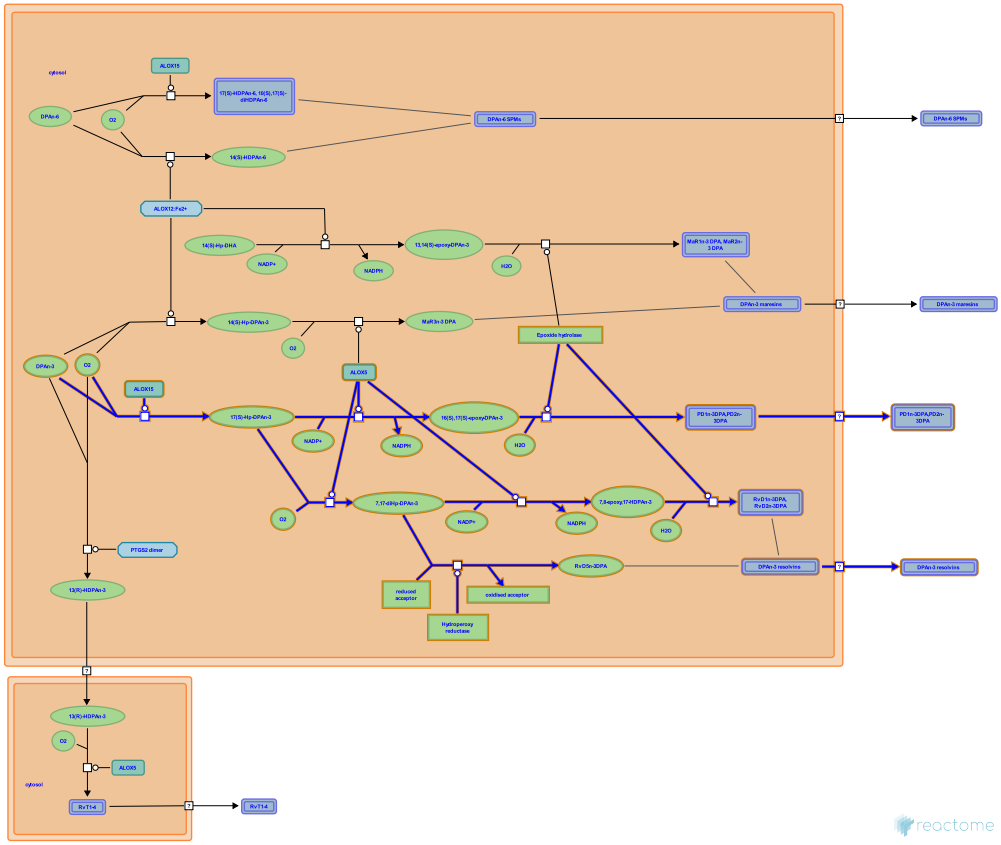
Biosynthesis of DPAn-3-derived protectins and resolvins



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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.

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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. ↗

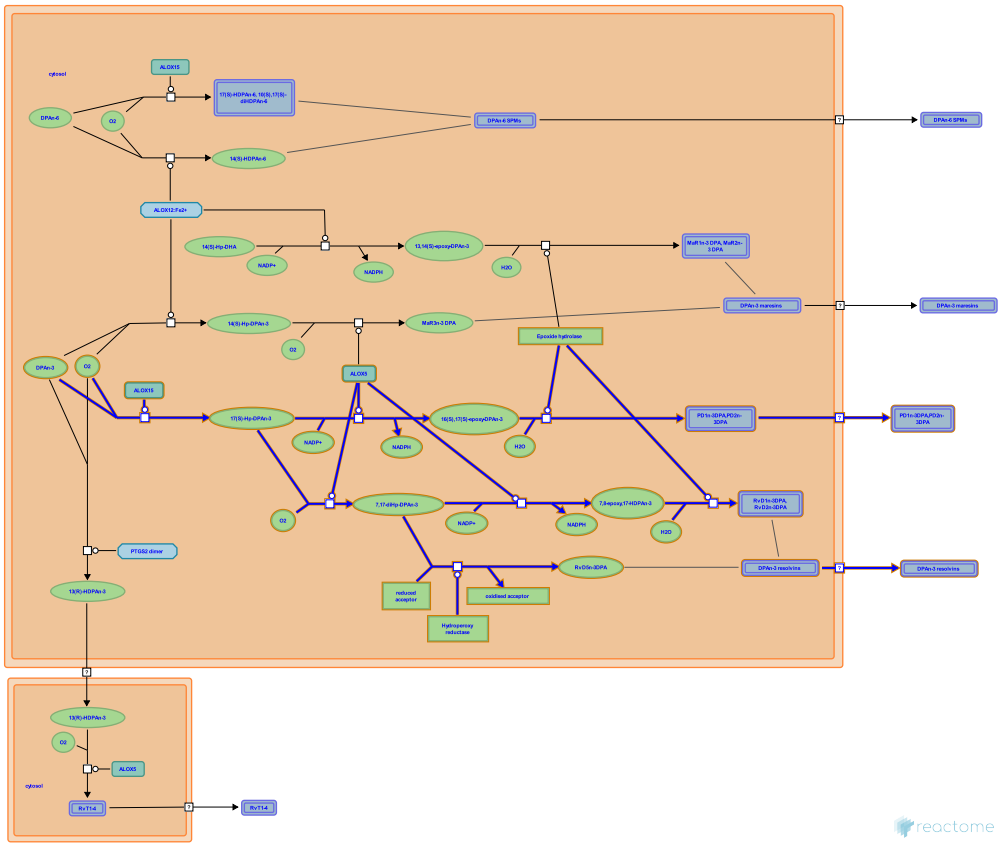
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

Biosynthesis of DPAn-3-derived protectins and resolvins ↗

Stable identifier: R-HSA-9026286



The polyunsaturated fatty acid (PUFA) ω-3 cis-7,10,13,16,19-docosapentaenoic acid (DPAn-3) is an intermediate in the biosynthesis of docosahexaenoic acid (DHA) from eicosapentaenoic acid (EPA) and is also a precursor for the production of novel bioactive mediators. The proposed biosynthesis of resolvins and protectins derived from DPAn-3 is described here (Dalli et al. 2013, Hansen et al. 2017, Vik et al. 2017). 15-lipoxygenase oxygenates DPAn-3 to its 17(S) hydroperoxy epimer from which resolvins and protectins are formed via a combination of oxygenation, reduction and hydrolysis reactions (Dalli et al. 2013). The products of the ω-3 isomer were characterised based on docosahexaenoic acid (DHA)-derived resolvins and protectins (Serhan et al. 2002) and were demonstrated to have similar potent systemic anti-inflammatory and tissue protective actions as DHA-derived specialised proresolving mediators (SPMs) (Dalli et al. 2013). The same biosynthetic route as DHA-derived SPMs is probably how DPAn-3 products are also formed (Dalli et al. 2013).

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940. ↗

Serhan, CN., Hansen, TV., Dalli, J. (2017). The novel lipid mediator PD1n-3 DPA: An overview of the structural elucidation, synthesis, biosynthesis and bioactions. *Prostaglandins Other Lipid Mediat.*. ↗

Hansen, TV., Vik, A., Dalli, J. (2017). Recent advances in the chemistry and biology of anti-inflammatory and specialized pro-resolving mediators biosynthesized from n-3 docosapentaenoic acid. *Bioorg. Med. Chem. Lett., 27*, 2259-2266. ↗

Editions

2017-10-19	Authored, Edited	Jassal, B.
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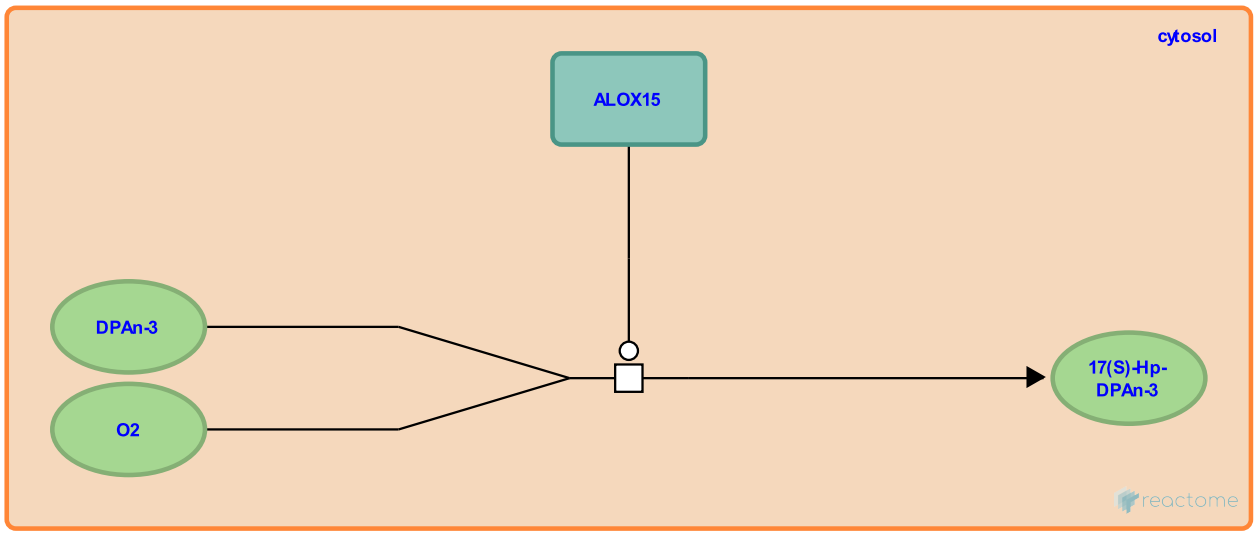
ALOX15 oxidises DPAn-3 to 17(S)-Hp-DPAn-3

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9026003

Type: transition

Compartments: cytosol



At sites of injury, 15 lipoxygenase (ALOX15) can oxygenate ω-3 docosapentaenoic acid (DPAn-3) to form the 17(S) epimer 17(S)-hydroperoxy docosapentaenoic acid (17(S)-Hp-DPAn-3) in neutrophils (Dalli et al. 2013). The formations of individual hydroperoxy intermediates are supported by chemical synthesis experiments (Aursnes et al. 2014, Primdahl et al. 2017) and are the pivotal intermediates in the production of DPAn-3 derived protectins and resolvins.

Followed by: ALOX5 dehydrogenates 17(S)-Hp-DPAn-3 to 16(S),17(S)-epoxy-DPAn-3, ALOX5 oxidises 17(S)-Hp-DPAn-3 to 7,17-diHp-DPAn-3

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940.

Serhan, CN., Colas, RA., Cheng, CY., Hansen, TV., Tungen, JE., Aursnes, M. et al. (2014). Total synthesis of the lipid mediator PD1n-3 DPA: configurational assignments and anti-inflammatory and pro-resolving actions. *J. Nat. Prod., 77*, 910-6.

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.*.

Editions

2017-10-16	Authored, Edited	Jassal, B.
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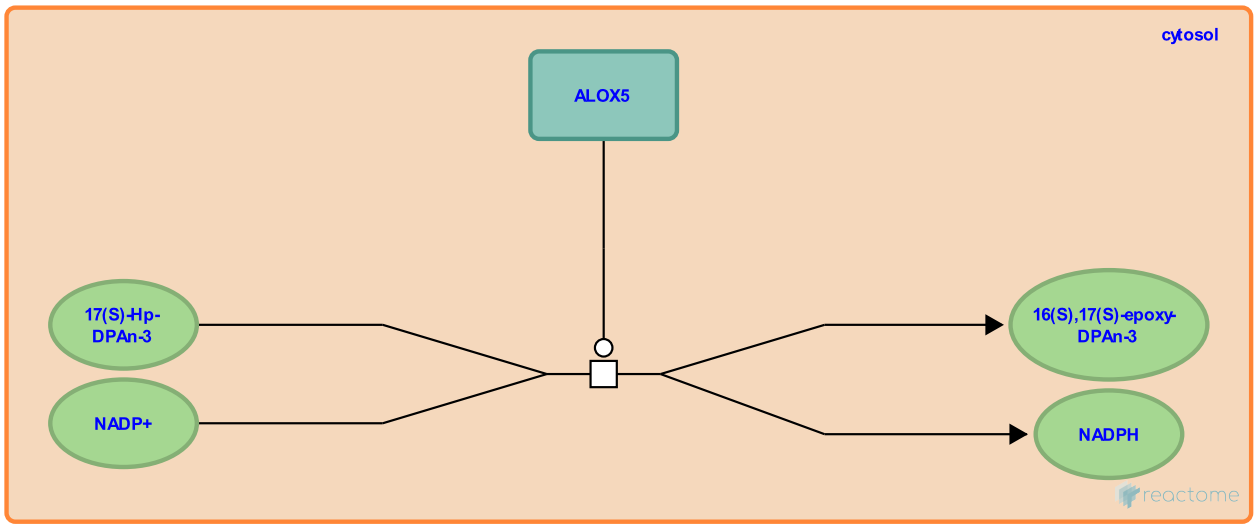
ALOX5 dehydrogenates 17(S)-Hp-DPAn-3 to 16(S),17(S)-epoxy-DPAn-3 ↗

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9025999

Type: transition

Compartments: cytosol



In neutrophils, an unknown lipoxygenase may mediate hydrogen abstraction from 17(S)-hydroperoxy-docosapentaenoic acid (17(S)-Hp-DPAn-3) to form 16(S),17(S)-epoxy-docosapentaenoic acid (16(S),17(S)-epoxy-DPAn-3) (Dalli et al. 2013). If, as assumed, DPA metabolism follows the same path as DHA metabolism, the lipoxygenase could be the dual-functional 5-lipoxygenase (ALOX5). The formation of this epoxy intermediate is supported by chemical synthesis experiments (Aursnes et al. 2014, Primdahl et al. 2017).

Preceded by: ALOX15 oxidises DPAn-3 to 17(S)-Hp-DPAn-3

Followed by: Epoxide hydrolase hydrolyses 16(S),17(S)-epoxy-DPAn-3 to PD1n-3DPA or PD2n-3DPA

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940. ↗

Serhan, CN., Colas, RA., Cheng, CY., Hansen, TV., Tungen, JE., Aursnes, M. et al. (2014). Total synthesis of the lipid mediator PD1n-3 DPA: configurational assignments and anti-inflammatory and pro-resolving actions. *J. Nat. Prod., 77*, 910-6. ↗

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.*. ↗

Editions

2017-10-16	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

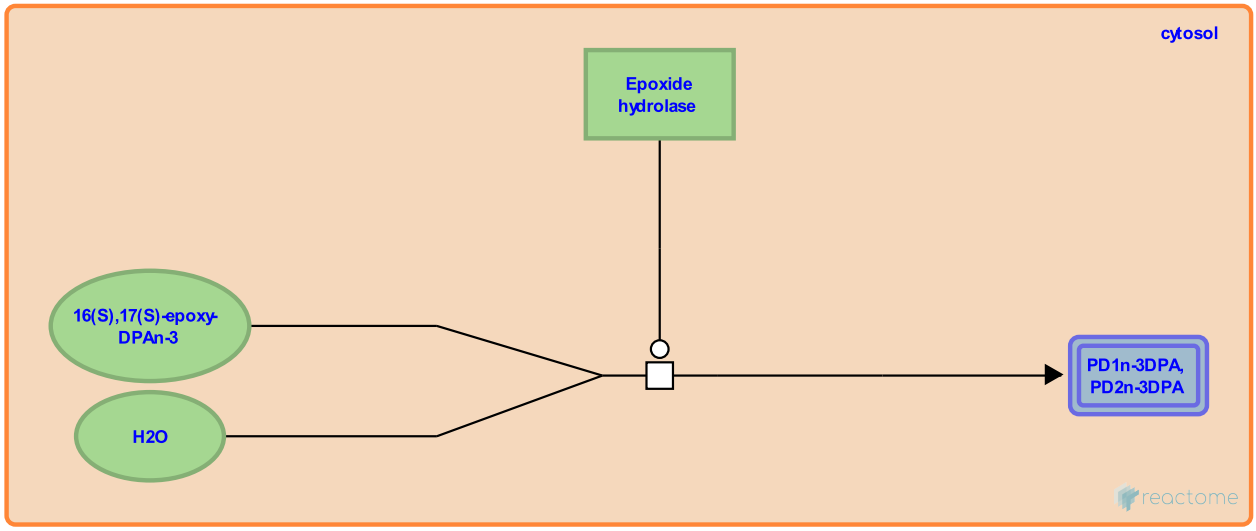
Epoxide hydrolase hydrolyses 16(S),17(S)-epoxy-DPAn-3 to PD1n-3DPA or PD2n-3DPA ↗

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9026000

Type: transition

Compartments: cytosol



In neutrophils, an epoxide hydrolase can hydrolyse 16(S),17(S)-epoxy-docosapentaenoic acid (16(S),17(S)-epoxy-DPAn-3) to either 10(R),17(S)-dihydroxy-docosapentaenoic acid (PD1n-3DPA) or 16,17(S)-dihydroxy-docosapentaenoic acid (PD2n-3DPA) (Dalli et al. 2013). The formation of these protectins is supported by chemical synthesis experiments (Aursnes et al. 2014, Primdahl et al. 2017). These DPAn-3-derived protectins demonstrate potent anti-inflammatory activities together with pro-resolving actions, stimulating human macrophage phagocytosis and efferocytosis (Dalli et al. 2013, Aursnes et al. 2014, Primdahl et al. 2017, Gobbetti et al. 2017).

Preceded by: ALOX5 dehydrogenates 17(S)-Hp-DPAn-3 to 16(S),17(S)-epoxy-DPAn-3

Followed by: PD1n-3, PD2n-3 translocate from cytosol to extracellular region

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940. ↗

Serhan, CN., Colas, RA., Cheng, CY., Hansen, TV., Tungen, JE., Aursnes, M. et al. (2014). Total synthesis of the lipid mediator PD1n-3 DPA: configurational assignments and anti-inflammatory and pro-resolving actions. *J. Nat. Prod., 77*, 910-6. ↗

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.*. ↗

Editions

2017-10-16	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

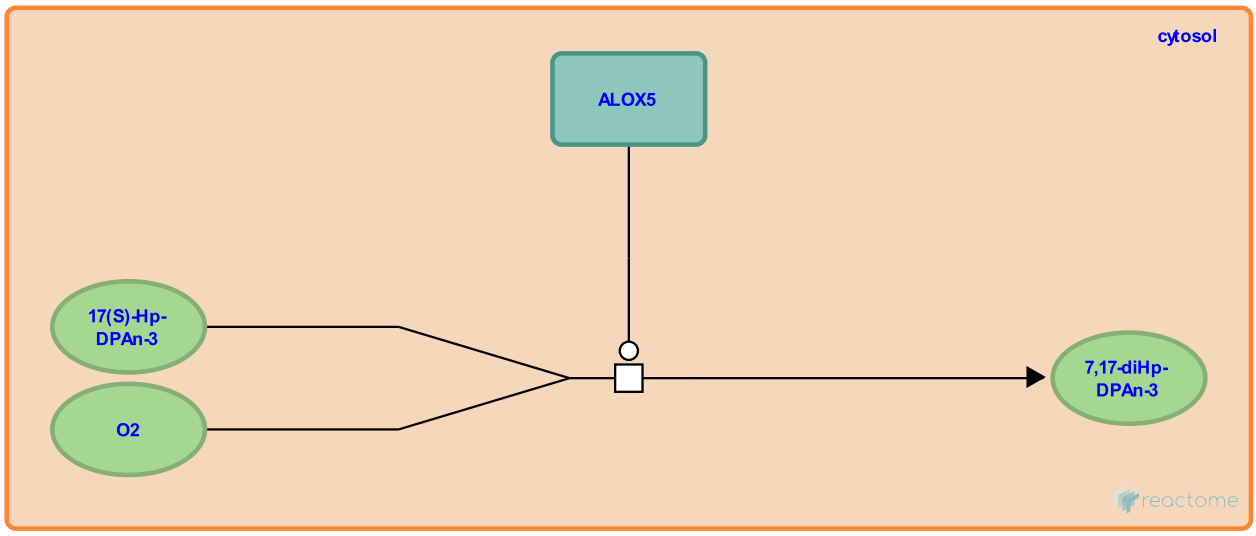
ALOX5 oxidises 17(S)-Hp-DPAn-3 to 7,17-diHp-DPAn-3

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9025996

Type: transition

Compartments: cytosol



In an alternative route to the production of protectins PD1n-3DPA and PD2n-3DPA, 17(S)-hydroperoxy-docosapentaenoic acid (17(S)-Hp-DPAn-3) can be further oxygenated by a lipoxygenase to form 7,17-dihydroperoxy-docosapentaenoic acid (7,17-diHp-DPAn-3) (Dalli et al. 2013). Although this is a proposed biosynthetic route, it is assumed DPAn-3-derived SPMs follow a similar synthesis route to DHA- and EPA-derived SPMs therefore the lipoxygenase could be the dual-functional 5-lipoxygenase (ALOX5).

Preceded by: ALOX15 oxidises DPAn-3 to 17(S)-Hp-DPAn-3

Followed by: Hydroperoxy reductase reduces 7,17-diHp-DPAn-3 to RvD5n-3DPA, ALOX5 dehydrogenates 7,17-diHp-DPAn-3 to 7,8-epoxy,17-HDPAn-3

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940.

Editions

2017-10-16	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

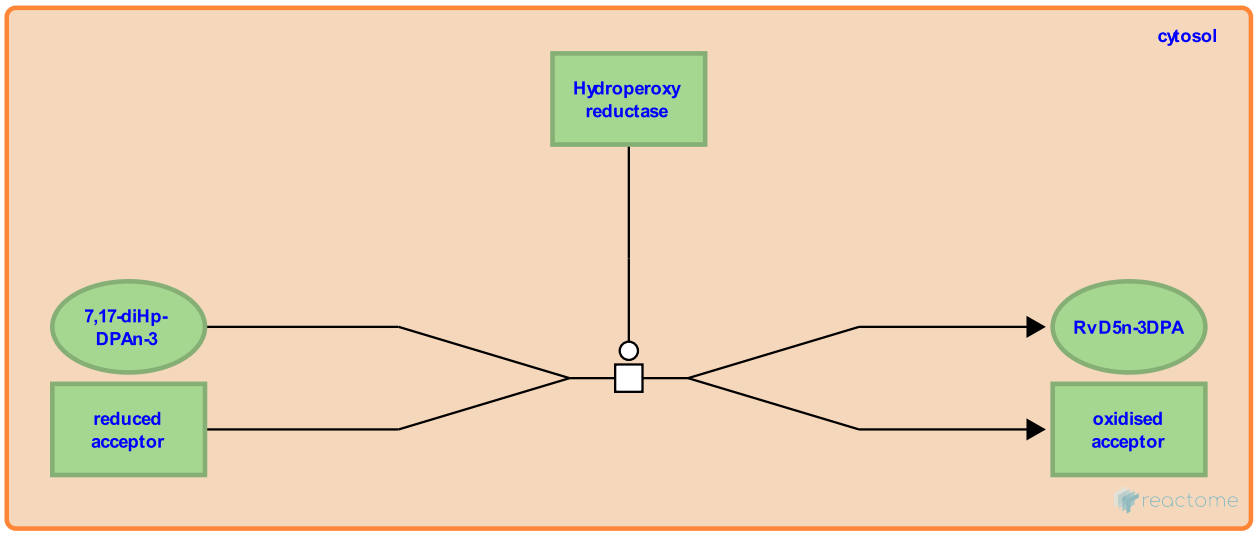
Hydroperoxy reductase reduces 7,17-diHp-DPAn-3 to RvD5n-3DPA ↗

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9026001

Type: transition

Compartments: cytosol



A hydroperoxy reductase probably reduces 7,17-dihydroperoxy-docosapentaenoic acid (7,17-diHp-DPAn-3) to the resolvin 7,17-dihydroxy-docosapentaenoic acid (RvD5n-3DPA) (Dalli et al. 2013). Treatment with RvD5n-3DPA reduced colitis and intestinal ischemia/reperfusion-induced inflammation in mice and reduced human neutrophil-endothelial cell interactions with TNF-α-activated human endothelial monolayers (Gobbetti et al. 2017). Although this is a proposed biosynthetic route for the formation of DPA-n-3 resolvins, it is assumed DPAn-3-derived SPMs follow a similar synthesis route to DHA- and EPA-derived SPMs.

Preceded by: ALOX5 oxidises 17(S)-Hp-DPAn-3 to 7,17-diHp-DPAn-3

Followed by: DPAn-3 resolvins translocate from cytosol to extracellular region

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940. ↗

Editions

2017-10-16	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

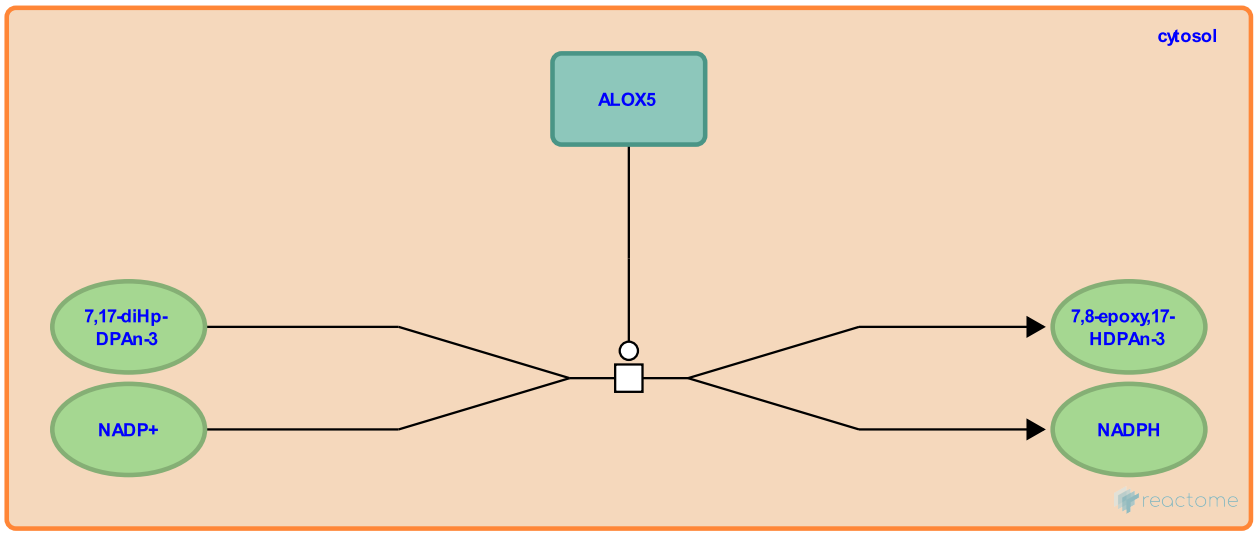
ALOX5 dehydrogenates 7,17-diHp-DPAn-3 to 7,8-epoxy,17-HDPAn-3

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9025995

Type: transition

Compartments: cytosol



Instead of the dihydroperoxy intermediate being reduced, a lipoxygenase may mediate hydrogen abstraction from 7,17-dihydroperoxy-docosapentaenoic acid (7,17-diHp-DPAn-3) to form 7,8-epoxy, 17-hydroxydocosapentaenoic acid (7,8-epoxy,17-HDPAn-3) (Dalli et al. 2013). Although this is a proposed biosynthetic route for the formation of DPA-n-3 resolvins, it is assumed DPAn-3-derived SPMs follow a similar synthesis route to DHA- and EPA-derived SPMs and therefore, the lipoxygenase could be the dual-functional 5-lipoxygenase (ALOX5).

Preceded by: ALOX5 oxidises 17(S)-Hp-DPAn-3 to 7,17-diHp-DPAn-3

Followed by: Epoxide hydrolase hydrolyses 7,8-epoxy-HDPAn-3 to RvD1n-3DPA or RvD2n-3DPA

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940.

Editions

2017-10-16	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

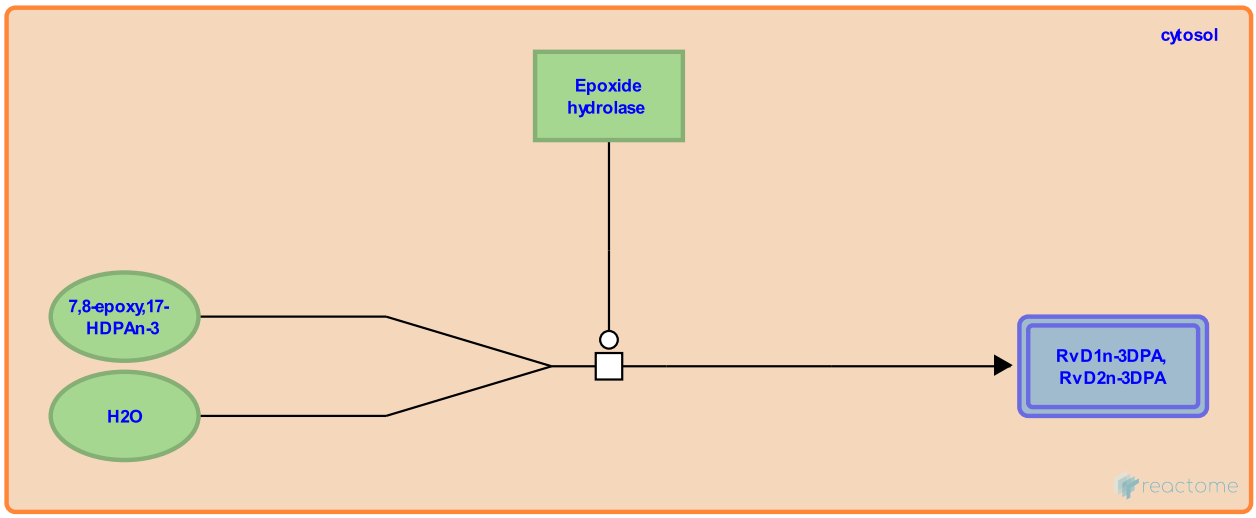
Epoxide hydrolase hydrolyses 7,8-epoxy-HDPAn-3 to RvD1n-3DPA or RvD2n-3DPA ↗

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9026008

Type: transition

Compartments: cytosol



In neutrophils, an epoxide hydrolase is thought to hydrolyse 7,8-epoxy-17-hydroxydocosapentaenoic acid (7,8-epoxy-HDPAn-3) to either of the resolvins 7,8,17-trihydroxy-docosapentaenoic acid (RvD1n-3DPA) or 7,16,17-trihydroxy-docosapentaenoic acid (RvD2n-3DPA) (Dalli et al. 2013). Treatment of induced inflammation in mice with RvD1n-3DPA and RvD2n-3DPA reduced neutrophil infiltration and adhesion and enhanced macrophage phagocytosis; all key steps in inflammatory resolution (Dalli et al. 2013, Gobbetti et al. 2017). Although this is a proposed biosynthetic route for the formation of DPA-n-3 resolvins, it is assumed DPAn-3-derived SPMs follow a similar synthesis route to DHA- and EPA-derived SPMs.

Preceded by: ALOX5 dehydrogenates 7,17-diHp-DPAn-3 to 7,8-epoxy,17-HDPAn-3

Followed by: DPAn-3 resolvins translocate from cytosol to extracellular region

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940. ↗

Editions

2017-10-16	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

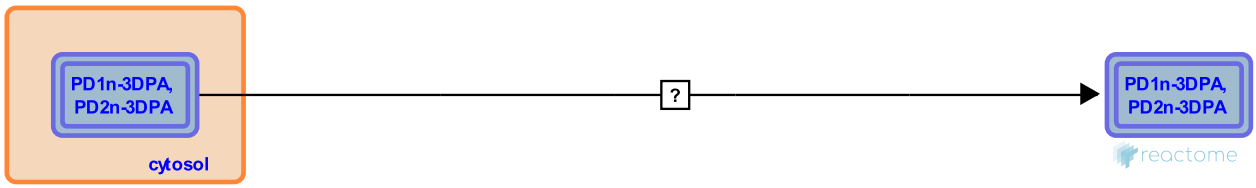
PD1n-3, PD2n-3 translocate from cytosol to extracellular region ↗

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9031896

Type: uncertain

Compartments: extracellular region, cytosol



To produce their pro-resolving effects, DPAn-3 derived protectins (PD1n-3 and PD2n-3) are released into the exudate of local inflammation sites (Dalli et al. 2013, Vik et al. 2017). The mechanism of translocation is unknown.

Preceded by: Epoxide hydrolase hydrolyses 16(S),17(S)-epoxy-DPAn-3 to PD1n-3DPA or PD2n-3DPA

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940. ↗

Hansen, TV., Vik, A., Dalli, J. (2017). Recent advances in the chemistry and biology of anti-inflammatory and specialized pro-resolving mediators biosynthesized from n-3 docosapentaenoic acid. *Bioorg. Med. Chem. Lett., 27*, 2259-2266. ↗

Editions

2017-12-04	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

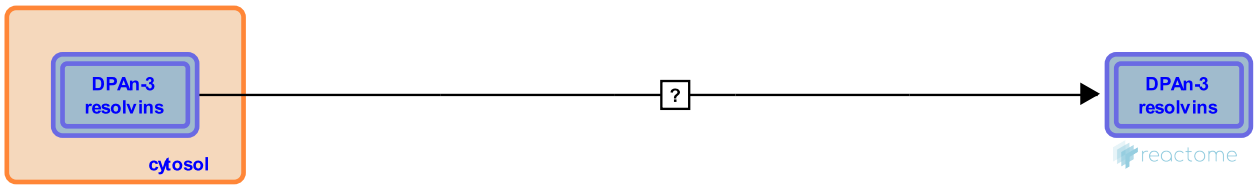
DPAn-3 resolvins translocate from cytosol to extracellular region ↗

Location: Biosynthesis of DPAn-3-derived protectins and resolvins

Stable identifier: R-HSA-9031881

Type: uncertain

Compartments: extracellular region, cytosol



To produce their pro-resolving effects, DPAn-3 derived resolvins (RvD1n-3DPA, RvD2n-3DPA and RvD5n-3DPA) are released into the exudate of local inflammation sites (Dalli et al. 2013, Vik et al. 2017). The mechanism of translocation is unknown.

Preceded by: Hydroperoxy reductase reduces 7,17-diHp-DPAn-3 to RvD5n-3DPA, Epoxide hydrolase hydrolyses 7,8-epoxy-HDPAn-3 to RvD1n-3DPA or RvD2n-3DPA

Literature references

Serhan, CN., Colas, RA., Dalli, J. (2013). Novel n-3 immunoresolvents: structures and actions. *Sci Rep, 3*, 1940. ↗

Hansen, TV., Vik, A., Dalli, J. (2017). Recent advances in the chemistry and biology of anti-inflammatory and specialized pro-resolving mediators biosynthesized from n-3 docosapentaenoic acid. *Bioorg. Med. Chem. Lett., 27*, 2259-2266. ↗

Editions

2017-12-04	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

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