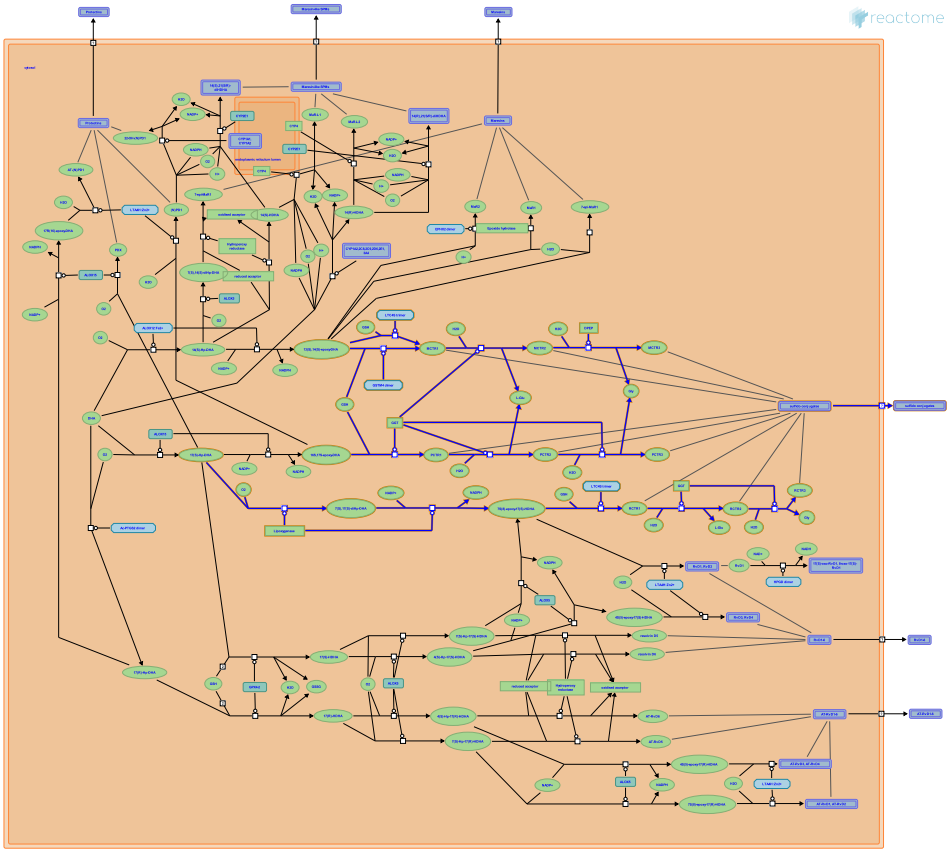
Biosynthesis of DHA-derived sulfido conjugates



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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. ↗

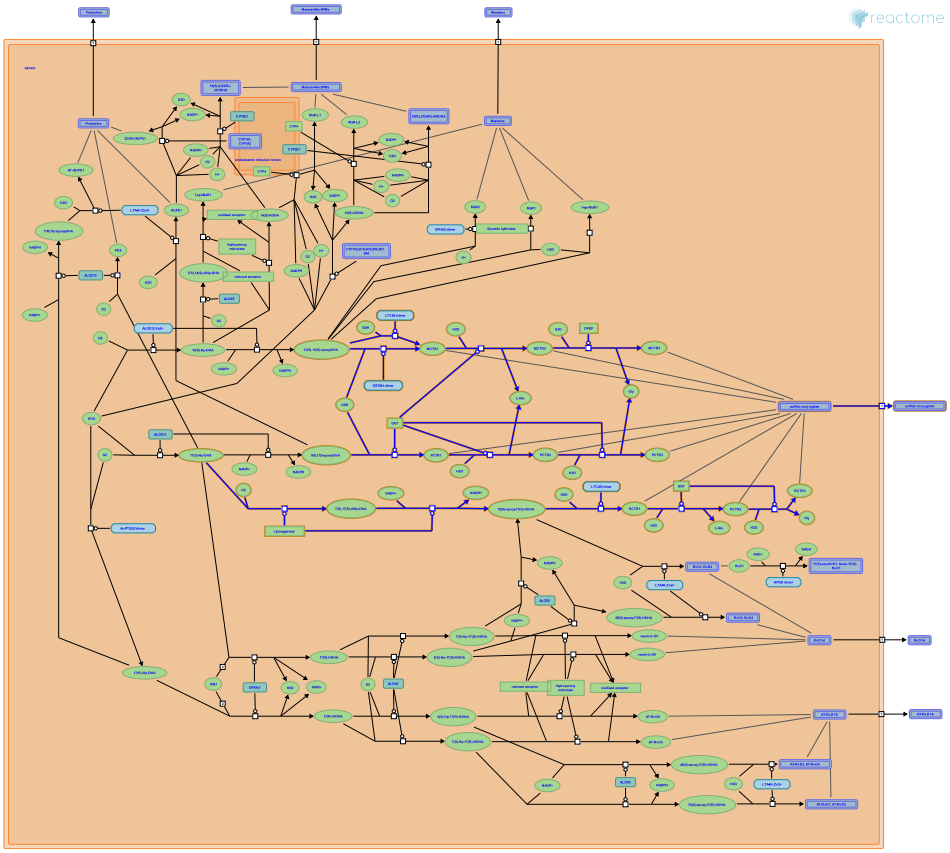
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways and 1 reaction (see Table of Contents)

Biosynthesis of DHA-derived sulfido conjugates ↗

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

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

Serhan, CN., Chiang, N., Dalli, J. (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. ↗

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

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.
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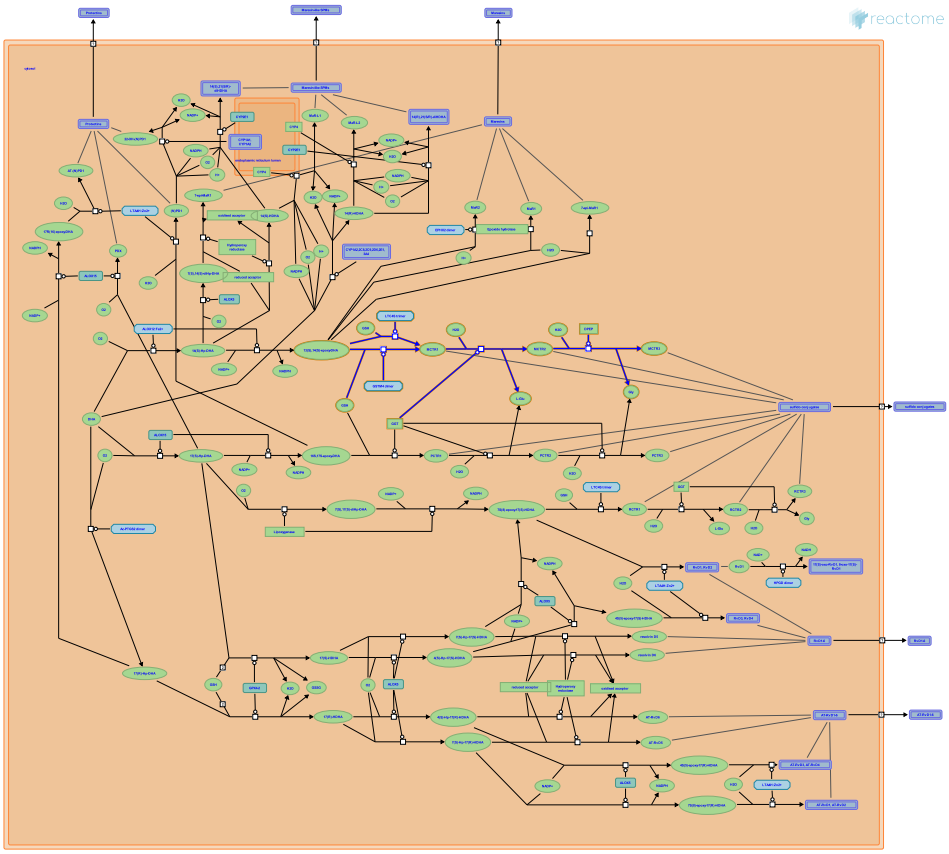
Biosynthesis of maresin conjugates in tissue regeneration (MCTR) ↗

Location: Biosynthesis of DHA-derived sulfido conjugates

Stable identifier: R-HSA-9026762



Resolution of inflammation is carried out by endogenous mediators termed specialised proresolving mediators (SPMs). Macrophages are central to the acute inflammatory response, governing both initiation and resolution phases, depending on the macrophage subtype activated. Human macrophages involved in resolution produce a family of bioactive peptide-conjugated mediators called maresin conjugates in tissue regeneration (MCTR). These mediators stimulate human phagocytotic functions, promote the resolution of bacterial infections, counterregulate the production of proinflammatory mediators and promote tissue repair and regeneration (Dalli et al. 2016). The proposed biosynthetic pathway is as follows. The maresin epoxide intermediate 13(S),14(S)-epoxy-MaR (13(S),14(S)-epoxy-docosahexaenoic acid) can be converted to MCTR1 (13(R)-glutathionyl, 14(S)-hydroxy-docosahexaenoic acid) by LTC4S and GSTM4. MCTR1 can be converted to MCTR2 (13(R)-cysteinylglycinyl, 14(S)-hydroxy-docosahexaenoic acid) by γ-glutamyl transferase (GGT). Finally, a dipeptidase can cleave the cysteinyl-glycinyl bond of MCTR2 to give MCTR3 (13(R)-cysteinyl, 14(S)-hydroxy-docosahexaenoic acid) (Dalli et al. 2016, Serhan et al. 2017).

Literature references

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

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

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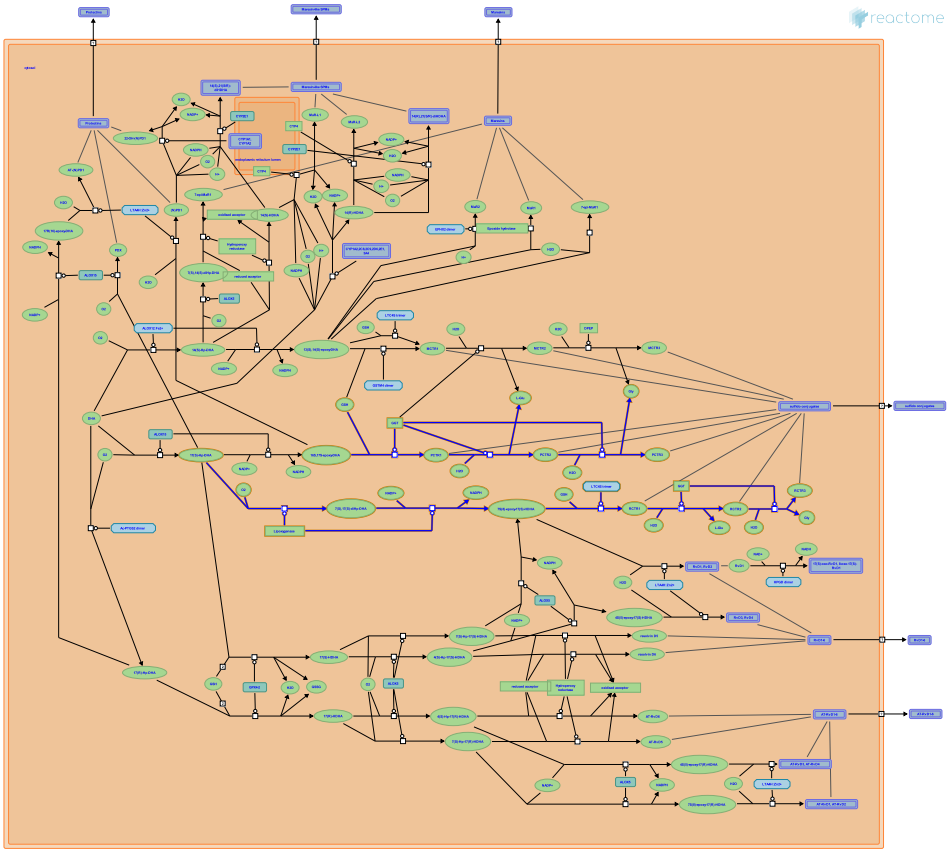
Biosynthesis of protectin and resolvin conjugates in tissue regeneration (PCTR and RCTR) ↗

Location: Biosynthesis of DHA-derived sulfido conjugates

Stable identifier: R-HSA-9026766



Activated human macrophages and PMNs are able to produce 17-series sulfido-conjugated specialised proresolving mediators (SPMs) that are able to resolve acute inflammation and promote tissue regeneration. The ω-3 polyunsaturated fatty acid docosahexaenoic acid (DHA) is the source of these novel SPMs termed resolvin conjugates in tissue regeneration (RCTR) and protectin conjugates in tissue regeneration (PCTR). protectin conjugate in tissue regeneration PCTR and RCTR are thus named because they share proposed biosynthetic pathways, structural features, and biological actions with the DHA-derived protectins and resolvins (respectively) as well as displaying potent tissue-regenerative actions (Serhan et al. 2014).

The proposed biosynthetic pathways for PCTRs and RCTRs are described here (Dalli et al. 2015, Serhan et al. 2017). Mammalian lipoxygenases insert molecular oxygen predominantly in the S-stereochemistry, so the hydroxy groups at the 7- and 17-positions are presumed to be in the S-configuration. The R-containing diastereomers of these products may also possess biological activity in the resolution of inflammation and tissue regeneration but they are not described here.

Literature references

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

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

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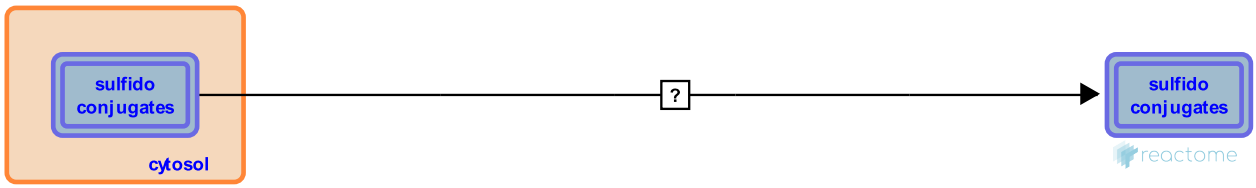
Sulfido conjugates translocate from cytosol to extracellular region ↗

Location: Biosynthesis of DHA-derived sulfido conjugates

Stable identifier: R-HSA-9031856

Type: uncertain

Compartments: extracellular region, cytosol



To produce their pro-resolving effects, DHA-derived sulfido conjugates (MCTR1-3, PCTR1-3 and RCTR1-3) are released into the exudate of local inflammation sites (Dalli et al. 2015, 2016). The mechanism of translocation is unknown.

Literature references

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

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

Editions

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