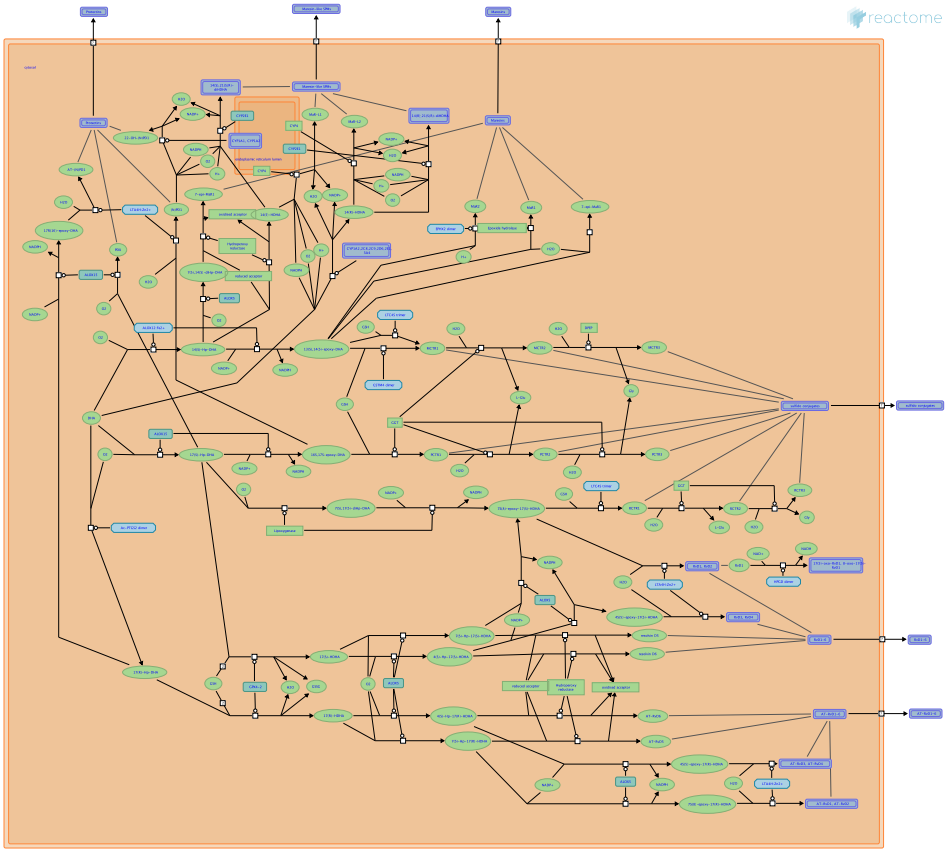
Biosynthesis of DHA-derived SPMs



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25/09/2021

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

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. ↗

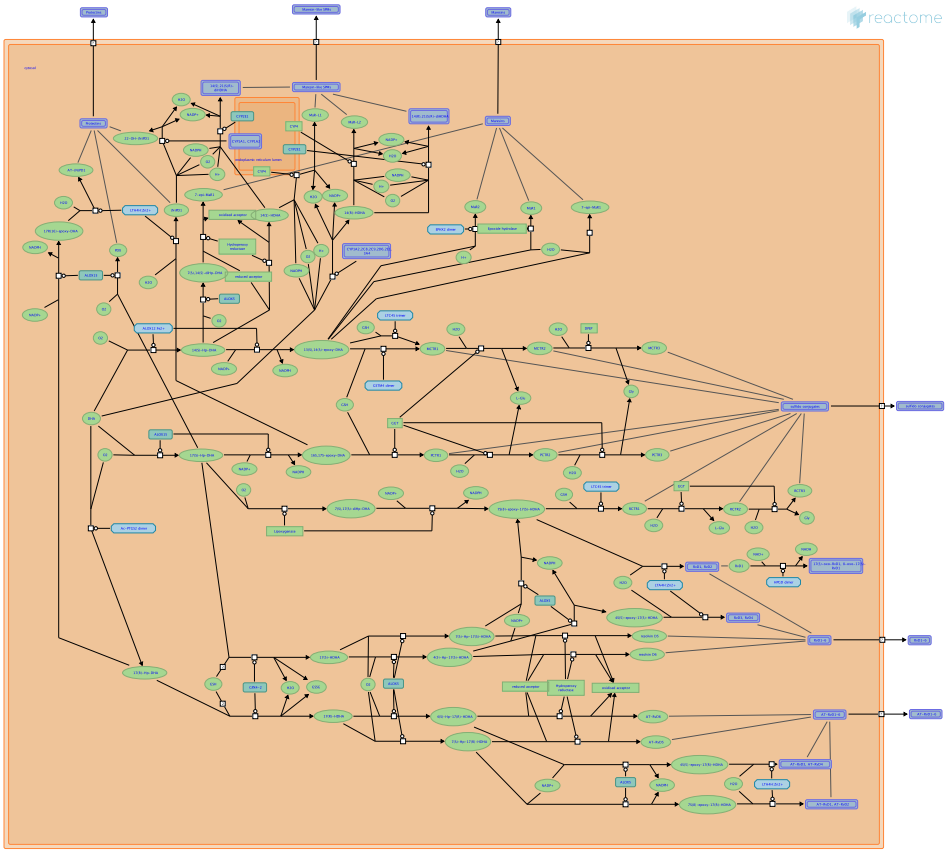
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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 DHA-derived SPMs ↗

Stable identifier: R-HSA-9018677



Docosahexaenoic acid (DHA), a major ω-3 polyunsaturated fatty acid (PUFA) found in fish oil is the source of D-series resolvins (RvDs), one of the specialized proresolving mediators (SPMs) that show potent anti-inflammatory and pro-resolving actions (Molfino et al. 2017). The biosynthesis of RvDs occurs mainly during the process of inflammation when endothelial cells interact with leukocytes. Dietary DHA circulates in plasma or is present in cellular membranes as it can easily integrate into membranes. On injury or infection, DHA moves with edema into the tissue sites of acute inflammation where it is converted to exudate RvDs to interact with local immune cells (Kasuga et al. 2008). The initial transformation of DHA by aspirin-acetylated cyclooxygenase-2 or cyclooxygenase-mediated catalysis can produce stereospecific D-resolvins (18(R)- or 18(S)-RvDs respectively). Combinations of oxidation, reduction and hydrolysis reactions determine the type of D-resolvin formed (RvD1-6) (Serhan et al. 2002, Serhan & Petasis 2011, Serhan et al. 2014).

Literature references

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

Serhan, CN., Petasis, NA. (2011). Resolvins and protectins in inflammation resolution. *Chem. Rev., 111*, 5922-43. ↗

Serhan, CN., Hong, S., Gronert, K., Colgan, SP., Devchand, PR., 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

2017-09-04	Authored, Edited	Jassal, B.
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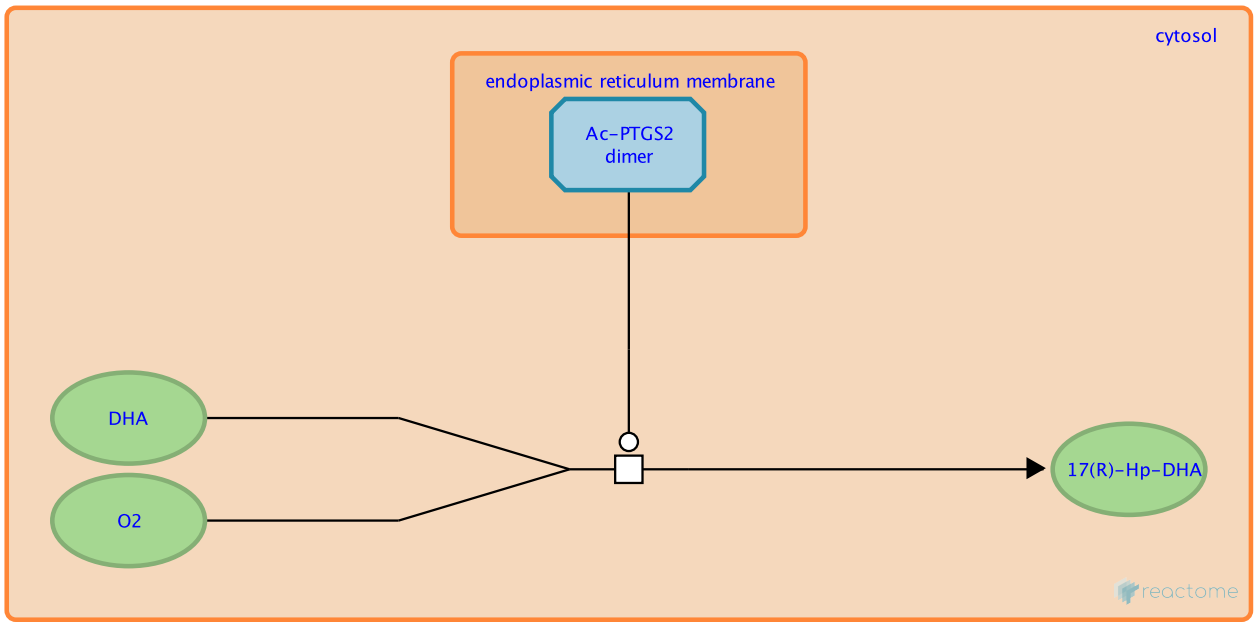
Ac-PTGS2 dimer oxidises DHA to 17(R)-Hp-DHA ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9020261

Type: transition

Compartments: cytosol



Normally, cyclooxygenases (COX) carry out stereospecific oxygenation of arachidonic acid to generate prostaglandins. When treated with aspirin (acetylsalicylic acid, ASA), dimeric cyclooxygenase-2 (COX2, PTGS2 dimer) can be acetylated. ASA covalently modifies PTGS2 by acetylating a serine residue at position 530 within the cyclooxygenase active site (Lucido et al. 2016). Acetylated PTGS2 dimer (Ac-PTGS2 dimer) changes the oxygenation stereospecificity towards its substrates, perhaps by steric shielding effects (Tosco 2013), producing a shift in lipid mediator production. Ac-PTGS2 dimer is able to incorporate molecular oxygen into ω-3 fatty acid docosahexaenoic acid (DHA), present in inflammatory exudates, to form the 17(R) epimer 17(R)-hydroperoxy-docosahexaenoic acid (17(R)-Hp-DHA) (Serhan et al. 2002, Sun et al. 2007). The product can either be transformed into aspirin-triggered D-resolvins or aspirin-triggered protectin D1 (Serhan et al. 2015).

Literature references

Serhan, CN., Hong, S., Gronert, K., Colgan, SP., Devchand, PR., 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. ↗

Sun, YP., Oh, SF., Uddin, J., Yang, R., Gotlinger, K., Campbell, E. 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. ↗

Editions

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

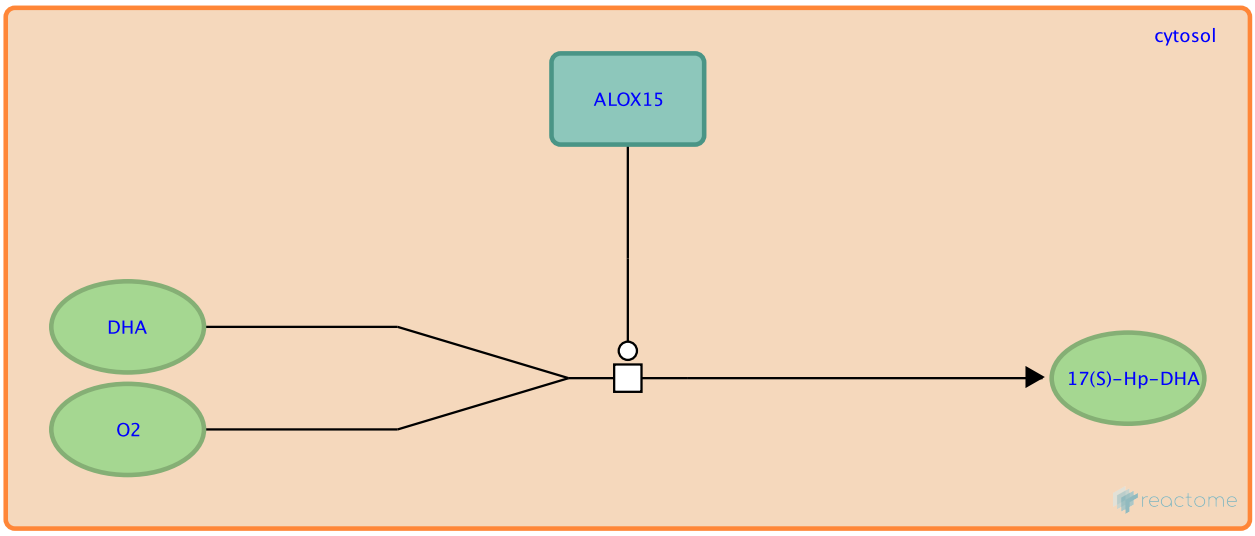
ALOX15 oxidises DHA to 17(S)-Hp-DHA ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9020275

Type: transition

Compartments: cytosol



In the absence of aspirin in human whole blood, isolated leukocytes and glial cells, 15-lipoxygenase (ALOX15) can oxygenate docosahexanoic acid (DHA) (Kim et al. 1990) to the 17(S) epimer 17(S)-hydroperoxy-docosahexanoic acid (17(S)-Hp-DHA) (Hong et al. 2003). This intermediate leads to the production of 17(S) epimer D-resolvins (as opposed to aspirin-triggered 17(R) epimer D-resolvins), as well as being the precursor for protectins and the proposed precursor for the production of protectin conjugates in tissue regeneration (PCTRs) and resolvin conjugates in tissue regeneration (RCTRs) (Dalli et al. 2015, Ramon et al. 2016).

Followed by: ALOX15 dehydrogenates 17(S)-Hp-DHA to 16S,17S-epoxy-DHA

Literature references

Hong, S., Gronert, K., Devchand, PR., Moussignac, RL., Serhan, CN. (2003). Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *J. Biol. Chem., 278*, 14677-87. ↗

Kim, HY., Karanian, JW., Salem, N. (1990). Formation of 15-lipoxygenase product from docosahexaenoic acid (22:6w3) by human platelets. *Prostaglandins, 40*, 539-49. ↗

Editions

2017-09-05	Authored, Edited	Jassal, B.
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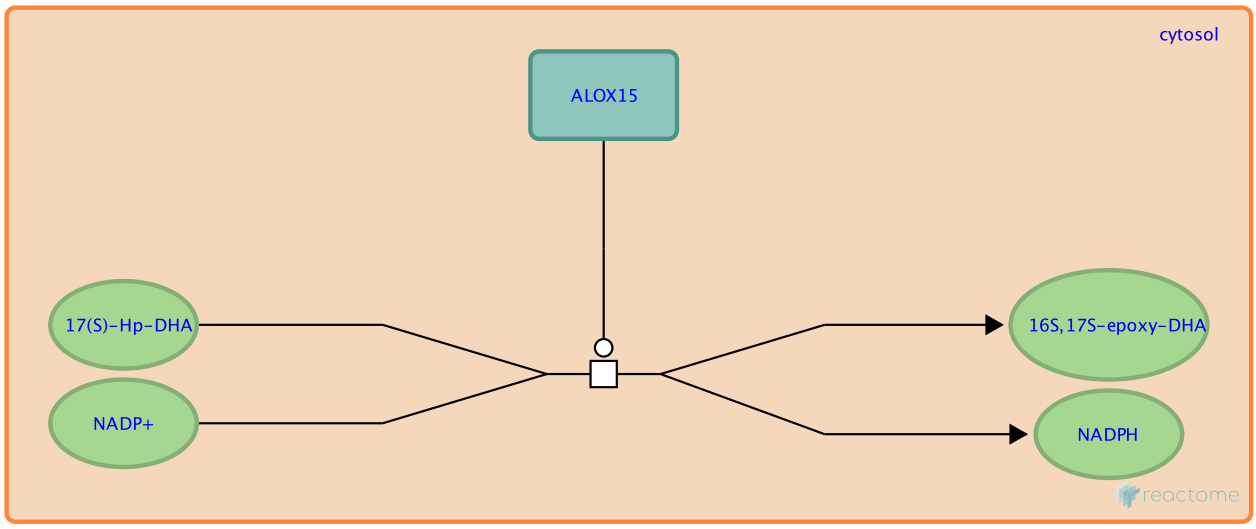
ALOX15 dehydrogenates 17(S)-Hp-DHA to 16S,17S-epoxy-DHA ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9024881

Type: transition

Compartments: cytosol



Instead of undergoing a second oxygenation (to form PDX), the hydroperoxide intermediate 17(S)-Hp-DHA undergoes a hydrogen abstraction by 15-lipoxygenase (ALOX15) to form an intermediate epoxide, 16S,17S-epoxy-DHA (Hong et al. 2003, Serhan et al. 2006, Hong et al. 2007, Aursnes et al. 2015). This epoxide has now proved to be the precursor for the production of (neuro)protectin D1 ((N)PD1) as well as production of protectin conjugates in tissue regeneration (PCTRs) (Dalli et al. 2015, Ramon et al. 2016, Aursnes et al. 2015).

Preceded by: ALOX15 oxidises DHA to 17(S)-Hp-DHA

Literature references

Aursnes, M., Tungen, JE., Colas, RA., Vlasakov, I., Dalli, J., Serhan, CN. et al. (2015). Synthesis of the 16S,17S-Epoxyprotectin Intermediate in the Biosynthesis of Protectins by Human Macrophages. *J. Nat. Prod., 78*, 2924-31. ↗

Hong, S., Gronert, K., Devchand, PR., Moussignac, RL., Serhan, CN. (2003). Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *J. Biol. Chem., 278*, 14677-87. ↗

Hong, S., Lu, Y., Yang, R., Gotlinger, KH., Petasis, NA., Serhan, CN. (2007). Resolvin D1, protectin D1, and related docosahexaenoic acid-derived products: Analysis via electrospray/low energy tandem mass spectrometry based on spectra and fragmentation mechanisms. *J. Am. Soc. Mass Spectrom., 18*, 128-44. ↗

Ramon, S., Dalli, J., Sanger, JM., Winkler, JW., Aursnes, M., Tungen, JE. et al. (2016). The Protectin PCTR1 Is Produced by Human M2 Macrophages and Enhances Resolution of Infectious Inflammation. *Am. J. Pathol., 186*, 962-73. ↗

Serhan, CN., Gotlinger, K., Hong, S., Lu, Y., Siegelman, J., Baer, T. et al. (2006). Anti-inflammatory actions of neuroprotectin D1/protectin D1 and its natural stereoisomers: assignments of dihydroxy-containing docosatrienes. *J. Immunol., 176*, 1848-59. ↗

Editions

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

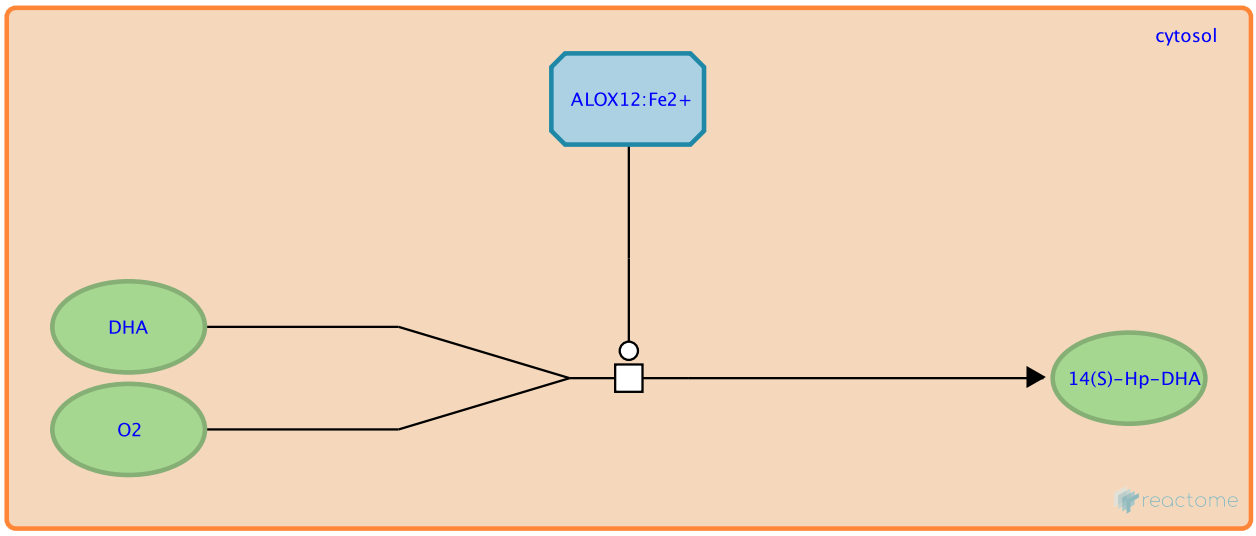
ALOX12:Fe2+ oxidises DHA to 14(S)-Hp-DHA ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9020274

Type: transition

Compartments: cytosol



Maresins are a family of anti-inflammatory and pro-resolving lipid mediators biosynthesized from docosahexaenoic acid (DHA) by macrophages. In the first step, DHA is oxygenated by lipoxygenase 12 using Fe2+ cofactor (ALOX12:Fe2+) to 14(S)-hydroperoxy-docosahexaenoic acid (14(S)-Hp-DHA) (Serhan et al. 2009, Deng et al. 2014). Maresin-like mediators MaR-L1 and Mar-L2 are produced by leukocytes and platelets and have been shown to restore reparative functions of diabetic macrophages in wounds (Brem & Tomic-Canic 2007, Hong et al. 2014). The same reaction as above can occur in human leukocytes and platelets to produce MaR-L1 and MaR-L2. The 14(S)-Hp-DHA intermediate can also serve as a precursor for maresin conjugates in tissue regeneration (MCTR) (Dalli et al. 2016).

Followed by: ALOX12:Fe2+ dehydrogenates 14(S)-Hp-DHA to 13(S),14(S)-epoxy-DHA

Literature references

Serhan, CN., Yang, R., Martinod, K., Kasuga, K., Pillai, PS., Porter, TF. et al. (2009). Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. *J. Exp. Med., 206*, 15-23. ↗

Deng, B., Wang, CW., Arnardottir, HH., Li, Y., Cheng, CY., Dalli, J. et al. (2014). Maresin biosynthesis and identification of maresin 2, a new anti-inflammatory and pro-resolving mediator from human macrophages. *PLoS ONE, 9*, e102362. ↗

Editions

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

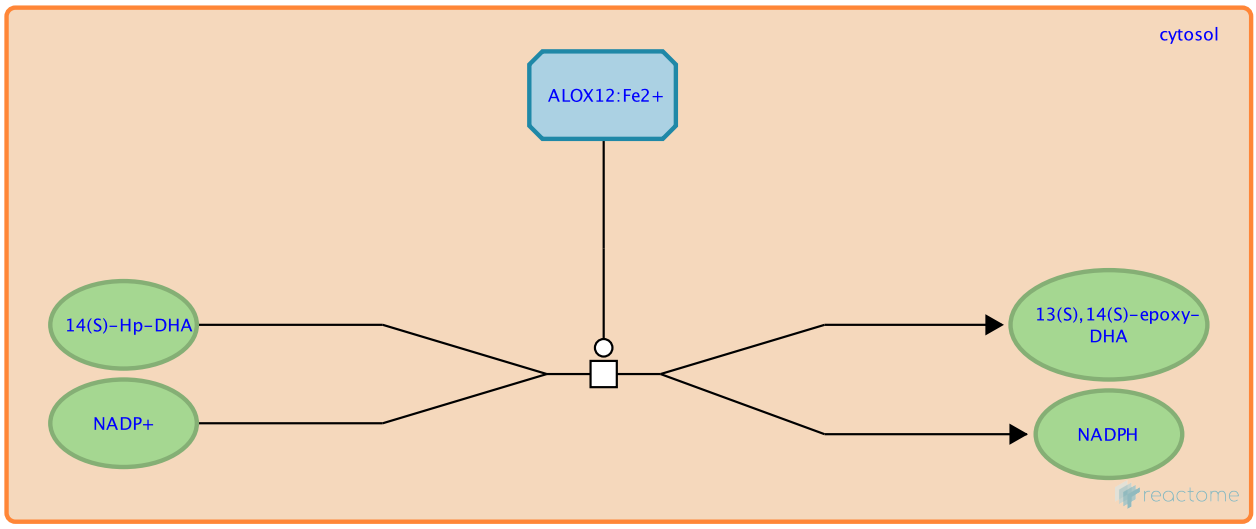
ALOX12:Fe2+ dehydrogenates 14(S)-Hp-DHA to 13(S),14(S)-epoxy-DHA ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9024983

Type: transition

Compartments: cytosol



In macrophages, lipoxygenase 12 (ALOX12:Fe2+) may abstract hydrogen from 14(S)-hydroperoxy-docosahexaenoic acid (14(S)-Hp-DHA) to form 13(S),14(S)-epoxy-DHA (Serhan et al. 2009, Dalli et al. 2013, Deng et al. 2014). This epoxy product is a central intermediate in maresin MaR1 and MaR2 and maresin conjugates in tissue regeneration (MCTR) biosyntheses (Dalli et al. 2016) as well as possessing potent proresolving activity (Dalli et al 2013).

Preceded by: ALOX12:Fe2+ oxidises DHA to 14(S)-Hp-DHA

Literature references

Dalli, J., Zhu, M., Vlasenko, NA., Deng, B., Haeggström, JZ., Petasis, NA. et al. (2013). The novel 13S,14S-epoxy-maresin is converted by human macrophages to maresin 1 (MaR1), inhibits leukotriene A4 hydrolase (LTA4H), and shifts macrophage phenotype. *FASEB J., 27*, 2573-83. ↗

Serhan, CN., Yang, R., Martinod, K., Kasuga, K., Pillai, PS., Porter, TF. et al. (2009). Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. *J. Exp. Med., 206*, 15-23. ↗

Deng, B., Wang, CW., Arnardottir, HH., Li, Y., Cheng, CY., Dalli, J. et al. (2014). Maresin biosynthesis and identification of maresin 2, a new anti-inflammatory and pro-resolving mediator from human macrophages. *PLoS ONE, 9*, e102362. ↗

Editions

2017-10-11	Authored, Edited	Jassal, B.
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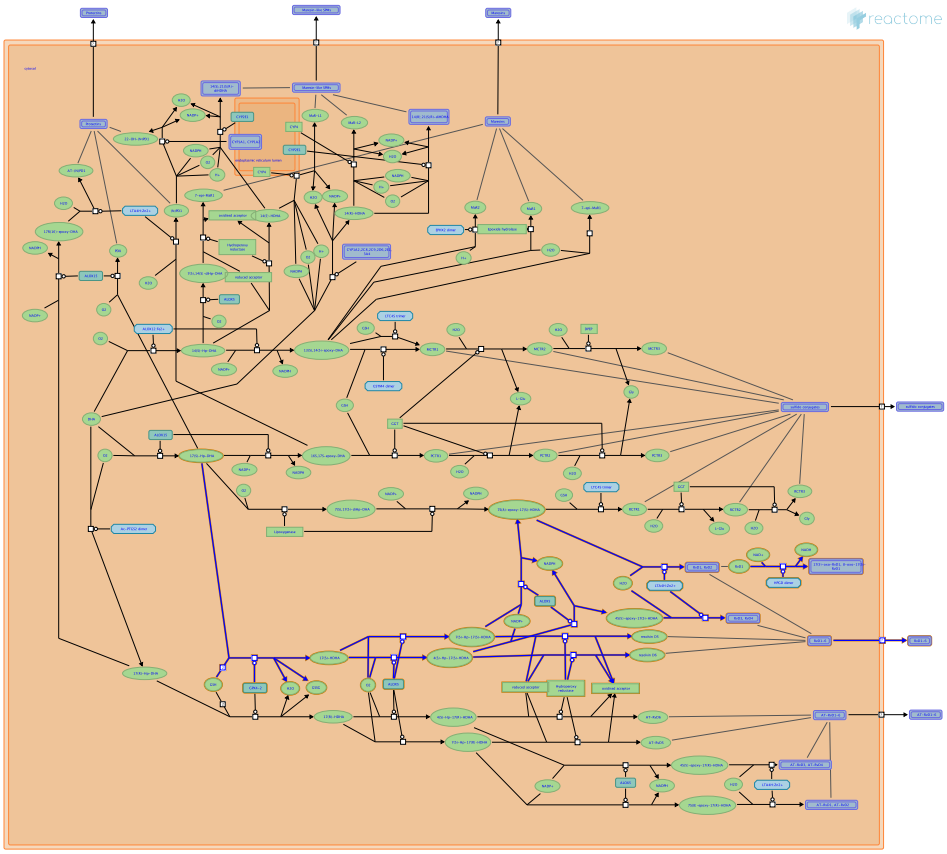
Biosynthesis of D-series resolvins ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9018676



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

Literature references

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

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

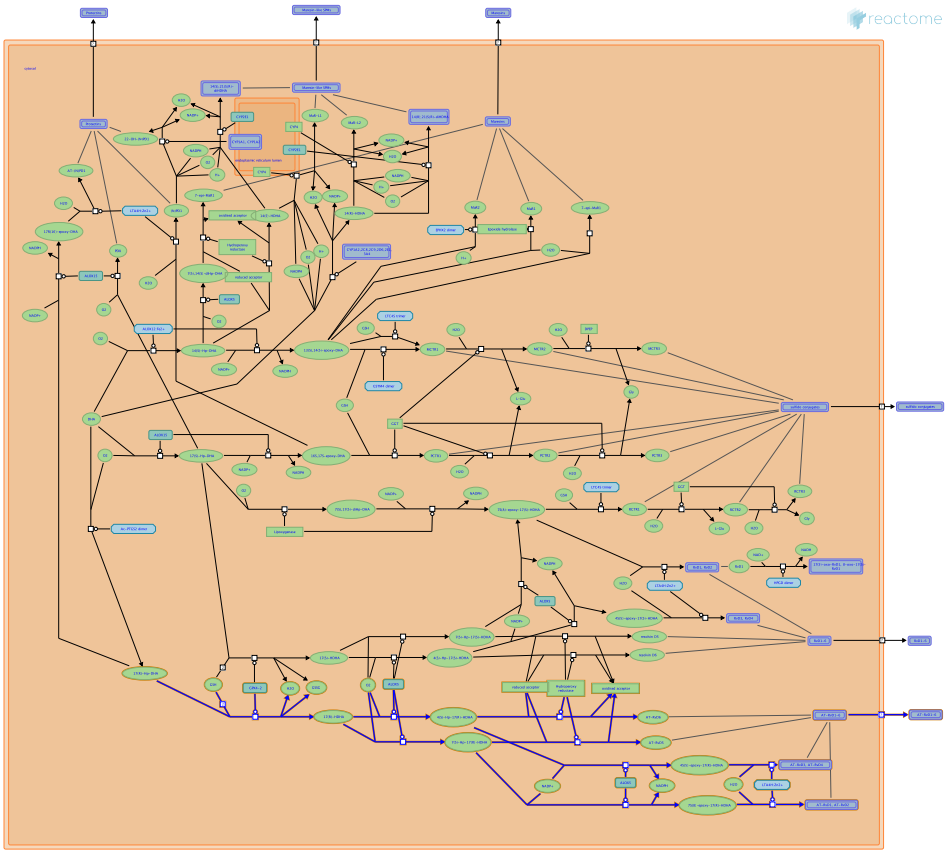
Editions

2017-09-04	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

Biosynthesis of aspirin-triggered D-series resolvins ↗

Location: Biosynthesis of DHA-derived SPMs

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

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

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

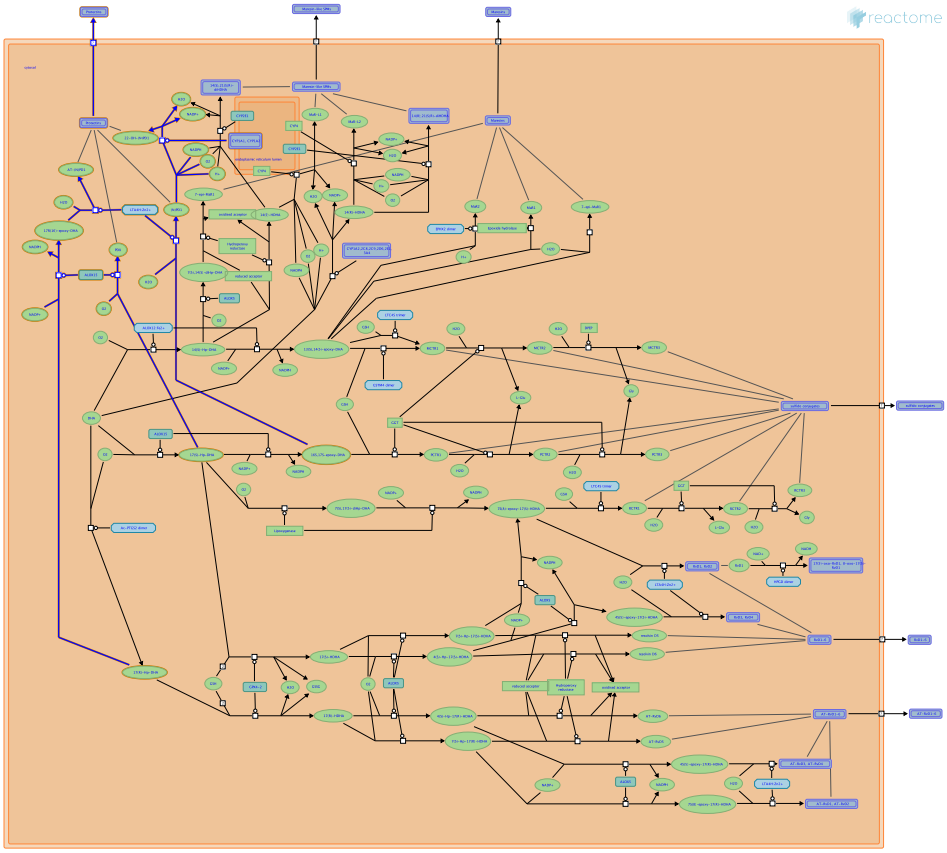
Editions

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

Biosynthesis of protectins ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9018681



Docosahexaenoic acid (DHA), a major ω-3 polyunsaturated fatty acid (PUFA) found in fish oil is the source of protectins (PDs), one of the specialized proresolving mediators (SPMs) that show potent anti-inflammatory and pro-resolving actions (Molfino et al. 2017, Balas & Durand 2016). The switch from synthesis of pro-inflammatory eicosanoids, such as the prostaglandins and the thromboxanes, to the pro-resolving lipoxins, resolvins and protectins, occurs via induction of the 15-lipoxygenase enzyme.

Protectin, identified as (N)PD1 (N signifies neuroprotectin when produced in neural tissues) is derived from DHA through the actions of 15-lipoxygenase then enzymatic hydrolysis. Aspirin can also trigger the formation of epimeric protectin (AT-PD1) (Serhan et al. 2015). An additional protectin (DX) is formed through the sequential actions of two lipoxygenase reactions. The biosynthesis of these protectins is described here (Balas & Durand 2016, Balas et al. 2014, Serhan et al. 2014, Serhan et al. 2015).

Literature references

Balas, L., Durand, T. (2016). Dihydroxylated E,E,Z-docosatrienes. An overview of their synthesis and biological significance. *Prog. Lipid Res., 61*, 1-18. ↗

Balas, L., Guichardant, M., Durand, T., Lagarde, M. (2014). Confusion between protectin D1 (PD1) and its isomer protectin DX (PDX). An overview on the dihydroxy-docosatrienes described to date. *Biochimie, 99*, 1-7. ↗

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

Serhan, CN., Dalli, J., Colas, RA., Winkler, JW., Chiang, N. (2015). Protectins and maresins: New pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. *Biochim. Biophys. Acta, 1851*, 397-413. ↗

Editions

2017-09-04	Authored, Edited	Jassal, B.
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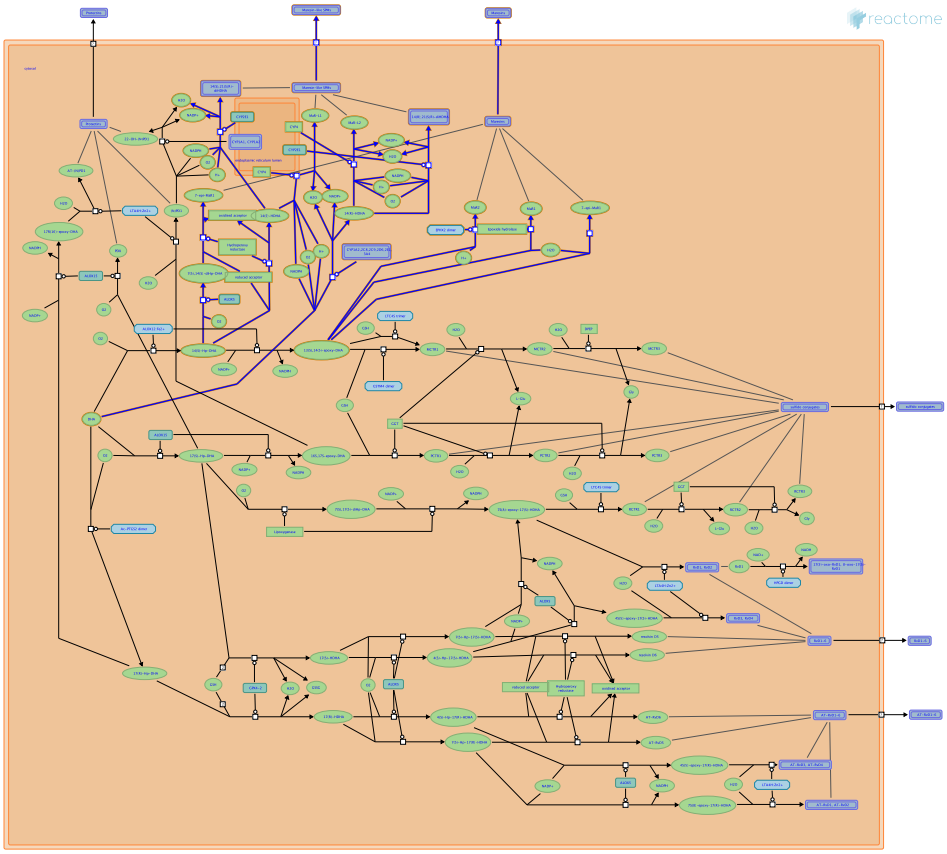
Biosynthesis of maresins ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9018682



Maresins 1 and 2 (MaR1 and MaR2) are derived through the action of lipoxygenase 12 on the ω-3 fatty acid docosahexaenoic acid (DHA). MaRs are mainly produced by macrophages hence the derivation of the name from MAcrophage mediator RESolving INflammation. MaR1 exhibits potent anti-inflammatory, pro-resolving, analgesic and wound healing activities. Major cellular targets for the actions of MaR1 are vascular smooth muscle (VSM) cells and vascular endothelial cells. In these cells MaR1 attenuates the adhesion of monocytes to the endothelium induced by TNF-alpha. Maresin 1 also inhibits the production of reactive oxygen species by both VSM and endothelial cells. The major mechanism through which MaR1 exerts these effects is through down-regulation of the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). MaR2 has been shown to reduce neutrophil infiltration and to enhance macrophage-mediated phagocytosis of dead and dying cells, a process termed efferocytosis. Two related structures, the maresin-like mediators (MaR-L1 and MaR-L2), are generated when the maresins produced by macrophages are released and acted upon by leukocytes and platelets (Hong et al. 2014). These, together with 14,21-dihydroxy-DHAs, rescue the reparative function of diabetes-impaired macrophages in diabetic wound healing (Hong et al. 2014, Tian et al. 2011, Boniakowski et al. 2017).

Literature references

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

Serhan, CN., Dalli, J., Colas, RA., Winkler, JW., Chiang, N. (2015). Protectins and maresins: New pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. *Biochim. Biophys. Acta, 1851*, 397-413. ↗

Balas, L., Durand, T. (2016). Dihydroxylated E,E,Z-docosatrienes. An overview of their synthesis and biological significance. *Prog. Lipid Res., 61*, 1-18. ↗

Hong, S., Lu, Y., Tian, H., Alapure, BV., Wang, Q., Bunnell, BA. et al. (2014). Maresin-like lipid mediators are produced by leukocytes and platelets and rescue reparative function of diabetes-impaired macrophages. *Chem. Biol., 21*, 1318-1329. ↗

Tian, H., Lu, Y., Shah, SP., Hong, S. (2011). Autacoid 14S,21R-dihydroxy-docosahexaenoic acid counteracts diabetic impairment of macrophage prohealing functions. *Am. J. Pathol., 179*, 1780-91. ↗

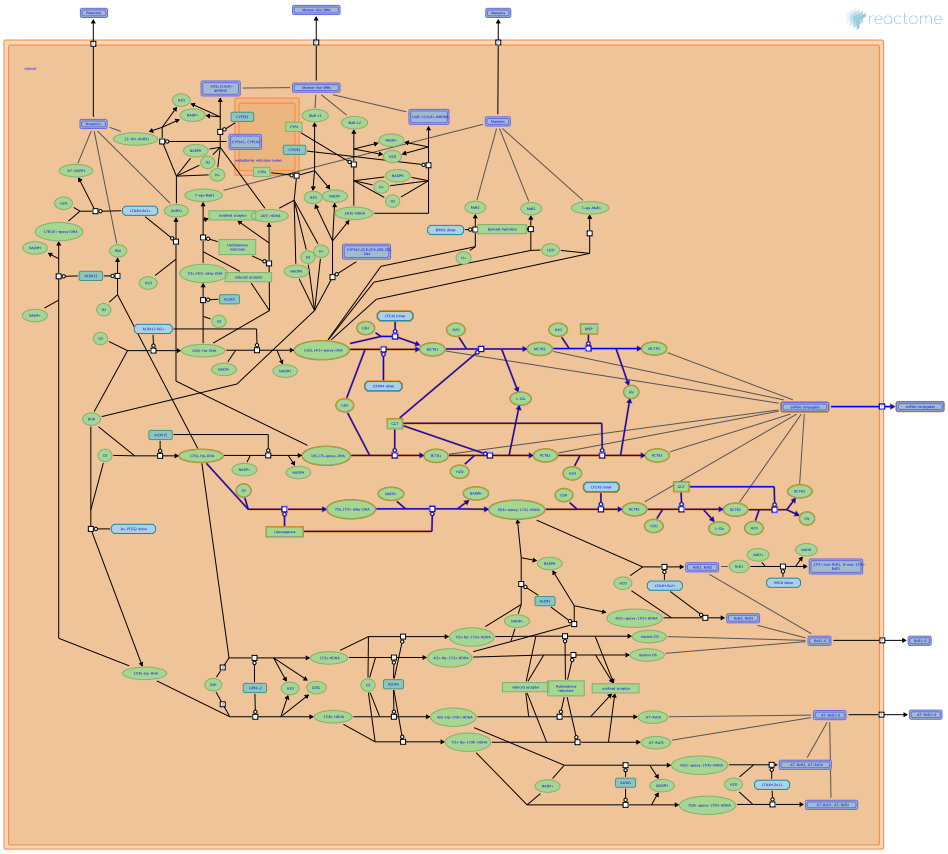
Editions

2017-09-04	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

Biosynthesis of DHA-derived sulfido conjugates ↗

Location: Biosynthesis of DHA-derived SPMs

Stable identifier: R-HSA-9026395



The polyunsaturated fatty acid (PUFA) ω-3 docosahexaenoic acid (DHA) is a precursor for the production of novel sulfido-peptide conjugated mediators with structural similarity to the cysteinyl-leukotrienes and with novel biological properties. They are produced from specialised proresolving mediators (SPMs) in human macrophages and are termed protectin conjugates in tissue regeneration (PCTR), resolvin conjugates in tissue regeneration (RCTR), and maresin conjugates in tissue regeneration (MCTR) because they regulate mechanisms in inflammation resolution as well as tissue regeneration (Dalli et al. 2014, 2015, 2016, Serhan et al. 2017). Their biosynthesis is descibed in this section.

Literature references

Dalli, J., Ramon, S., Norris, PC., Colas, RA., Serhan, CN. (2015). Novel proresolving and tissue-regenerative resolvin and protectin sulfido-conjugated pathways. *FASEB J., 29*, 2120-36. ↗

Dalli, J., Vlasakov, I., Riley, IR., Rodriguez, AR., Spur, BW., Petasis, NA. et al. (2016). Maresin conjugates in tissue regeneration biosynthesis enzymes in human macrophages. *Proc. Natl. Acad. Sci. U.S.A., 113*, 12232-12237. ↗

Dalli, J., Chiang, N., Serhan, CN. (2014). Identification of 14-series sulfido-conjugated mediators that promote resolution of infection and organ protection. *Proc. Natl. Acad. Sci. U.S.A., 111*, E4753-61. ↗

Serhan, CN., Chiang, N., Dalli, J. (2017). New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration. *Mol. Aspects Med.*. ↗

Editions

2017-10-19	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

Table of Contents