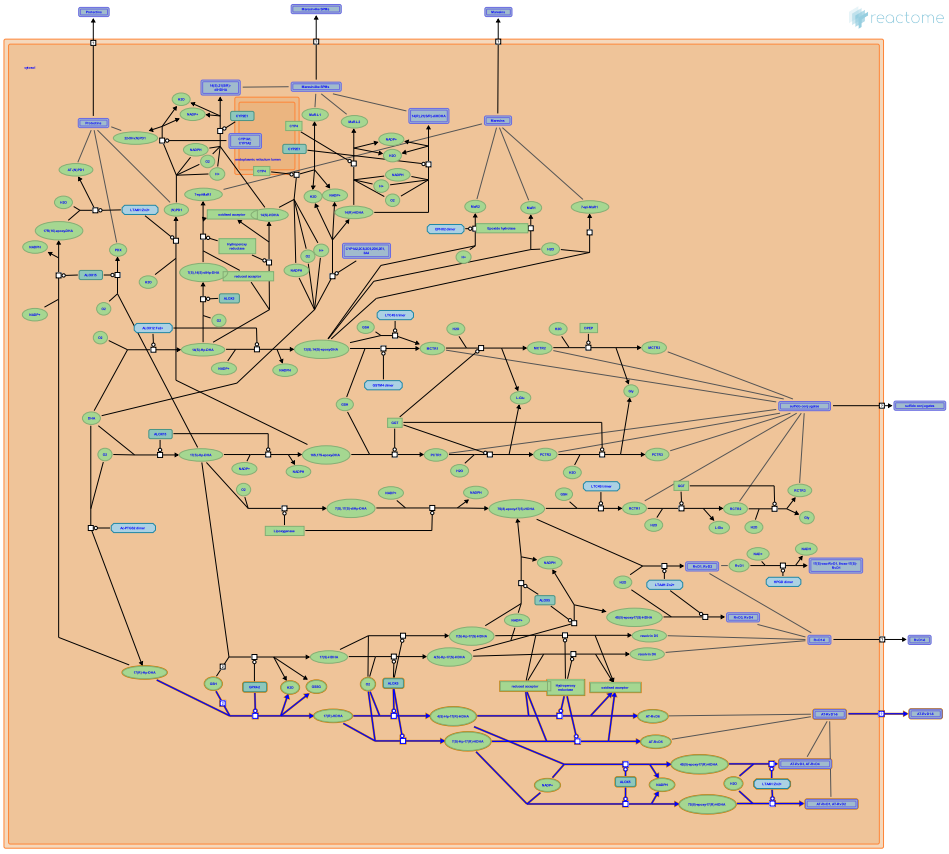
Biosynthesis of aspirin-triggered D-series resolvins



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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.

29/04/2024

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. ↗

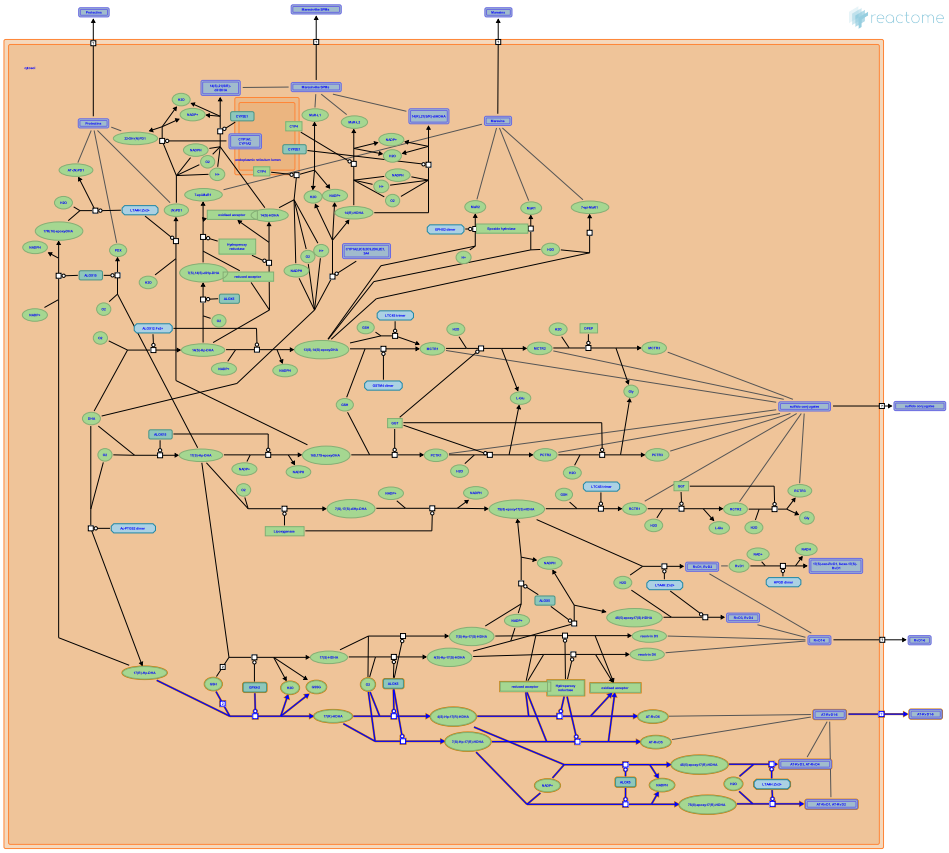
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Biosynthesis of aspirin-triggered D-series resolvins ↗

Stable identifier: R-HSA-9020265



The D-series resolvins (RvD1-6) are biosynthesised from the precursor ω-3 fatty acid docosahexaenoic acid (DHA), either via the lipoxygenase pathway (17(S)-RvDs) or via aspirin-triggered cylcooxygenase catalysis (described here) forming the epimeric 17(R)-RvD1-6 resolvins (Serhan et al. 2014, Bannenberg & Serhan 2010).

Literature references

Serhan, CN., Bannenberg, G. (2010). Specialized pro-resolving lipid mediators in the inflammatory response: An update. *Biochim. Biophys. Acta, 1801*, 1260-73. ↗

Serhan, CN., Levy, BD., Chiang, N., Dalli, J. (2014). Lipid mediators in the resolution of inflammation. *Cold Spring Harb Perspect Biol, 7*, a016311. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

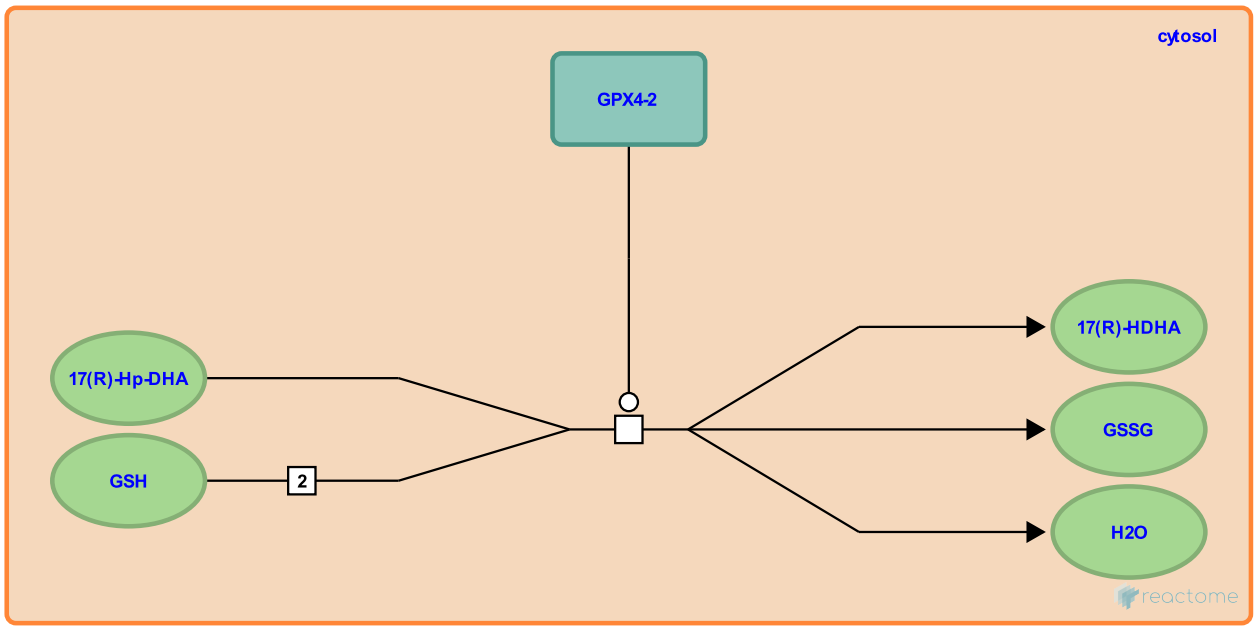
GPX4-2 reduces 17(R)-Hp-DHA to 17(R)-HDHA ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9020271

Type: transition

Compartments: cytosol



Cytosolic phospholipid hydroperoxide glutathione peroxidase (GPX4 isoform 2, GPX4-2) (Yagi et al. 1996) is a likely candidate for the reduction of organic hydroperoxides such as 17(R)-hydroperoxy-docosahexaenoic acid (17(R)-Hp-DHA) to 17(R)-hydroxydocosahexaenoic acid (17(R)-HDHA) (Han et al. 2013) using glutathione (GSH) as an electron donor (Brigelius-Flohe & Maiorino 2013). 17(R)-HDHA can then be transformed into 17(R)-D-resolvins and a 17-oxo electrophilic product 17-oxo-DHA (Groeger et al. 2010).

Followed by: ALOX5 oxidises 17(R)-HDHA to 4(S)-Hp-17(R)-HDHA, ALOX5 oxidises 17(R)-HDHA to 7(S)-Hp-17(R)-HDHA

Literature references

Hao, Y., Fan, Z., Yu, Y., Huo, R., Han, X., Wei, J. et al. (2013). Expression and characterization of recombinant human phospholipid hydroperoxide glutathione peroxidase. *IUBMB Life, 65*, 951-6. ↗

Nagata, N., Komura, S., Ohishi, N., Sun, Q., Yagi, K., Nishikimi, M. et al. (1996). Expression of human phospholipid hydroperoxide glutathione peroxidase gene for protection of host cells from lipid hydroperoxide-mediated injury . *Biochem. Biophys. Res. Commun., 219*, 486-91. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

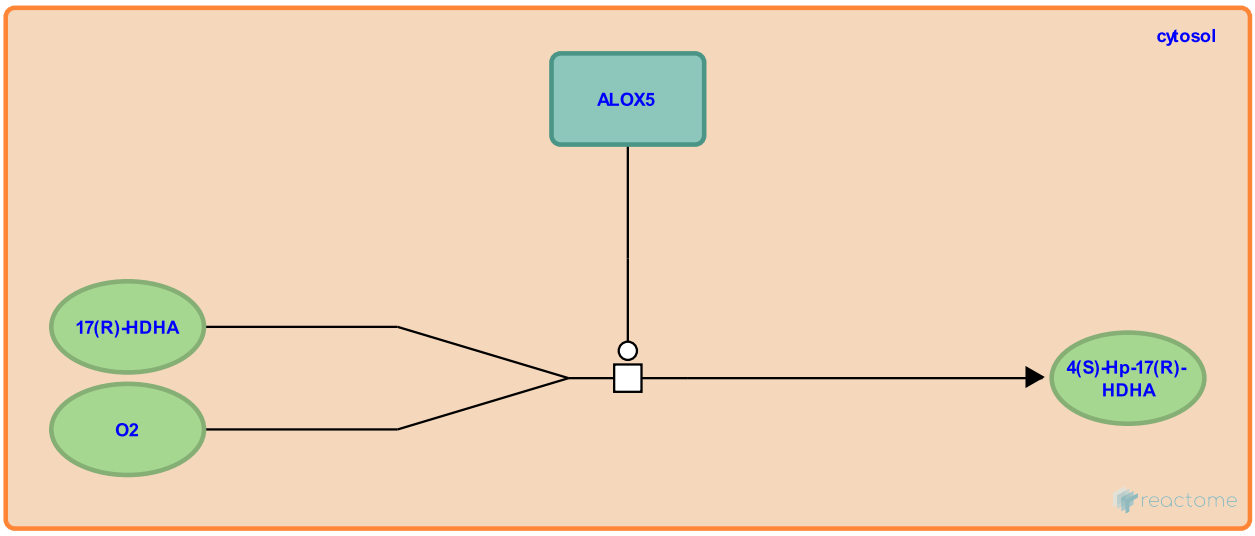
ALOX5 oxidises 17(R)-HDHA to 4(S)-Hp-17(R)-HDHA ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9020259

Type: transition

Compartments: cytosol



Lipoxygenase 5 (ALOX5) can oxidise 17(R)-hydroxydocosahexaenoic acid (17(R)-HDHA) into two hydroperoxy intermediates in human polymorphonuclear leukocytes (PMNs) (Serhan et al. 2002). The formation of 4(S)-hydroperoxy-17(R)-hydroxydocosahexaenoic acid (4(S)-Hp-17(R)-HDHA) is decribed here.

Preceded by: GPX4-2 reduces 17(R)-Hp-DHA to 17(R)-HDHA

Followed by: Hydroperoxy reductase reduces 4(S)-Hp-17(R)-HDHA to AT-RvD6, ALOX5 dehydrogenates 4(S)-Hp-17(R)-HDHA to 4S(5)-epoxy-17(R)-HDHA

Literature references

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

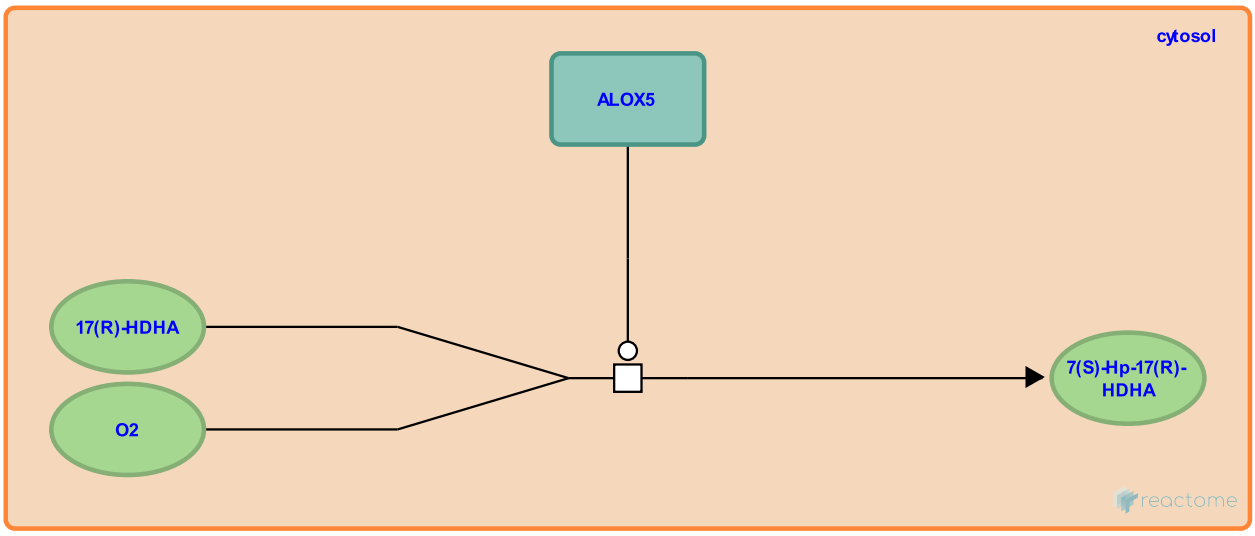
ALOX5 oxidises 17(R)-HDHA to 7(S)-Hp-17(R)-HDHA ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9020251

Type: transition

Compartments: cytosol



Lipoxygenase 5 (ALOX5) can oxidise 17(R)-hydroxydocosahexaenoic acid (17(R)-HDHA) into two hydroperoxy intermediates in human polymorphonuclear leukocytes (PMNs) (Serhan et al. 2002). The formation of 7(S)-hydroperoxy-17(R)-hydroxydocosahexaenoic acid (7(S)-Hp-17(R)-HDHA) is decribed here.

Preceded by: GPX4-2 reduces 17(R)-Hp-DHA to 17(R)-HDHA

Followed by: Hydroperoxy reductase reduces 7(S)-Hp-17(R)-HDHA to AT-RvD5, ALOX5 dehydrogenates 7(S)-Hp-17R-HDHA to 7S(8)-epoxy-17R-HDHA

Literature references

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

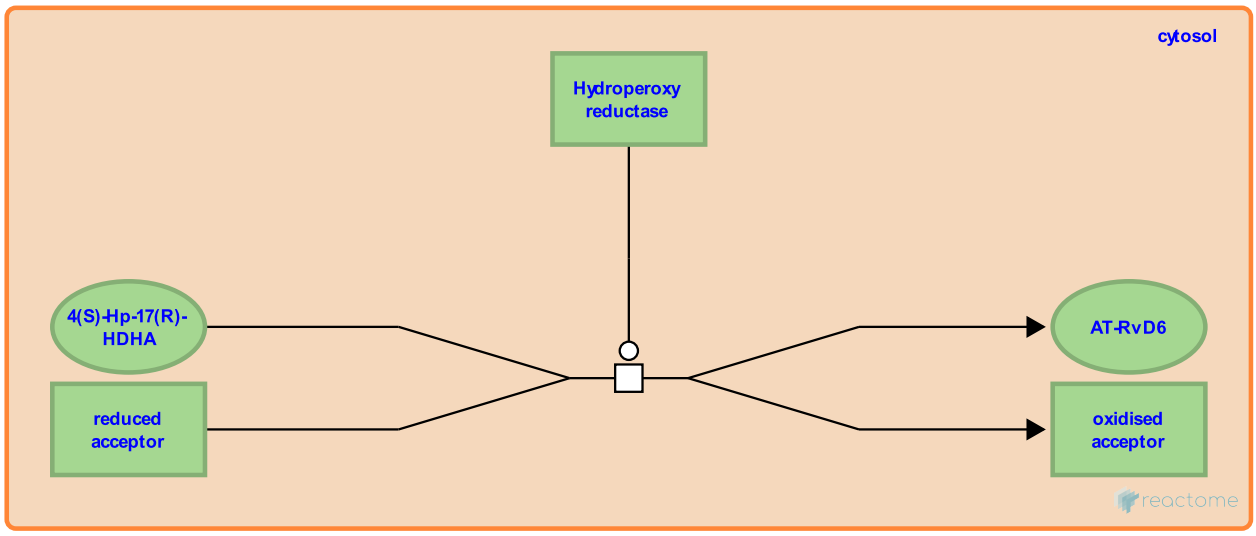
Hydroperoxy reductase reduces 4(S)-Hp-17(R)-HDHA to AT-RvD6 ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9024624

Type: transition

Compartments: cytosol



An unknown reductase mediates the reduction of 4(S)-hydroperoxy-17(R)-hydroxydocosahexaenoic acid (4(S)-Hp-17(R)-HDHA) to 4(S),17(R)-dihydroxydocosahexaenoic acid (AT-RvD6) (Serhan et al. 2002).

Preceded by: ALOX5 oxidises 17(R)-HDHA to 4(S)-Hp-17(R)-HDHA

Followed by: AT-RvD1-6 translocate from cytosol to extracellular region

Literature references

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

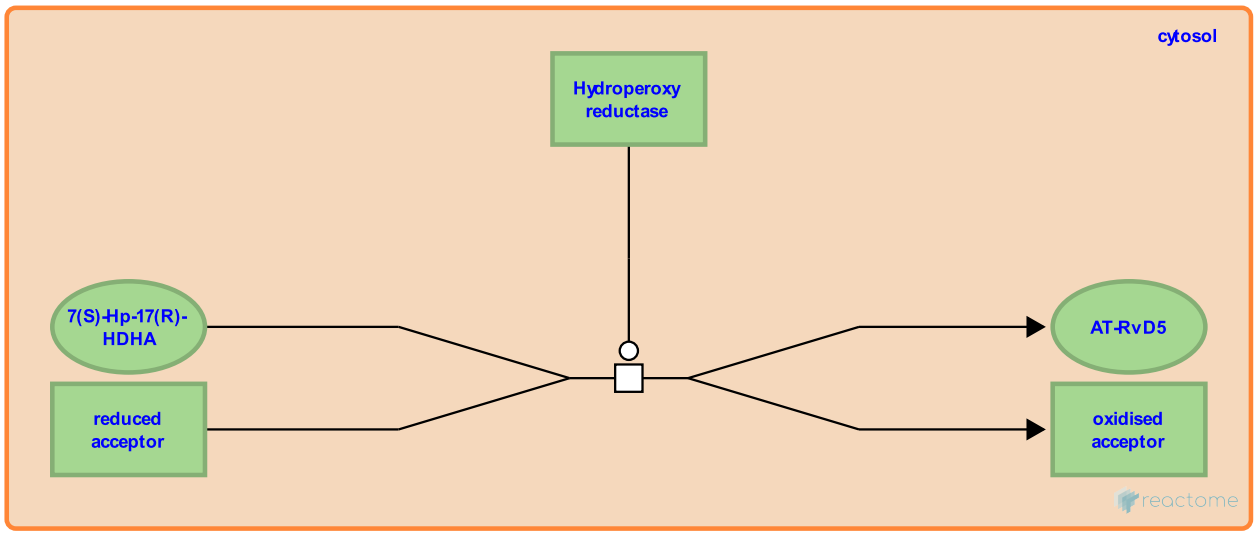
Hydroperoxy reductase reduces 7(S)-Hp-17(R)-HDHA to AT-RvD5 ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9024630

Type: transition

Compartments: cytosol



An unknown reductase mediates the reduction of 7(S)-hydroperoxy-17(R)-hydroxydocosahexaenoic acid (7(S)-Hp-17(R)-HDHA) to AT-RvD5 (Serhan et al. 2002), the structure of which has been chemically synthesised as 7(S),17(R)-dihydroxydocosahexaenoic acid (Ogawa et al. 2017). In mice with E.coli infection, several specialized pro-resolving mediators (SPMs) including RvD5, together with antibiotics, accelerated resolution and heightened host antimicrobial responses (Chiang et al. 2012).

Preceded by: ALOX5 oxidises 17(R)-HDHA to 7(S)-Hp-17(R)-HDHA

Followed by: AT-RvD1-6 translocate from cytosol to extracellular region

Literature references

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37. ↗

Morita, M., Suganuma, Y., Kobayashi, Y., Ogawa, N., Sugiyama, T. (2017). Total Synthesis of Resolvin D5. *J. Org. Chem., 82*, 2032-2039. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

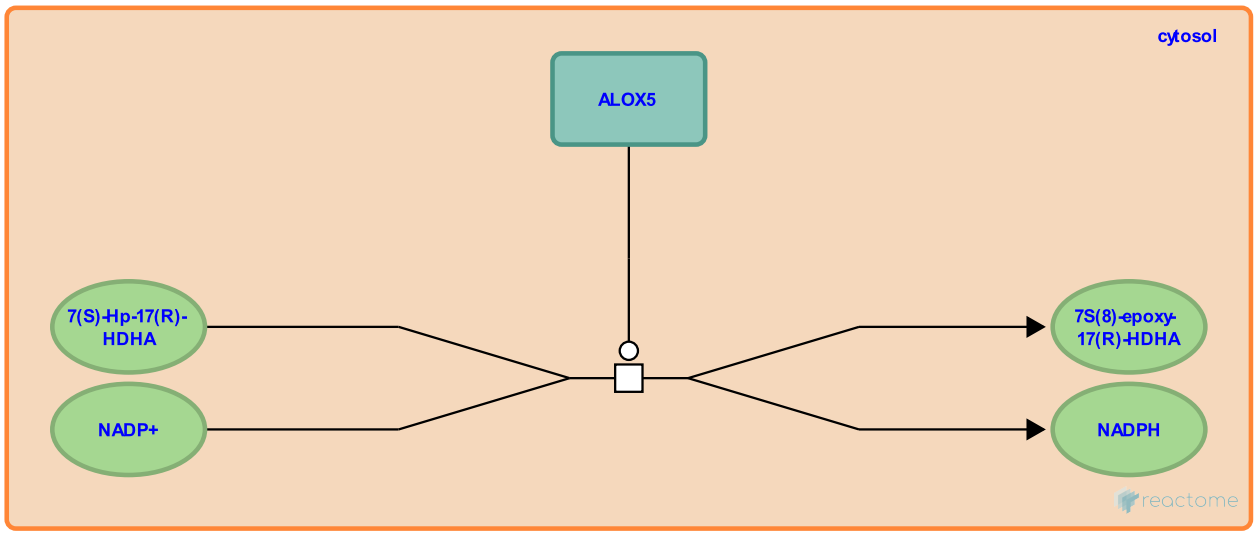
ALOX5 dehydrogenates 7(S)-Hp-17R-HDHA to 7S(8)-epoxy-17R-HDHA ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9020256

Type: transition

Compartments: cytosol



5-lipoxygenase (ALOX5) possesses dual lipoxygenase activity (Shimizu et al. 1984). In polymorphonuclear (PMN) cells, ALOX5 can epoxygenate (via dehydration) 7(S)-hydroperoxy-17(R)-hydroxydocosahexaenoic acid (7(S)-Hp-17(R)-HDHA) to form 7S(8)-epoxy-17(R)-hydroxydocosahexaenoic acid (7S(8)-epoxy-17(R)-HDHA (Serhan et al. 2002).

Preceded by: ALOX5 oxidises 17(R)-HDHA to 7(S)-Hp-17(R)-HDHA

Followed by: LTA4H:Zn2+ hydrolyses 7S(8)-epoxy-17(R)-HDHA to AT-RvD1 or AT-RvD2

Literature references

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

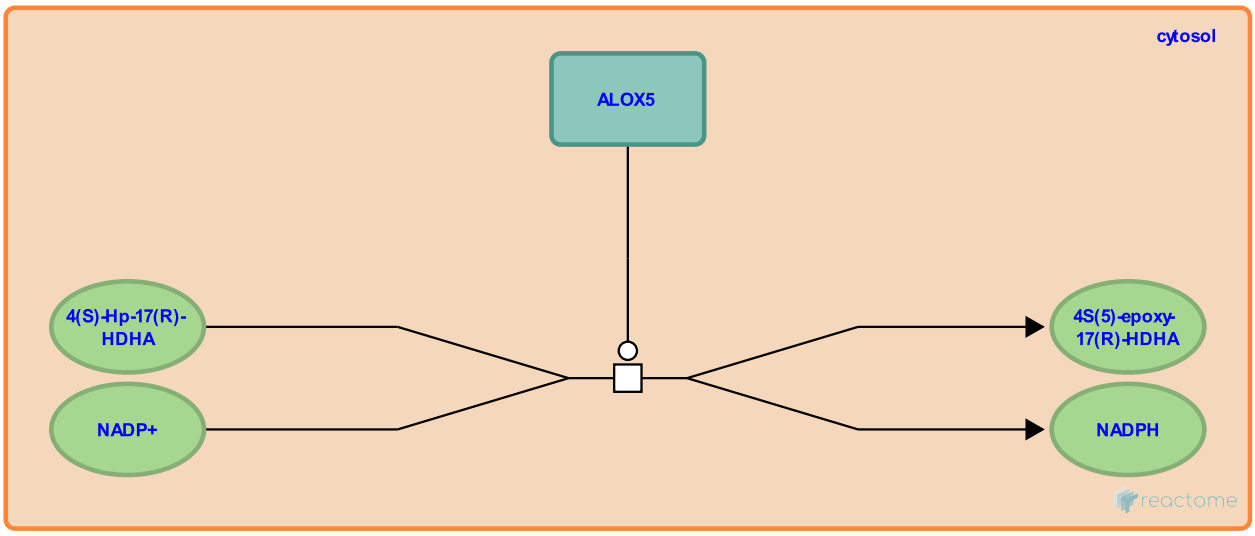
ALOX5 dehydrogenates 4(S)-Hp-17(R)-HDHA to 4S(5)-epoxy-17(R)-HDHA ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9020278

Type: transition

Compartments: cytosol



5-lipoxygenase (ALOX5) possesses dual lipoxygenase activity (Shimizu et al. 1984). In polymorphonuclear (PMN) cells, ALOX5 can epoxygenate (via dehydration) 4(S)-hydroperoxy-17(R)-hydroxydocosahexaenoic acid (4(S)-Hp-17(R)-HDHA) to form 4S(5)-epoxy-17(R)-hydroxydocosahexaenoic acid (4S(5)-epoxy-17(R)-HDHA (Serhan et al. 2002).

Preceded by: ALOX5 oxidises 17(R)-HDHA to 4(S)-Hp-17(R)-HDHA

Followed by: LTA4H:Zn2+ hydrolyses 4S(5)-epoxy-17(R)-HDHA to AT-RvD3 or AT-RvD4

Literature references

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

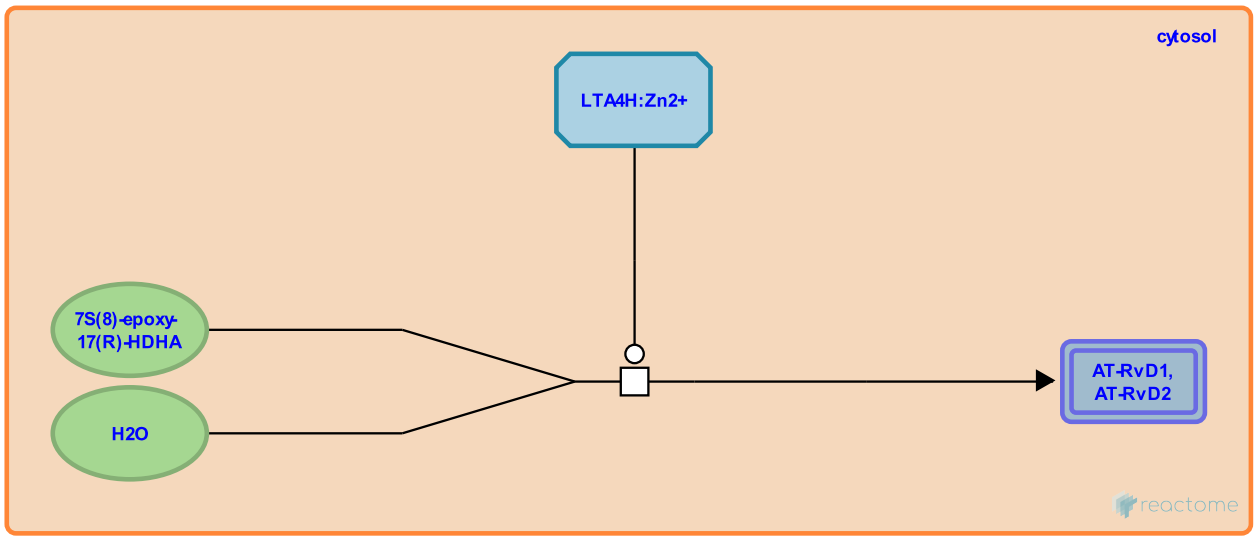
LTA4H:Zn2+ hydrolyses 7S(8)-epoxy-17(R)-HDHA to AT-RvD1 or AT-RvD2 ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9020252

Type: transition

Compartments: cytosol



Leukotriene A4 hydrolase (LTA4H) is a monomeric, soluble enzyme that uses a Zn2+ cofactor to catalyse the hydrolysis of the allylic epoxide leukotriene A4 (LTA4) (McGee & Fitzpatrick 1985). LTA4H can also catalyse the hydrolysis of 7S(8)-epoxy-17(R)-hydroxydocosahexaenoic acid (7S(8)-epoxy-17(R)-HDHA) to the trihydroxydocosahexaenoic acids 7(S), 8(R), 17(R)-triHDHA and 7(S), 16(R), 17(R)-triHDHA (AT-RvD1 and AT-RvD2 respectively) (Sun et al. 2007, Spite et al. 2009, Serhan et al. 2002). The D-resolvins are anti-inflammatory, pro-resolving, and non-phlogistic (that is, they mediate the clearance of leukocytes without eliciting an inflammatory response) (Serhan et al. 2008).

Preceded by: ALOX5 dehydrogenates 7(S)-Hp-17R-HDHA to 7S(8)-epoxy-17R-HDHA

Followed by: AT-RvD1-6 translocate from cytosol to extracellular region

Literature references

Cooper, D., Serhan, CN., Spite, M., Perretti, M., Petasis, NA., Flower, RJ. et al. (2009). Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. *Nature, 461*, 1287-91. ↗

Serhan, CN., Campbell, E., Colgan, SP., Oh, SF., Petasis, NA., Gotlinger, K. et al. (2007). Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. *J. Biol. Chem., 282*, 9323-34. ↗

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

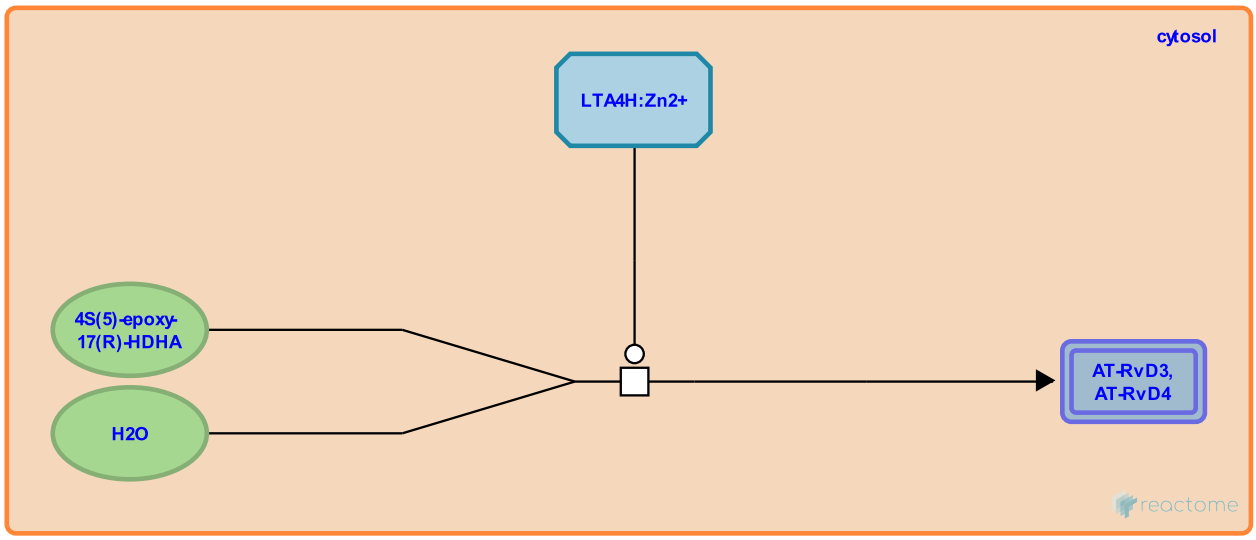
LTA4H:Zn2+ hydrolyses 4S(5)-epoxy-17(R)-HDHA to AT-RvD3 or AT-RvD4

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9020270

Type: transition

Compartments: cytosol



Leukotriene A4 hydrolase (LTA4H) is a monomeric, soluble enzyme that uses a Zn2+ cofactor to catalyse the hydrolysis of the allylic epoxide leukotriene A4 (LTA4) (McGee & Fitzpatrick 1985). LTA4H can also catalyse the hydrolysis of 4S(5)-epoxy-17(R)-hydroxydocosahexaenoic acid (4S(5)-epoxy-17(R)-HDHA) to the trihydroxydocosahexaenoic acids 4(S), 11(R), 17(R)-triHDHA and 4(S), 5(R), 17(R)-triHDHA (AT-RvD3 and AT-RvD4 respectively) (Dalli et al. 2013, Serhan et al. 2002, Winkler et al. 2013, 2016). The D-resolvins are anti-inflammatory, pro-resolving, and non-phlogistic (that is, they mediate the clearance of leukocytes without eliciting an inflammatory response) (Serhan et al. 2008).

Preceded by: ALOX5 dehydrogenates 4(S)-Hp-17(R)-HDHA to 4S(5)-epoxy-17(R)-HDHA

Followed by: AT-RvD1-6 translocate from cytosol to extracellular region

Literature references

Serhan, CN., Cheng, CY., Winkler, JW., Sanger, JM., Petasis, NA., Chiang, N. et al. (2016). Resolvin D4 stereoassignment and its novel actions in host protection and bacterial clearance. *Sci Rep, 6*, 18972.

Gronert, K., Serhan, CN., Devchand, PR., Colgan, SP., Hong, S., Mirick, G. et al. (2002). Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med., 196*, 1025-37.

Colas, RA., Hansen, TV., Tungen, JE., Vik, A., Dalli, J., Primdahl, KG. et al. (2017). Stereocontrolled synthesis and investigation of the biosynthetic transformations of 16(S),17(S)-epoxy-PDn-3 DPA. *Org. Biomol. Chem.*.

Serhan, CN., Colas, RA., Cheng, CY., Winkler, JW., Petasis, NA., Chiang, N. et al. (2013). Resolvin D3 and aspirin-triggered resolvin D3 are potent immunoresolvents. *Chem. Biol., 20*, 188-201.

Editions

2017-09-05	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

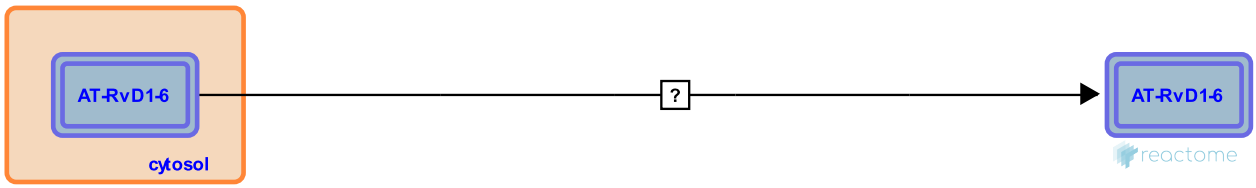
AT-RvD1-6 translocate from cytosol to extracellular region ↗

Location: Biosynthesis of aspirin-triggered D-series resolvins

Stable identifier: R-HSA-9024586

Type: uncertain

Compartments: extracellular region, cytosol



To produce their pro-resolving effects, 17(R)-RvD1-6 are released into the exudate of local inflammation sites (Serhan et al. 2000). The mechanism of translocation is unknown.

Preceded by: Hydroperoxy reductase reduces 7(S)-Hp-17(R)-HDHA to AT-RvD5, Hydroperoxy reductase reduces 4(S)-Hp-17(R)-HDHA to AT-RvD6, LTA4H:Zn2+ hydrolyses 4S(5)-epoxy-17(R)-HDHA to AT-RvD3 or AT-RvD4, LTA4H:Zn2+ hydrolyses 7S(8)-epoxy-17(R)-HDHA to AT-RvD1 or AT-RvD2

Literature references

Chiang, N., Colgan, SP., Serhan, CN., Brannon, J., Gronert, K., Clish, CB. (2000). Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. *J. Exp. Med., 192*, 1197-204. ↗

Editions

2017-10-06	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

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