffiths, WJ., Sjöberg, J., Porwit, A. et al. (2008). Hodgkin Reed-Sternberg cells express 15-lipoxygenase-1 and are putative producers of eoxins in vivo: novel insight into the inflammatory features of classical Hodgkin lymphoma. *FEBS J, 275*, 4222-34. ↗

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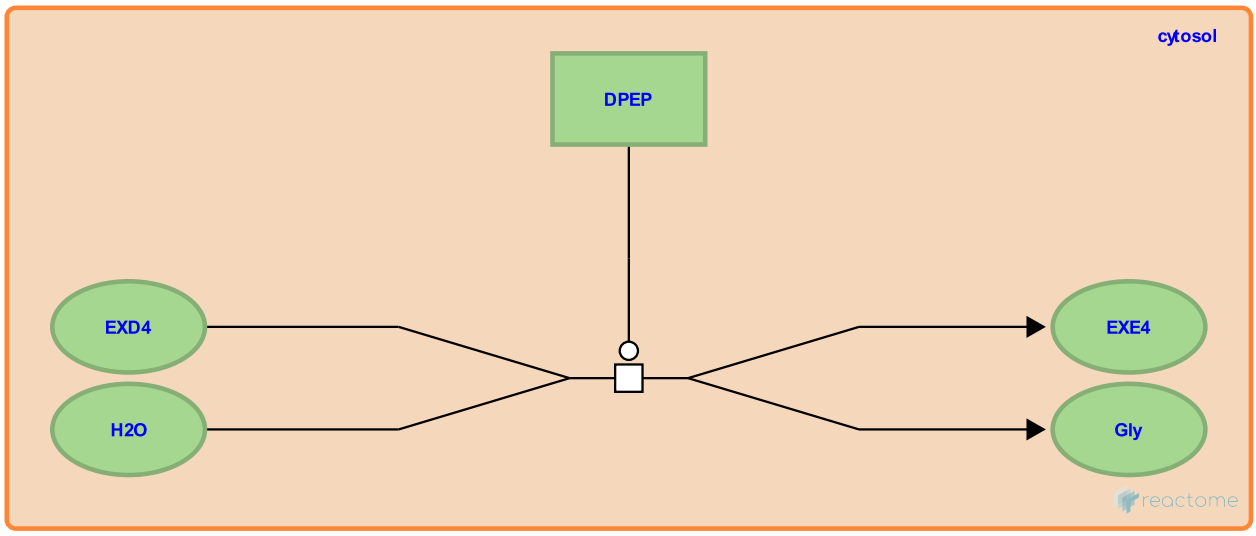
EXD4 is converted to EXE4 by DPEP ↗

Location: Synthesis of Leukotrienes (LT) and Eoxins (EX)

Stable identifier: R-HSA-2161868

Type: transition

Compartments: cytosol



In an analogous reaction to the formation of leukotriene E4 (LTE4), eoxin D4 (EXD4) is converted to eoxin E4 (EXE4) by a dipeptidase (DPEP) (Feltenmark et al. 2008, Claesson et al. 2008) which has not yet been identified.

Preceded by: EXC4 is converted to EXD4 by GGT

Literature references

Griffiths, W., Brunnström, A., Edenius, C., Backman, L., Björkholm, M., Gautam, N. et al. (2008). Eoxins are proinflammatory arachidonic acid metabolites produced via the 15-lipoxygenase-1 pathway in human eosinophils and mast cells. *Proc Natl Acad Sci U S A, 105*, 680-5. ↗

Brunnström, A., Björkholm, M., Johnson, HA., Griffiths, WJ., Sjöberg, J., Porwit, A. et al. (2008). Hodgkin Reed-Sternberg cells express 15-lipoxygenase-1 and are putative producers of eoxins in vivo: novel insight into the inflammatory features of classical Hodgkin lymphoma. *FEBS J, 275*, 4222-34. ↗

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