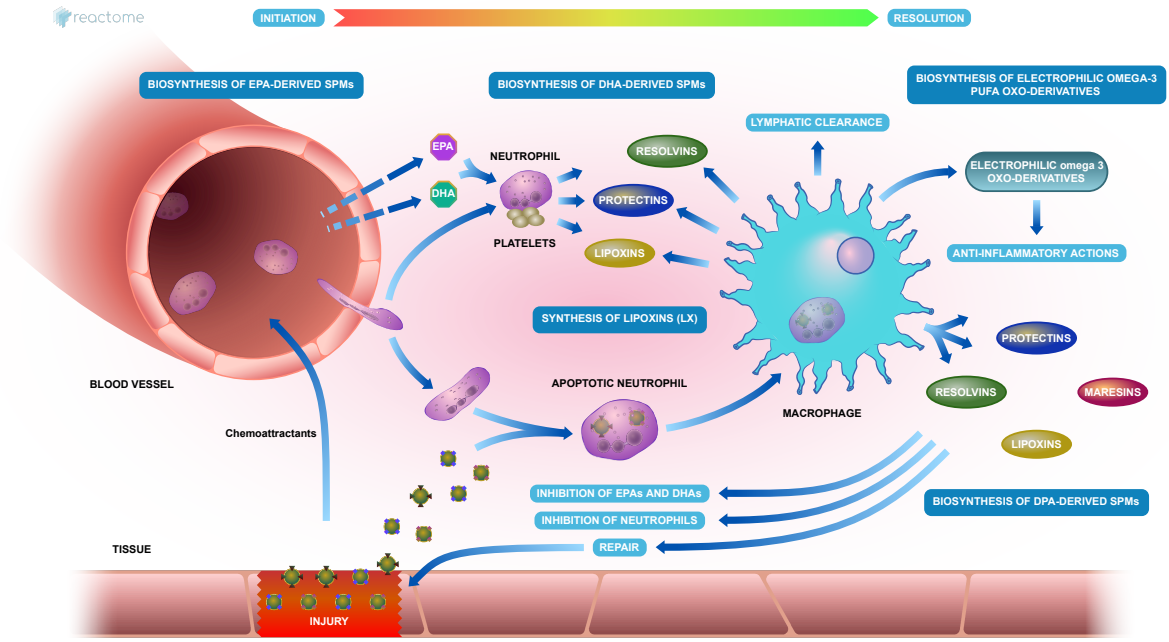
Biosynthesis of specialized proresolving mediators (SPMs)



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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.

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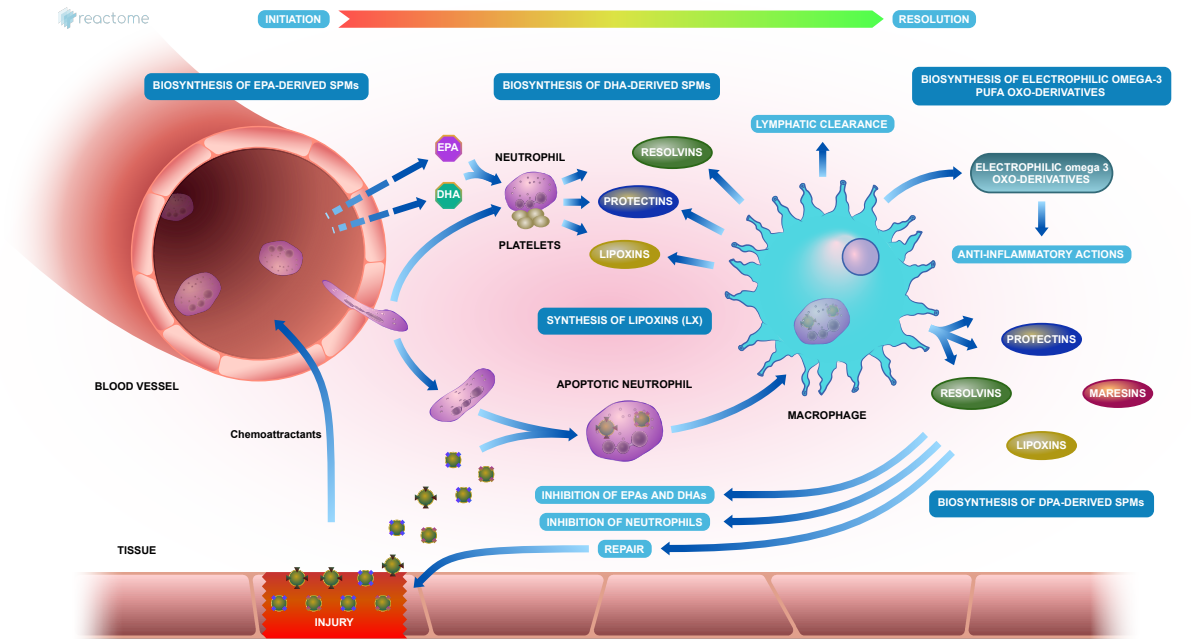
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 6 pathways (see Table of Contents)

Biosynthesis of specialized proresolving mediators (SPMs) ↗

Stable identifier: R-HSA-9018678



A host's normal protective response to tissue injury or pathogenic infection is acute inflammation. The condition of acute inflammation is created by the release of pro-inflammatory lipid mediators such as leukotrienes (LTs) and prostaglandins (PGs) that launch a series of signaling cascades to destroy invading pathogens and to repair damaged tissue (Libby 2007). The potent chemotactic agent leukotriene B4 (LTB4) promotes the recruitment of neutrophils (PMNs) to inflamed tissues, while the prostaglandins E2 and D2 (PGE2 and PGD2) further accelerate the inflammatory process. If left unchecked, the inflammatory response can initiate chronic systemic inflammatory disorders associated with cardiovascular disease, rheumatoid arthritis, periodontal disease, asthma, diabetes, inflammatory bowel disease (IBD), Alzheimer's disease and age-related macular degeneration (AMD). The specific role by which inflammation contributes to their pathogenesis is not fully understood.

To prevent the onset of chronic inflammation, a *lipid mediator class switch* is thought to occur from the initial actions of pro-inflammatory lipid mediators to the anti-inflammatory and pro-resolving actions of lipoxins, resolvins, protectins and maresins (collectively called specialized proresolving mediators (SPMs)). Nanopicogram quantities of different lipid mediators are generated at different times during the evolution of the inflammatory response and these mediators coincide with distinct cellular events. The class switch activates leukocyte translational regulation of the enzymes required to produce pro-resolving lipid mediators (Levy et al. 2001). Each family of these PSMs exert specialized actions, including blocking neutrophil recruitment, promoting the recruitment and activation of monocytes, as well as mediating the nonphlogistic phagocytosis and lymphatic clearance of apoptotic neutrophils by activated macrophages (ie without inducing inflammation) and mediating tissue regeneration. Eventually, through the combined actions of these mediators, the resolution of inflammation is completed and homeostasis is reached (Serhan 2010, Bannenberg & Serhan 2010, Freire & Van Dyke 2013, Serhan et al. 2014).

SPMs are derived from polyunsaturated fatty acids (PUFAs) (Molfino et al. 2017). PUFAs of the ω-3 series are essential nutrients since they cannot be produced by humans (Duvall & Levy 2016) and are primarily found in dietary fish oils (Calder 2013) and in plants (Baker et al. 2016). The ω-3 PUFAs eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPAn-3) circulate in the bloodstream after dietary intake and are easily incorporated into cellular membranes in a time- and dose-dependent manner (Calder 2009), as well as being present in inflammatory exudates (Kasuga et al. 2008). They can be mobilised by phospholipase A2 from cellular membranes on injury or infection when they are converted to exudate SPMs (Serhan et al. 2002) to interact with local immune cells (Kasuga et al. 2008). EPA is the source for E-series resolvins while DHA is the source for D-series resolvins, protectins, maresins and sulfido conjugates in tissue regeneration mediators (Serhan et al. 2017). The ω-6 fatty acid arachidonic acid (AA) is the source for lipoxins. ω-3 or ω-6 PUFA docosapentaenoic acids (DPAn-3 and DPAn-6) are the sources of DPA-derived resolvins, protectins and maresins (Vik et al. 2017). Aspirin can also trigger the production of epimeric SPMs via acetylated PTGS2 (prostaglandin G/H synthase, COX2) (Serhan & Chiang 2002). Combinations of oxidation, reduction and hydrolysis can generate numerous SPMs. Electrophilic oxo-derivatives of ω-3 PUFAs are a class of oxidised derivatives that are generated in macrophages

and neutrophils by the actions of 5-lipoxygenase, cyclooxygenase-2 and acetylated cyclooxygenase-2, followed by dehydrogenation. Being electrophilic, oxo-derivative SPMs reversibly bind to nucleophilic residues on target proteins, triggering the activation of cytoprotective pathways (Cipollina 2015). The pathways in this section describe the biosynthesis of these SPMs.

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Editions

2017-09-04	Authored, Edited	Jassal, B.
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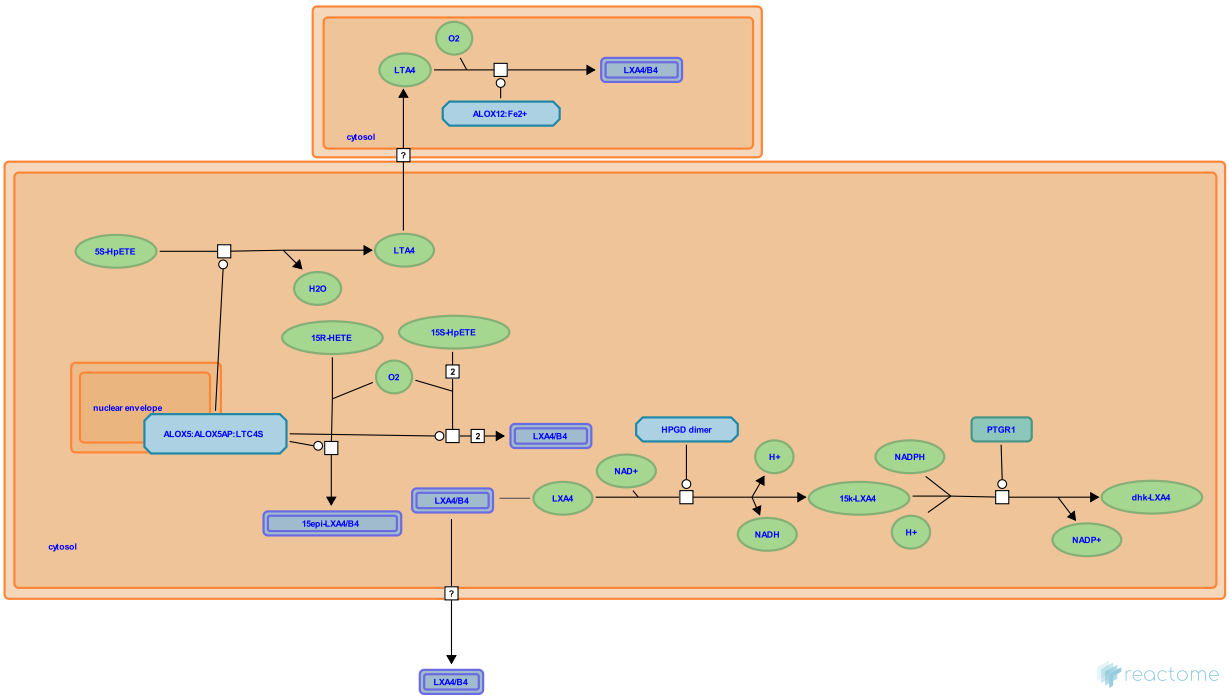
Synthesis of Lipoxins (LX) ↗

Location: Biosynthesis of specialized proresolving mediators (SPMs)

Stable identifier: R-HSA-2142700



Lipoxins A4 (LXA4) and B4 (LXB4), structurally characterized from human neutrophils incubated with 15-hydroperoxy-eicosatetraenoic acid (15-HpETE), each contain three hydroxyl moieties and a conjugated tetraene. The third hydroxyl of LXA4 is positioned at C-6, and of LXB4 at C-14. The action of arachidonate 5-lipoxygenase (ALOX5), in concert with an arachidonate 12-lipoxygenase (ALOX12) or arachidonate 15-lipoxygenase (ALOX15) activity, has been shown to produce lipoxins by three distinct pathways. Neutrophil ALOX5 can produce and secrete leukotriene A4 (LTA4) that is taken up by platelets, where it is acted upon by ALOX12 to form lipoxins. Likewise, ALOX15s can generate either 15-hydroperoxy-eicosatetraenoic acid (15-HpETE) or 15-hydro-eicosatetraenoic acid (15-HETE) that can be taken up by monocytes and neutrophils, where highly expressed ALOX5 uses it to generate lipoxins. Finally, aspirin acetylated prostaglandin G/H synthase 2 (PTGS2), rendered unable to synthesize prostaglandins, can act as a 15-lipoxygenase. This leads to the formation of 15R-HETE and culminates in creation of epi-lipoxins, which have altered stereochemistry at the C-15 hydroxyl but similar biological potency (Chiang et al. 2006, Buczynski et al. 2009, Vance & Vance 2008, Stsiapanava et al. 2017).

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Editions

2012-02-24	Authored, Edited	Williams, MG.
2012-11-10	Reviewed	Rush, MG.
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Biosynthesis of EPA-derived SPMs ↗

Location: Biosynthesis of specialized proresolving mediators (SPMs)

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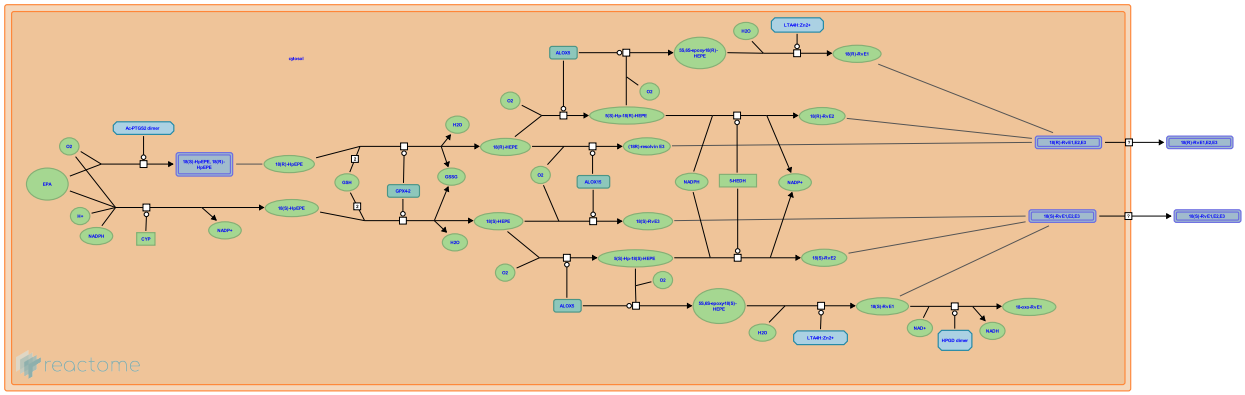

Eicosapentaenoic acid (EPA), a major ω-3 polyunsaturated fatty acid (PUFA) found in fish oil is the source of E-series resolvins (RvEs), one of the specialized proresolving mediators (SPMs) that show potent anti-inflammatory and pro-resolving actions (Molfino et al. 2017). The biosynthesis of RvEs occurs mainly during the process of inflammation when endothelial cells interact with leukocytes. EPA, circulating in plasma or released/mobilised from damaged cellular membranes on injury or infection, moves with edema into the tissue sites of acute inflammation where it is converted to exudate RvEs to interact with local immune cells (Kasuga et al. 2008). The initial transformation of EPA by aspirin-acetylated cyclooxygenase 2- and/or cytochrome P450-mediated catalysis can produce stereospecific resolvins (18(R)- or 18(S)-RvEs). Combinations of oxidation, reduction and hydrolysis reactions determine the type of resolvin formed (RvE1, RvE2 or RvE3) (Serhan et al. 2000, 2002, Serhan & Petasis 2011, Maehre et al. 2015).

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Biosynthesis of DHA-derived SPMs ↗

Location: Biosynthesis of specialized proresolving mediators (SPMs)

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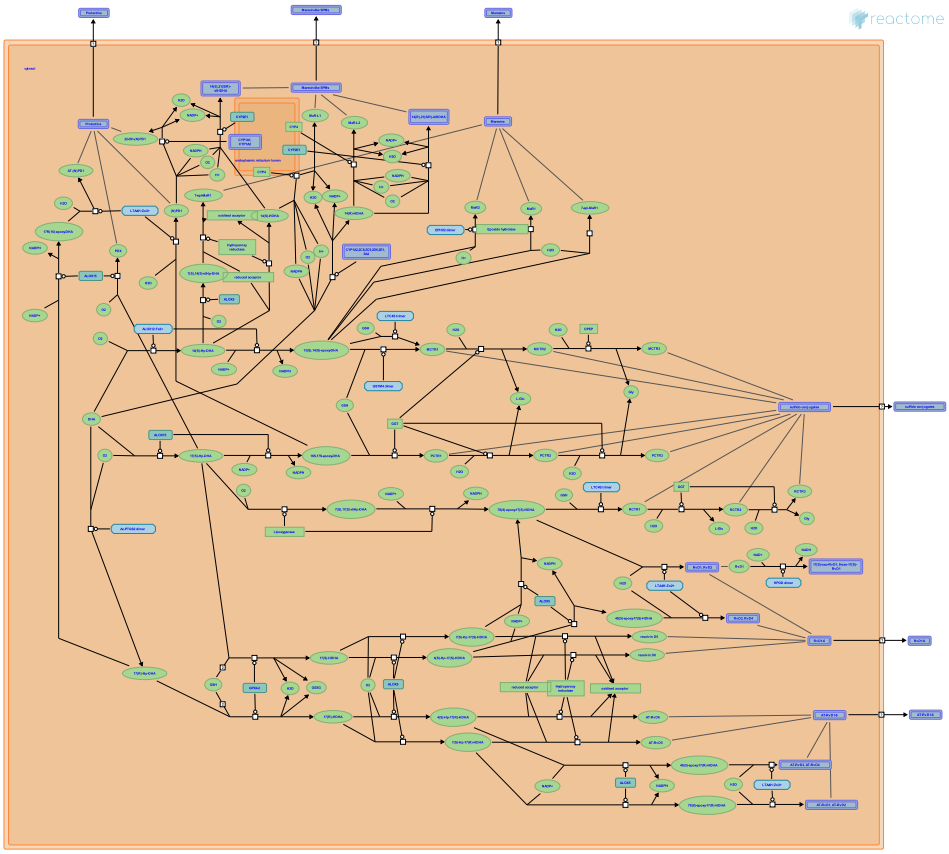

Docosahexaenoic acid (DHA), a major ω-3 polyunsaturated fatty acid (PUFA) found in fish oil is the source of D-series resolvins (RvDs), one of the specialized proresolving mediators (SPMs) that show potent anti-inflammatory and pro-resolving actions (Molfino et al. 2017). The biosynthesis of RvDs occurs 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).

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Biosynthesis of DPA-derived SPMs ↗

Location: Biosynthesis of specialized proresolving mediators (SPMs)

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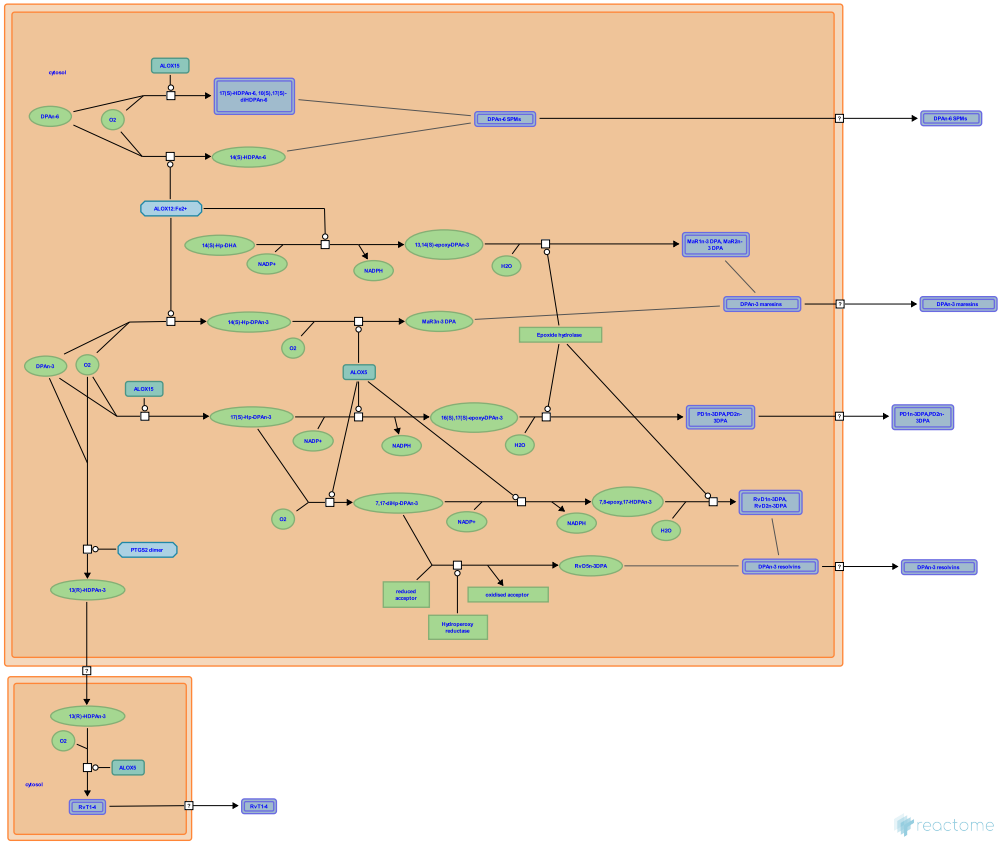

Docosapentaenoic acid (DPA), a C22:5 long-chain ω3 or ω6 polyunsaturated fatty acid (PUFA), is found in algal and fish oils, created via linoleic acid metabolism and is a metabolite in DHA metabolism. It can be acted upon by lipoxygenases to produce mono-, di- and tri-hydroxy derivatives in neutrophils and macrophages. These DPA derivatives are another branch of the specialised proresolving mediators (SPMs) produced from long-chain fatty acids which have anti-inflammatory properties, even though mechanisms of their anti-inflammatory action have not been fully elucidated (Bannenberg & Serhan 2010, Dangi et al. 2010, Vik et al. 2017, Hansen et al. 2017).

The biosynthesis of SPMs derived from the two isomers of DPA, DPAn-6 (cis-4,7,10,13,16-docosapentaenoic acid) and DPAn-3 (cis-7,10,13,16,19-docosapentaenoic acid), is described here. The only difference between the two isomers is the position of the first double bond; ω-3 for DPAn-3 and ω-6 for DPAn-6. The products of these isomers were characterised by analogy in structure and action to docosahexaenoic acid (DHA)-derived and eicosapentaenoic acid (EPA)-derived resolvins, protectins and maresins (Serhan et al. 2002, Bannenberg & Serhan 2010, Serhan et al. 2015).

Literature references

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Biosynthesis of electrophilic ω-3 PUFA oxo-derivatives ↗

Location: Biosynthesis of specialized proresolving mediators (SPMs)

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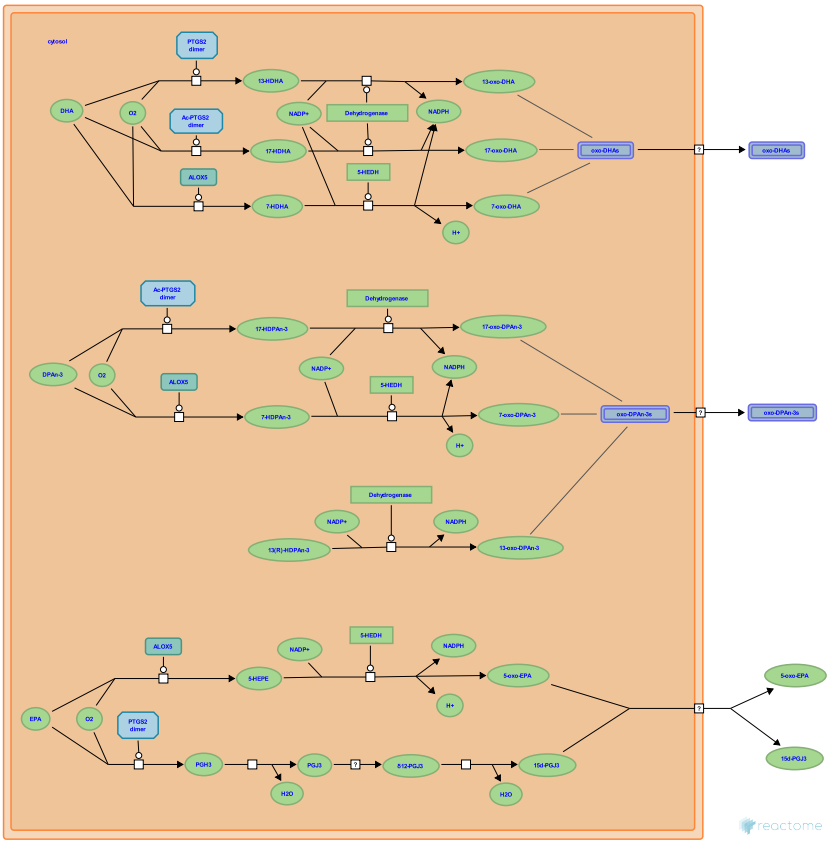

Electrophilic oxo-derivatives of ω-3 polyunsaturated fatty acids (ω-3 PUFAs) are generated in macrophages and neutrophils in response to inflammation and oxidative stress to promote the resolution of inflammation. Being electrophilic, these derivatives reversibly bind to nucleophilic residues on target proteins (thiolates of cysteines and amino groups of histidine and lysine), triggering the activation of cytoprotective pathways. These include the Nrf2 antioxidant response, the heat shock response and the peroxisome proliferator activated receptor γ (PPARγ) and suppressing the NF-κB proinflammatory pathway (Cipollina 2015). Thus, these electrophilic derivatives transduce anti-inflammatory actions rather than suppress the production of pro-inflammatory arachidonic acid metabolites. An oxo-derivative of EPA has been shown to ablate leukemia stem cells in mice, which may represent a novel chemoprotective action for some oxo-derivatives (Hedge et al. 2011, Finch et al. 2015). In humans, dietary supplementation with ω-3 PUFAs has been reported to increase the formation of oxo-derivatives (Yates et al. 2014). The enzymes cyclooxygenases (COX), lipoxygenases (LOs) and cytochromes P450s, acting alone or in concerted transcellular biosynthesis, initially form epoxy or hydroxy intermediates of ω-3 PUFAs docosahexaenoic acid (DHA), docosapentaenoic acid (DPAn-3) and eicosapentaenoic acid (EPA) before these are further oxidised to electrophilic α,β-unsaturated keto-derivatives by cellular dehydrogenases.

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Table of Contents