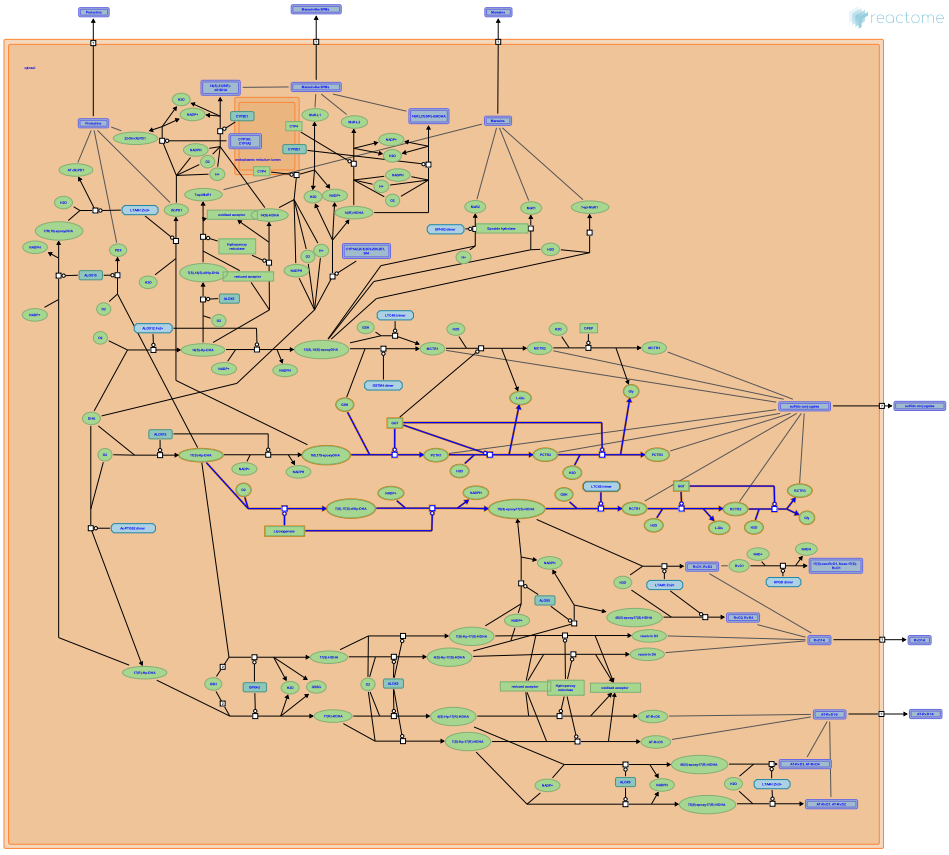
Biosynthesis of protectin and resolvin conjugates in tissue regeneration (PCTR and RCTR)



Hansen, TV., Jassal, B.

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

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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. ↗

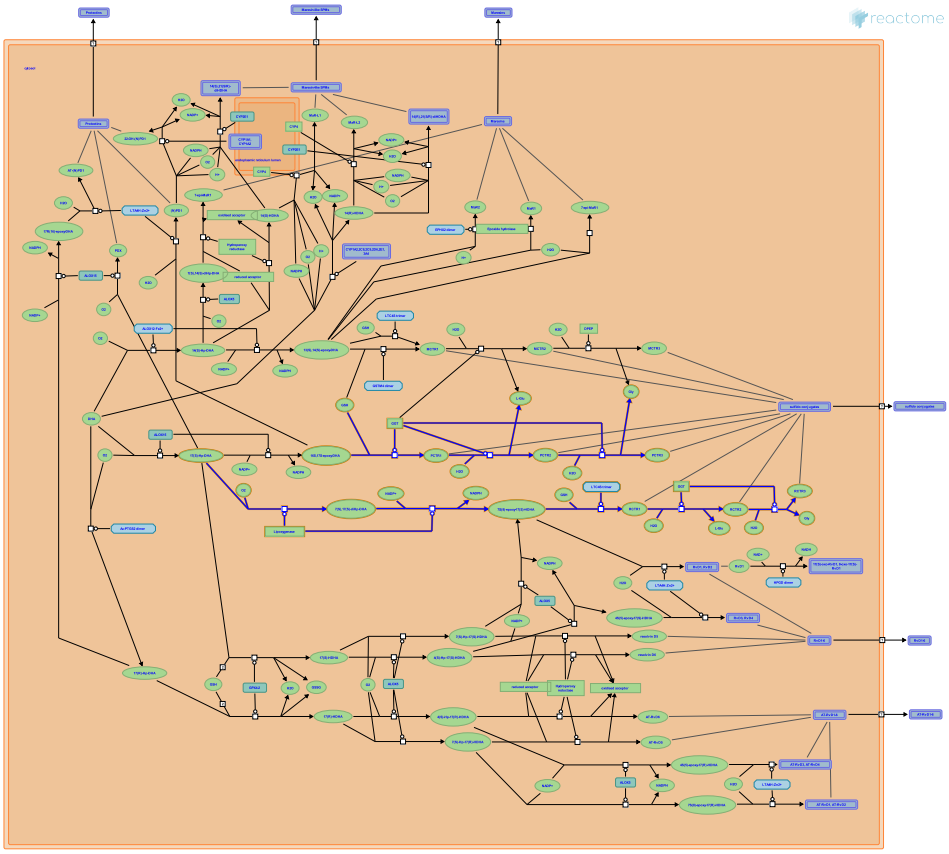
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

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

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.*.

Editions

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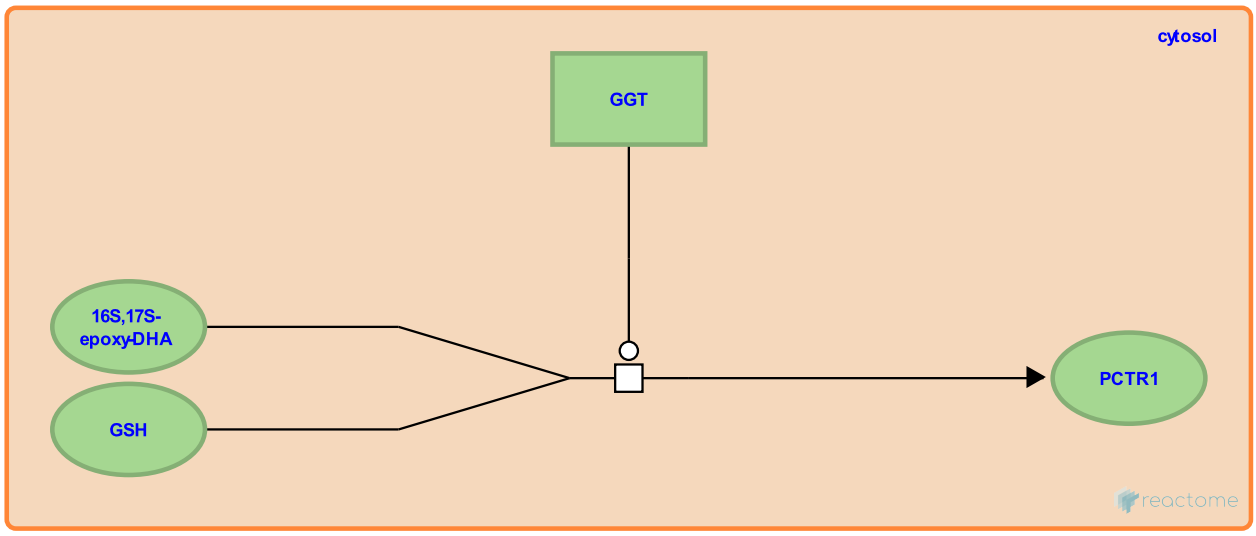
GGT transfers GSH to 16S,17S-epoxy-DHA to form PCTR1 ↗

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

Stable identifier: R-HSA-9026901

Type: transition

Compartments: cytosol



Human macrophages produce protectin conjugates in tissue regeneration (PCTR). PCTR are named as such because they share a proposed biosynthetic pathway, structural features, and biological actions with DHA-derived protectins as well as displaying potent tissue-regenerative actions. 16S,17S-epoxy-docosahexaenoic acid (16S,17S-epoxy-DHA) was found to be a substrate for a glutathione transferase (GGT) which produces PCTR1 (16-glutathionyl, 17-hydroxy-docosahexaenoic acid) in greater quantities in M2-type macrophages than M1-type macrophages and was found to enhance resolution of infectious inflammation (Ramon et al. 2016, Dalli et al. 2015).

Followed by: GGT hydrolyses PCTR1 to PCTR2

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

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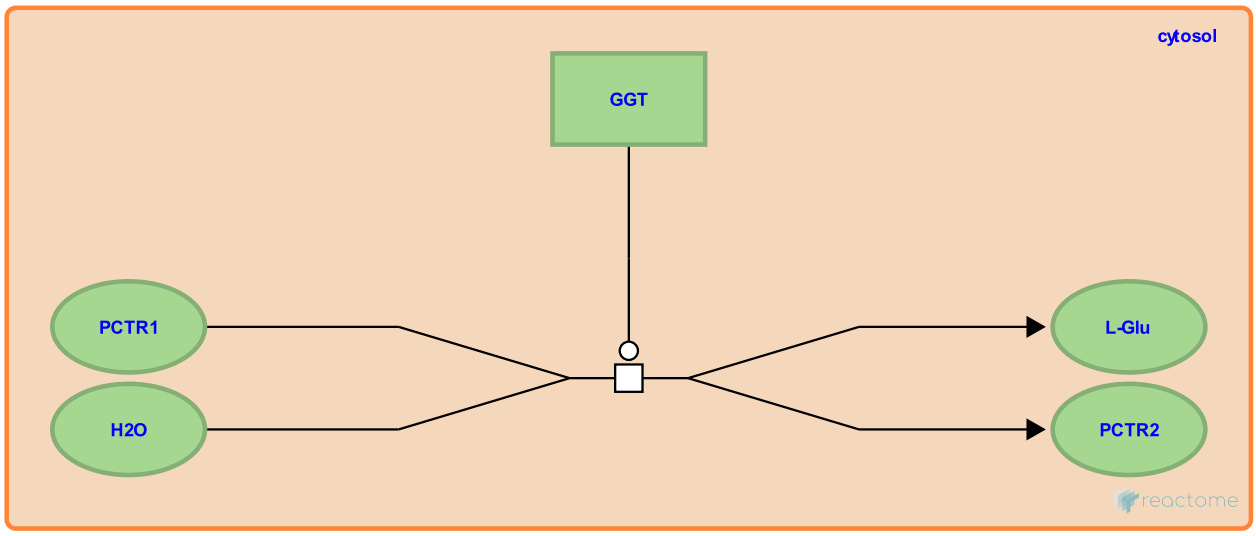
GGT hydrolyses PCTR1 to PCTR2 ↗

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

Stable identifier: R-HSA-9026912

Type: transition

Compartments: cytosol



In human macrophages, protectin conjugate in tissue regeneration 1 (PCTR1) is proposed to be hydrolysed to PCTR2 (16-cysteinylglycinyl, 17-hydroxy-docosahexaenoic acid) by the actions of a glutathione transferase (GGT). Human macrophages incubated with E. coli and a GGT inhibitor led to increased levels of PCTR1 and decreased levels of PCTR3, suggesting a role for GGT enzyme in PCTR2 and PCTR3 biosynthesis (Dalli et al. 2015).

Preceded by: GGT transfers GSH to 16S,17S-epoxy-DHA to form PCTR1

Followed by: GGT hydrolyses PCTR2 to PCTR3

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. ↗

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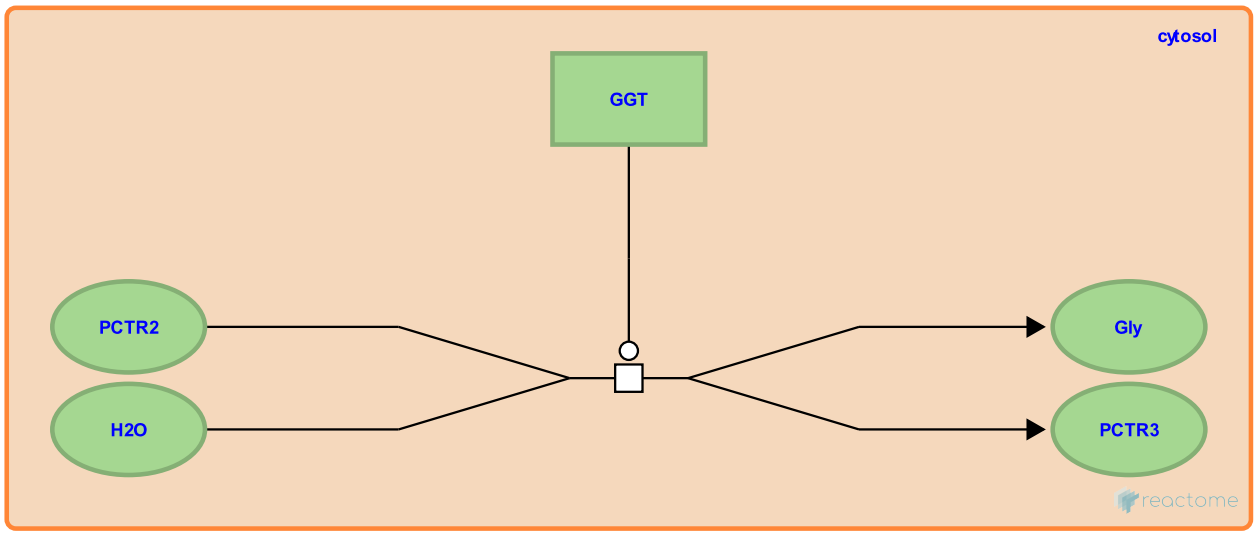
GGT hydrolyses PCTR2 to PCTR3 ↗

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

Stable identifier: R-HSA-9026907

Type: transition

Compartments: cytosol



In human macrophages, protectin conjugate in tissue regeneration 3 (PCTR2) is proposed to be hydrolysed to PCTR3 (16-cysteinyl, 17-hydroxy-docosahexaenoic acid) by the actions of a glutathione transferase (GGT). Human macrophages incubated with E. coli and a GGT inhibitor led to increased levels of PCTR1 and decreased levels of PCTR3, suggesting a role for GGT enzyme in PCTR2 and PCTR3 biosynthesis (Dalli et al. 2015).

Preceded by: GGT hydrolyses PCTR1 to PCTR2

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. ↗

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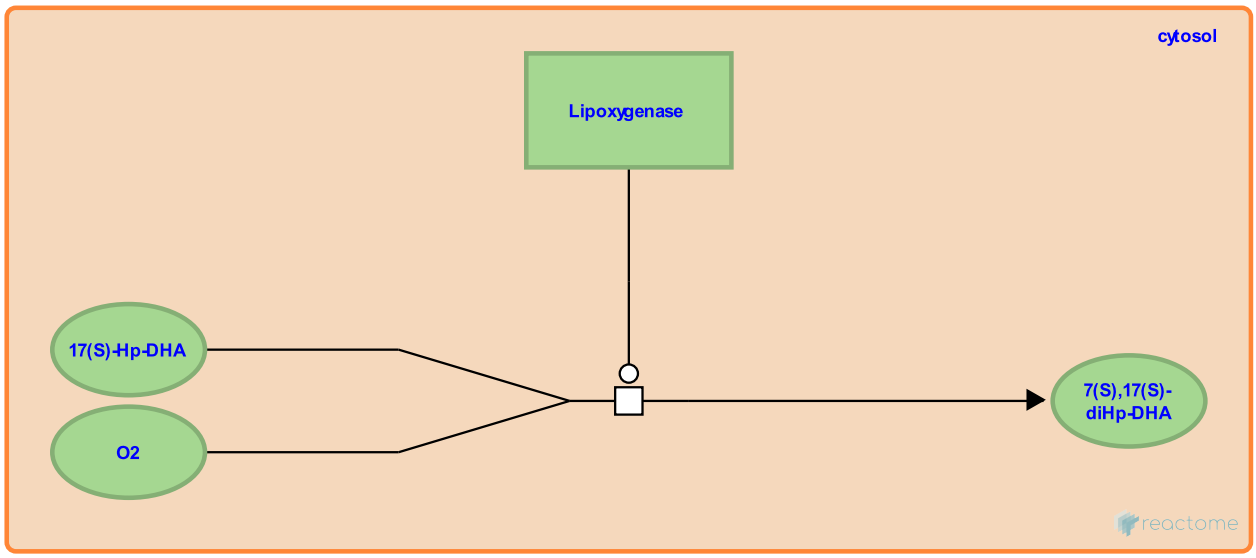
Lipoxygenase oxidises 17(S)-Hp-DHA to 7(S),17(S)-diHp-DHA ↗

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

Stable identifier: R-HSA-9026918

Type: transition

Compartments: cytosol



In an alternative route to PCTR production, 17(S)-hydroperoxy-docosahexaenoic acid (17(S)-Hp-DHA) can undergo a second lipoxygenation at carbon 7 position to yield 7S,17S-dihydroperoxy-docosahexaenoic acid (7(S),17(S)-diHp-DHA). A lipoxygenase mediates this reaction although the exact human enzyme is unknown (Dalli et al. 2015).

Followed by: Lipoxygenase dehydrogenates 7(S),17(S)-diHp-DHA to 7S(8)-epoxy-17(S)-HDHA

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. ↗

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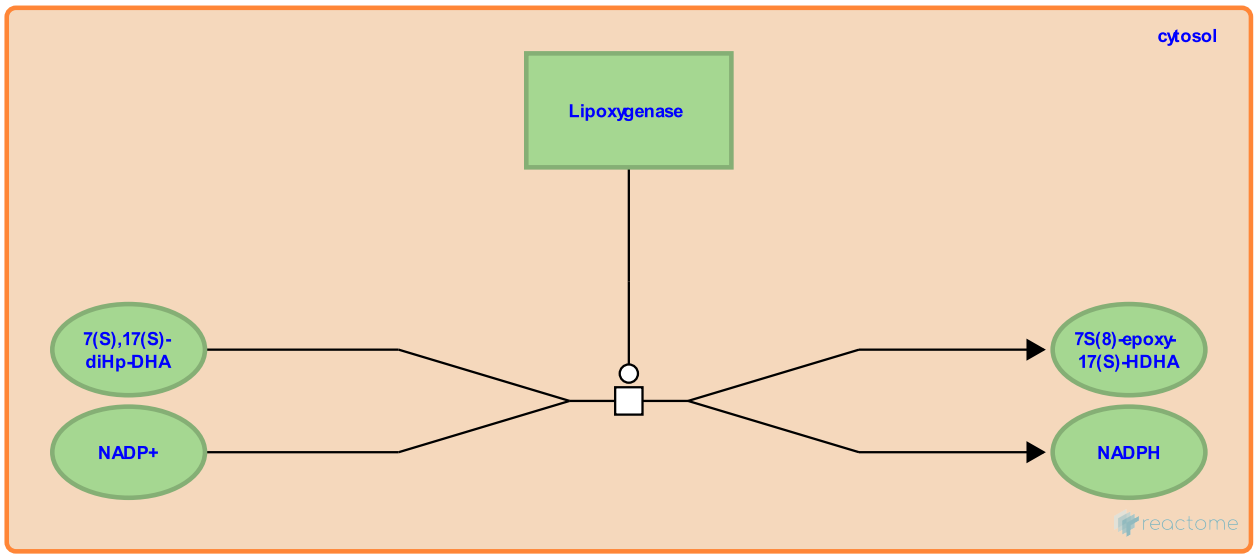
Lipoxygenase dehydrogenates 7(S),17(S)-diHp-DHA to 7S(8)-epoxy-17(S)-HDHA ↗

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

Stable identifier: R-HSA-9026917

Type: transition

Compartments: cytosol



A lipoxygenase may mediate hydrogen abstraction from 7(S),17(S)-dihydroperoxy-docosahexaenoic acid (7(S),17(S)-diHp-DHA) to form 7S(8)-epoxy-17(S)-hydroxy-docosahexaenoic acid (7S(8)-epoxy-17(S)-HDHA) (Dalli et al. 2015). This epoxy intermediate is the precursor for resolvin conjugates in tissue regeneration (RCTR).

Preceded by: Lipoxygenase oxidises 17(S)-Hp-DHA to 7(S),17(S)-diHp-DHA

Followed by: LTC4S trimer transfers GSH to 7S(8)-epoxy-17(S)-HDHA to form RCTR1

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. ↗

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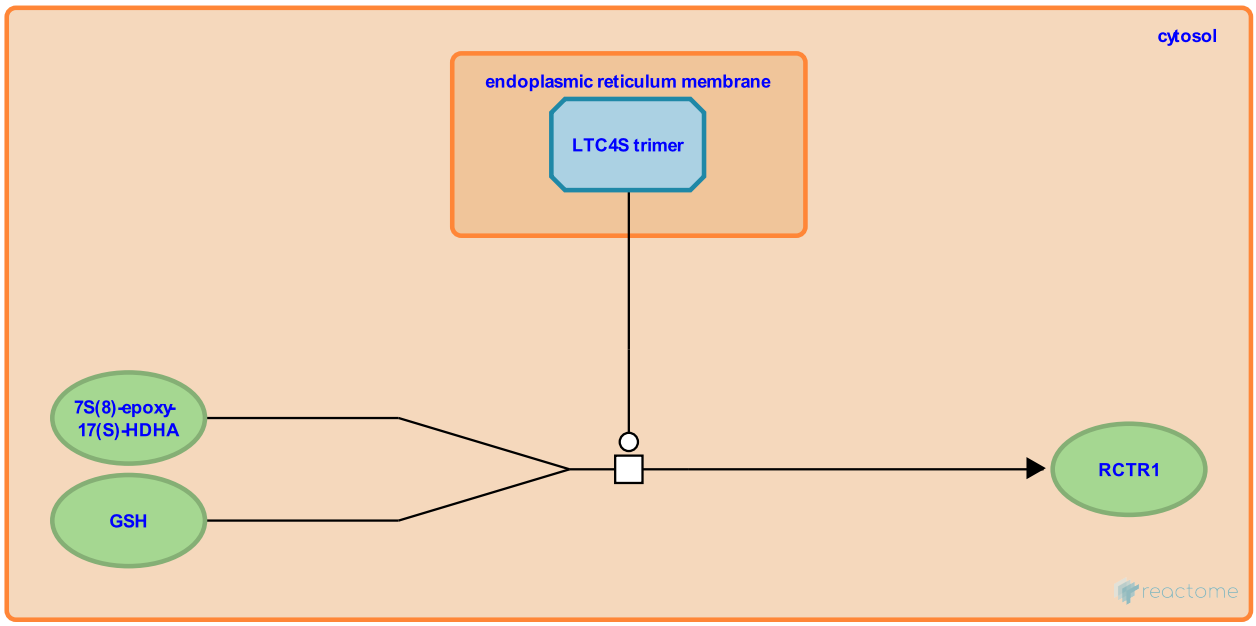
LTC4S trimer transfers GSH to 7S(8)-epoxy-17(S)-HDHA to form RCTR1 ↗

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

Stable identifier: R-HSA-9026911

Type: transition

Compartments: cytosol



Just as the addition of glutathione (GSH) to an allylic epoxide is governed by glutathione S-transferase enzymes in the biosynthesis of MCTR (Dalli et al. 2016), 7S(8)-epoxy-17(S)-hydroxy-docosahexaenoic acid (7S(8)-epoxy-17(S)-HDHA) may presumably be conjugated with GSH by trimeric leukotriene C4 synthase (LTC4S trimer) to form resolvin conjugate in tissue regeneration 1 (RCTR1, 8-glutathionyl, 7,17-dihydroxy-docosahexaenoic acid) (Dalli et al. 2015).

Preceded by: Lipoxygenase dehydrogenates 7(S),17(S)-diHp-DHA to 7S(8)-epoxy-17(S)-HDHA

Followed by: GGT hydrolyses RCTR1 to RCTR2

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. ↗

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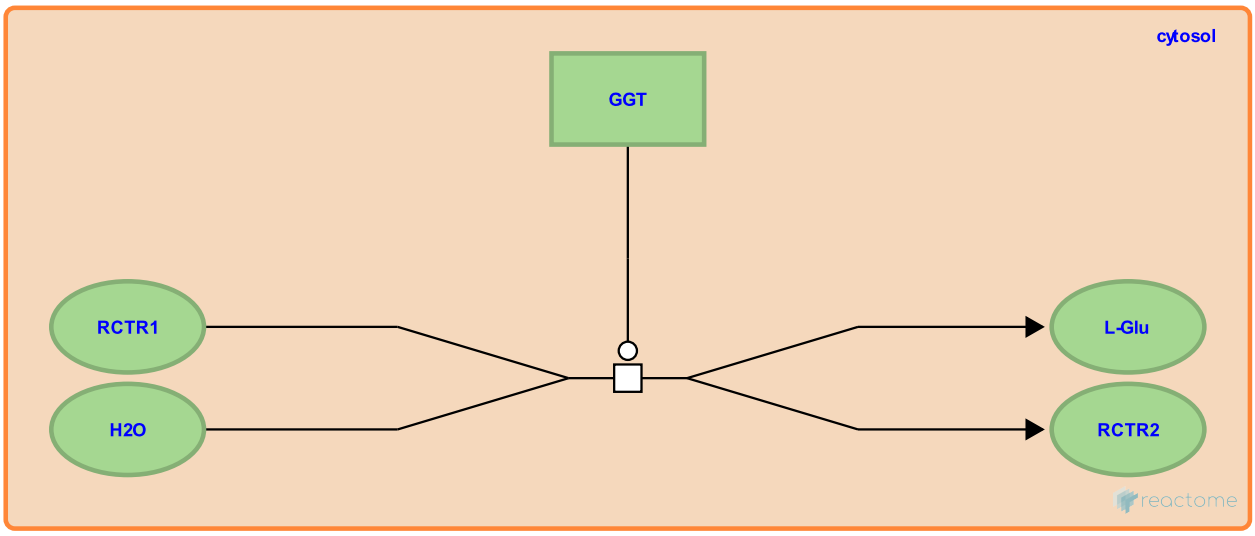
GGT hydrolyses RCTR1 to RCTR2 ↗

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

Stable identifier: R-HSA-9026927

Type: transition

Compartments: cytosol



Presumably following a similar synthesis route to protectin conjugate in tissue regeneration 2 (PCTR2), resolvin conjugate in tissue regeneration 1 (RCTR1) could be hydrolysed to RCTR2 (8-cysteinylglycinyl, 7,17-dihydroxy-docosahexaenoic acid) by the actions of a glutathione transferase (GGT) (Dalli et al. 2015).

Preceded by: LTC4S trimer transfers GSH to 7S(8)-epoxy-17(S)-HDHA to form RCTR1

Followed by: GGT hydrolyses RCTR2 to RCTR3

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. ↗

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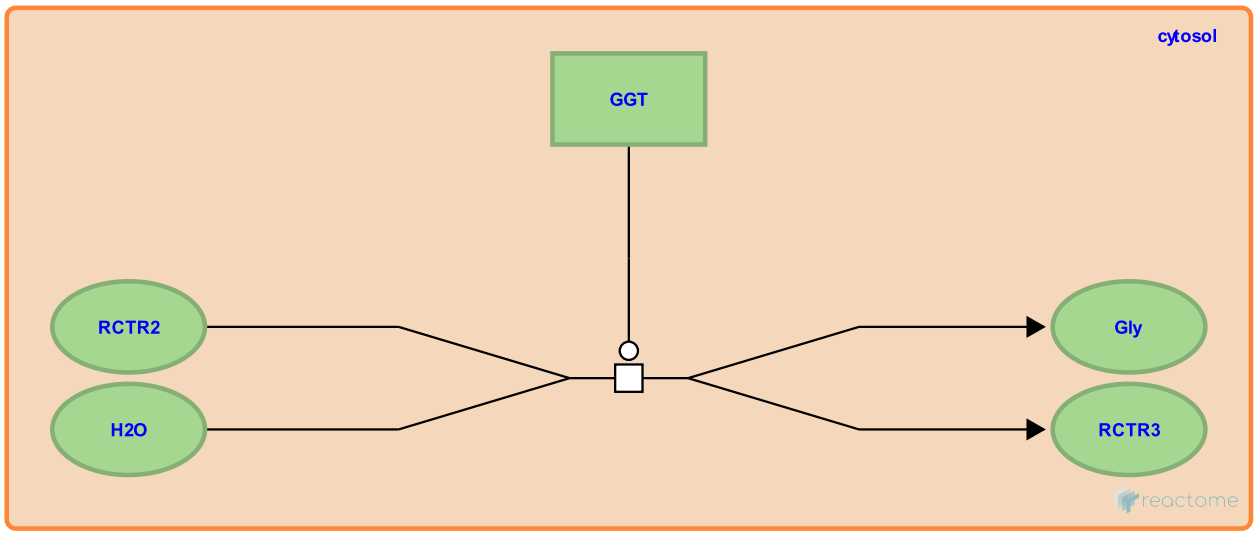
GGT hydrolyses RCTR2 to RCTR3 ↗

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

Stable identifier: R-HSA-9026916

Type: transition

Compartments: cytosol



Presumably following a similar synthesis route to protectin conjugate in tissue regeneration 3 (PCTR3), resolvin conjugate in tissue regeneration 2 (RCTR2) could be hydrolysed to RCTR3 (8-cysteinyl, 7,17-dihydroxy-docosahexaenoic acid) by the actions of a glutathione transferase (GGT) (Dalli et al. 2015).

Preceded by: GGT hydrolyses RCTR1 to RCTR2

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. ↗

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