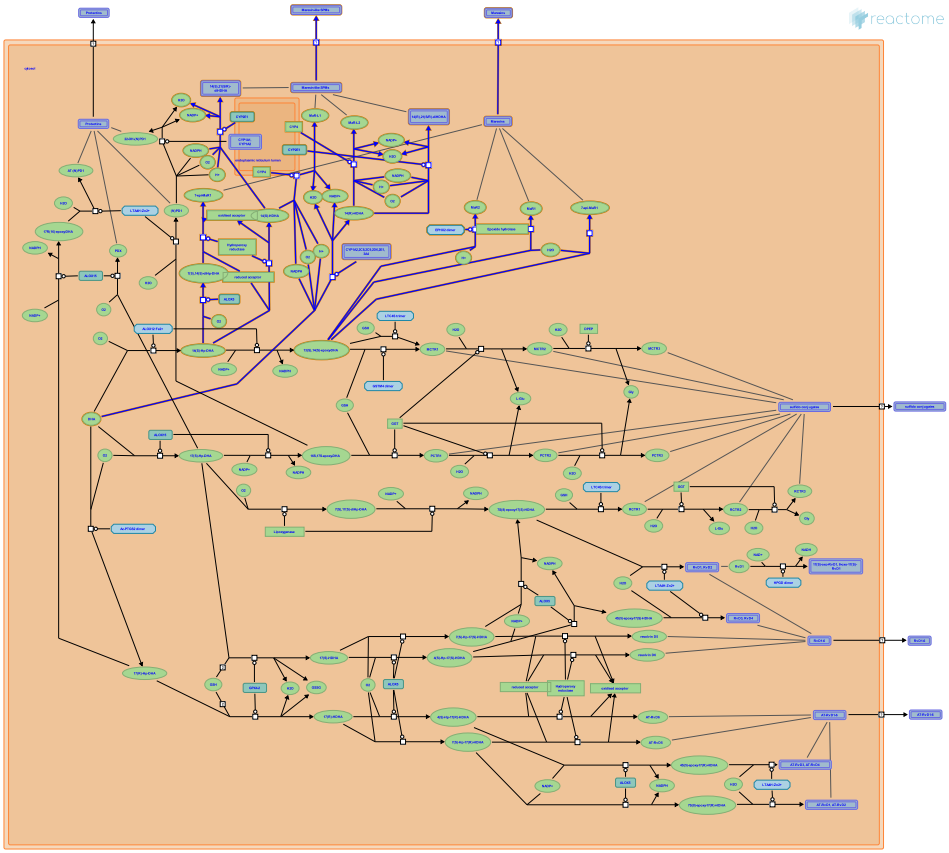
Biosynthesis of maresins



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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.

29/04/2024

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. ↗

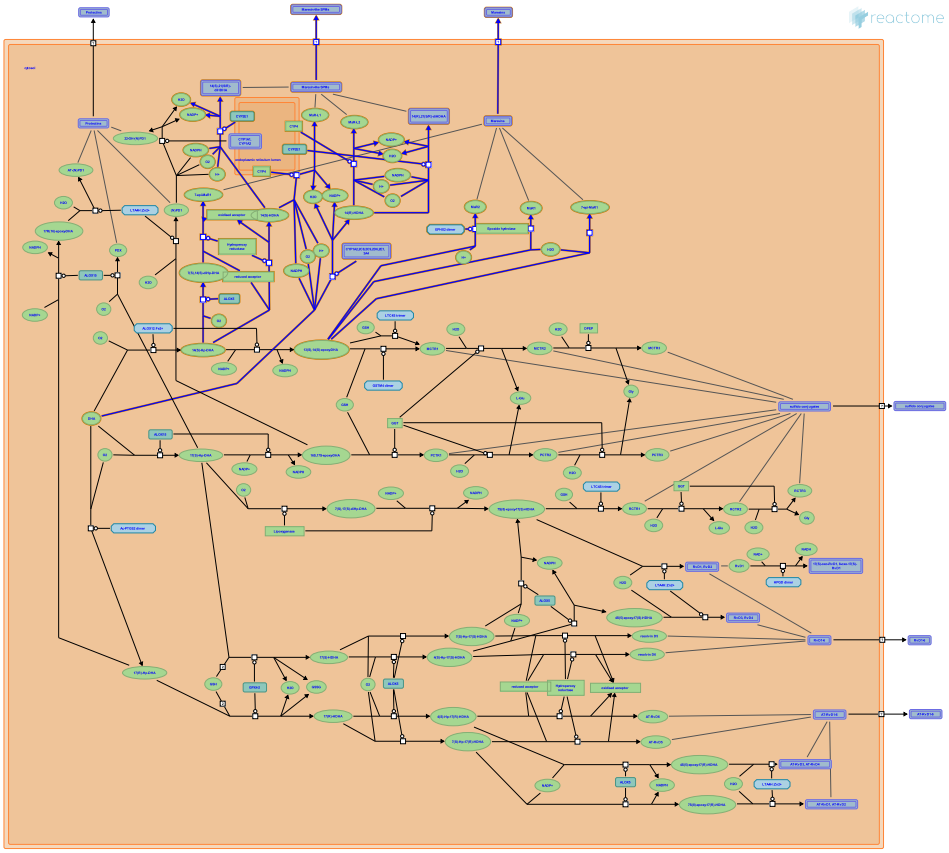
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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 maresins ↗

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

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

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

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

Boniakowski, AE., Kimball, AS., Kunkel, SL., Gallagher, KA., Jacobs, BN. (2017). Macrophage-Mediated Inflammation in Normal and Diabetic Wound Healing. *J. Immunol., 199*, 17-24. ↗

Alapure, BV., Lu, Y., Tian, H., Bunnell, BA., Wang, Q., Hong, S. 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. ↗

Editions

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

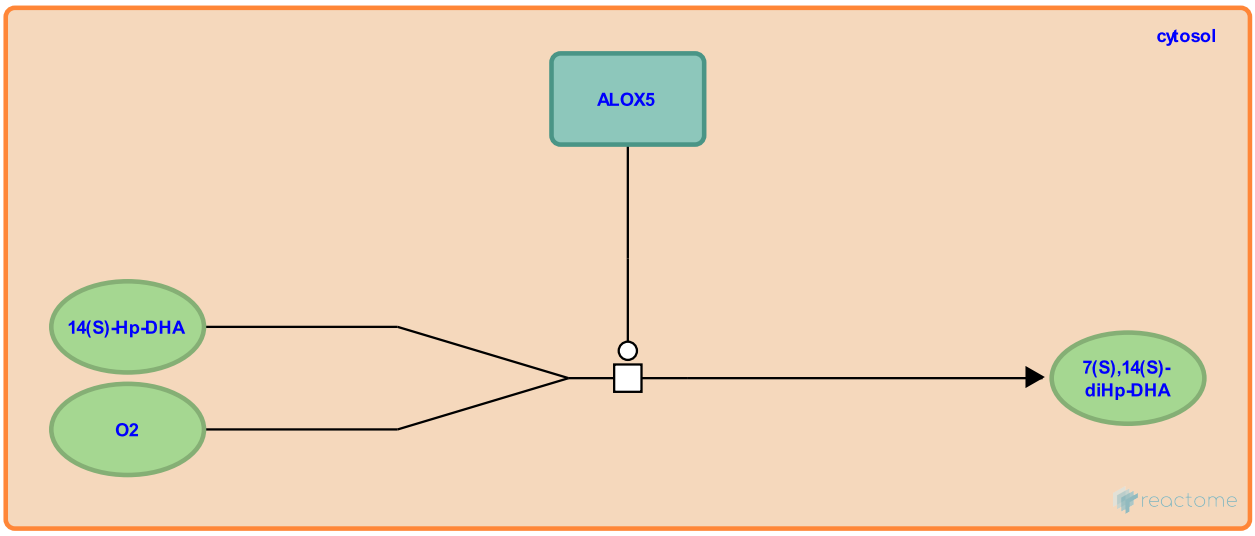
ALOX5 oxidises 14(S)-Hp-DHA to 7(S),14(S)-diHp-DHA ↗

Location: Biosynthesis of maresins

Stable identifier: R-HSA-9024997

Type: transition

Compartments: cytosol



In macrophages, lipoxygenase 5 (ALOX5) is proposed to further oxygenate 14(S)-hydroperoxy-docosahexaenoic acid (14(S)-Hp-DHA) to 7(S),14(S)-dihydroperoxy-docosaheaenoic acid (7(S),14(S)-diHp-DHA) (Serhan et al. 2009).

Followed by: Hydroperoxy reductase reduces 7(S),14(S)-diHp-DHA to 7-epi-MaR1

Literature references

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

Editions

2017-10-11	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

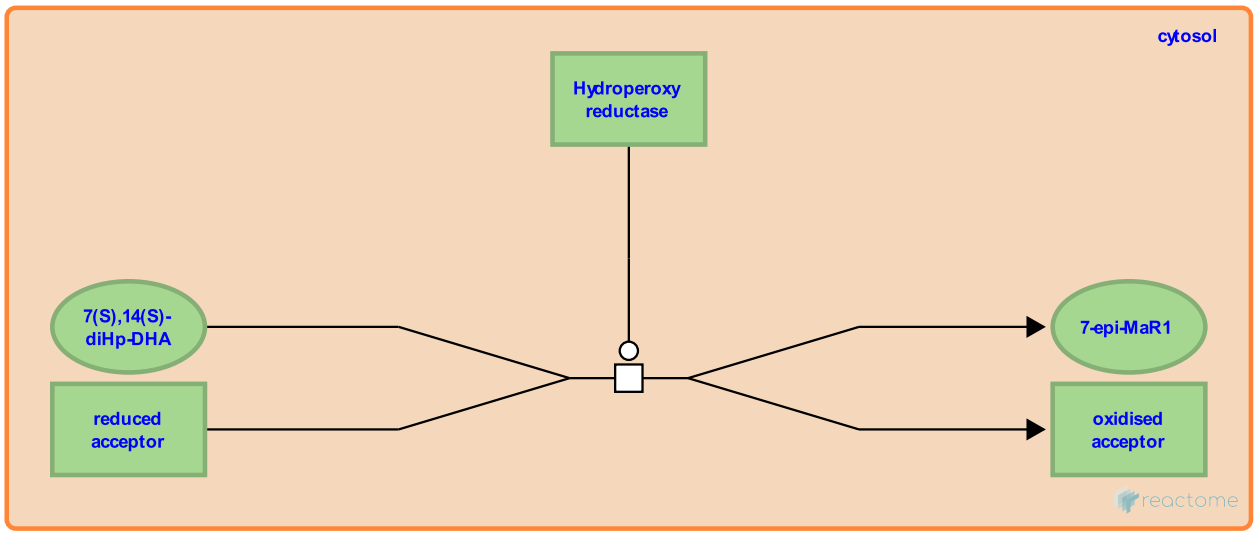
Hydroperoxy reductase reduces 7(S),14(S)-diHp-DHA to 7-epi-MaR1 ↗

Location: Biosynthesis of maresins

Stable identifier: R-HSA-9025007

Type: transition

Compartments: cytosol



An unknown hydroperoxy reductase mediates the production of the double dioxygenation product 7(S),14(S)-hydroxy-docosa-4Z,8E,10Z,12E,16Z,19Z-hexaenoic acid (7(S),14(S)-HDHA aka 7-epi-MaR1) that proved to have less potent pro-resolving and anti-inflammatory activity than either maresin 1 (MaR1) or protectin D1 (PD1) (Serhan et al. 2009, Bannenberg & Serhan 2010).

Preceded by: ALOX5 oxidises 14(S)-Hp-DHA to 7(S),14(S)-diHp-DHA

Followed by: Maresins translocate from cytosol to extracellular region

Literature references

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

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

Editions

2017-10-11	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

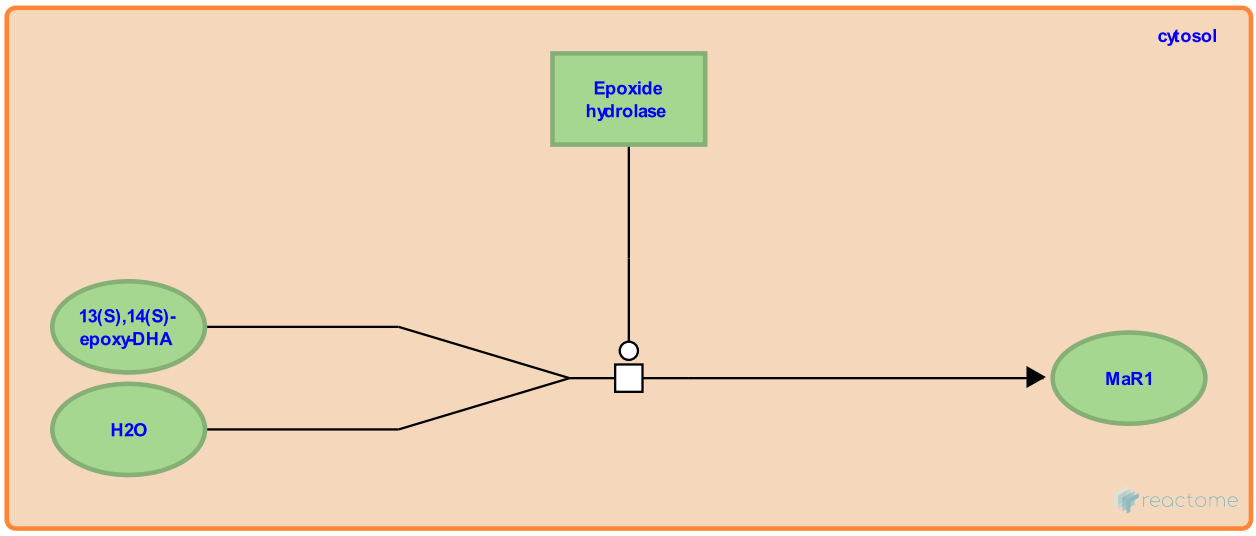
Epoxide hydrolase hydrolyses 13(S),14(S)-epoxy-DHA to MaR1 ↗

Location: Biosynthesis of maresins

Stable identifier: R-HSA-9024973

Type: transition

Compartments: cytosol



Maresin 1 (MaR1, 7(R),14(S)-dihydroxy-docosahexaenoic acid) is the first identified maresin. It is formed by hydrolysis of 13(R),14(S)-epoxy-docosahexaenoic acid (13(R),14(S)-epoxy-DHA) by an unknown epoxide hydrolase (Serhan et al. 2009). MaR1 displays potent anti-inflammatory and pro-resolving actions (Serhan et al. 2012, Chatterjee et al. 2014). MaR1 was found to inhibit proinflammatory mediator production by inhibiting LTA4 hydrolase, thereby shifting macrophage phenotype from proinflammatory mediator to proresolving mediator production (Dalli et al. 2013).

A novel double dioxygenation product can also be formed by non-enzymatic hydrolysis of 13(R),154(S)-epoxy-DHA, namely 7(S),14(S)-dihydroxy-docosahexaenoic acid (7-epi-MaR1). Although 7-epi-MaR1 possesses some bioactivity, it displays lower anti-inflammatory and pro-resolving actions than MaR1 (Serhan et al. 2009).

Followed by: Maresins translocate from cytosol to extracellular region

Literature references

Wang, CW., Serhan, CN., Cheng, CY., Arnardottir, HH., Li, Y., Deng, B. 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. ↗

Zhu, M., Serhan, CN., Vlasenko, NA., Haeggström, JZ., Petasis, NA., Deng, B. 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. ↗

Chatterjee, A., Toy, R., Chen, M., Conte, MS., Sharma, A., Mottola, G. (2014). The pro-resolving lipid mediator maresin 1 (MaR1) attenuates inflammatory signaling pathways in vascular smooth muscle and endothelial cells. *PLoS ONE, 9*, e113480. ↗

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

Zhu, M., Serhan, CN., Petasis, NA., Xu, ZZ., Ji, RR., Park, CK. et al. (2012). Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. *FASEB J., 26*, 1755-65. ↗

Editions

2017-10-11	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

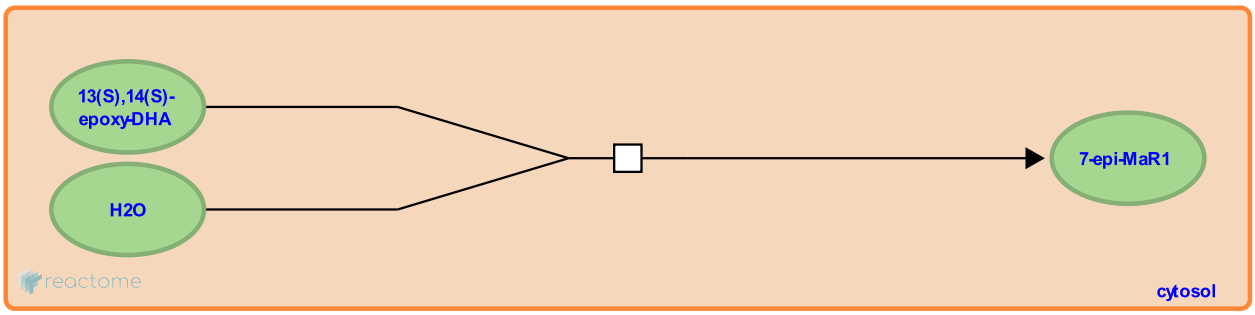
Non-enzymatic hydrolysis hydrolyses 13(S),14(S)-epoxy-DHA to 7-epi-MaR1 ↗

Location: Biosynthesis of maresins

Stable identifier: R-HSA-9026544

Type: transition

Compartments: cytosol



Maresin 1 (MaR1, 7(R),14(S)-dihydroxy-docosahexaenoic acid) is the first identified maresin and displays potent anti-inflammatory and pro-resolving actions (Serhan et al. 2012, Chatterjee et al. 2014). MaR1 was found to inhibit proinflammatory mediator production by inhibiting LTA4 hydrolase, thereby shifting macrophage phenotype from proinflammatory mediator to proresolving mediator production (Dalli et al. 2013). A novel double dioxygenation product can also be formed by non-enzymatic hydrolysis of 13(R),154(S)-epoxy-DHA, namely 7(S),14(S)-dihydroxy-docosahexaenoic acid (7-epi-MaR1). Although 7-epi-MaR1 possesses some bioactivity, it displays lower anti-inflammatory and pro-resolving actions than MaR1 (Serhan et al. 2009).

Followed by: Maresins translocate from cytosol to extracellular region

Literature references

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

Editions

2017-10-20	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

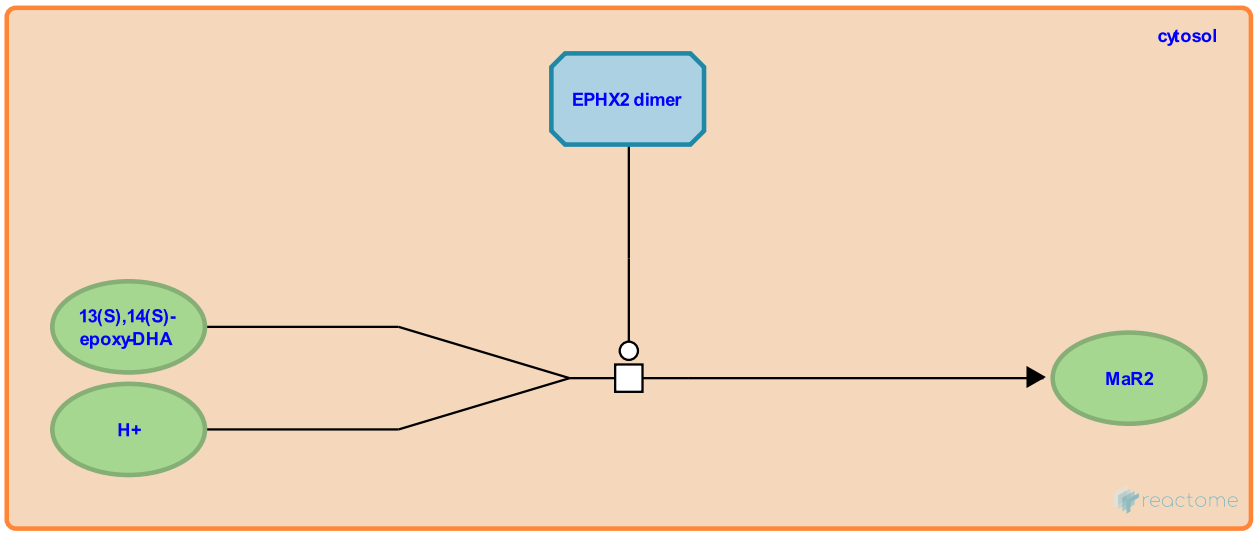
EPHX2 dimer hydrolyses 13(S),14(S)-epoxy-DHA to MaR2 ↗

Location: Biosynthesis of maresins

Stable identifier: R-HSA-9024993

Type: transition

Compartments: cytosol



Dimeric bifunctional epoxide hydrolase 2 (EPHX2 dimer, soluble epoxide hydrolase, sEH) hydrolyses 13(S),14(S)-epoxy-docosahexaenoic acid (13(S),14(S)-epoxy-DHA) to form 13(R),14(S)-dihydroxy-docosahexaenoic acid, aka maresin 2 (MaR2) (Deng et al. 2014). Like MaR1, MaR2 possesses anti-inflammatory and pro-resolving activities although it is not as potent as MaR1 (Deng et al. 2014).

Followed by: Maresins translocate from cytosol to extracellular region

Literature references

Wang, CW., Serhan, CN., Cheng, CY., Arnardottir, HH., Li, Y., Deng, B. 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.
2018-02-21	Reviewed	Hansen, TV.

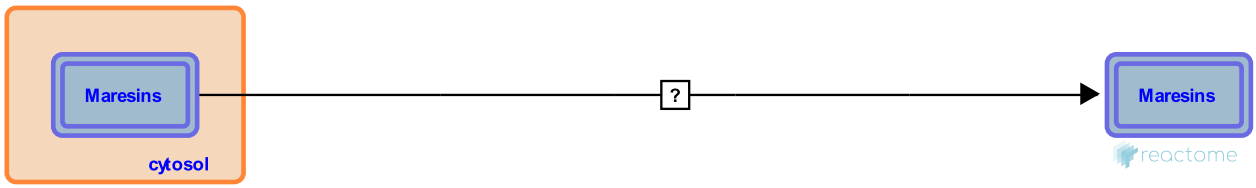
Maresins translocate from cytosol to extracellular region ↗

Location: Biosynthesis of maresins

Stable identifier: R-HSA-9031802

Type: uncertain

Compartments: extracellular region, cytosol



To produce their pro-resolving effects, maresins (MaR1, MaR2, 7(S), 14(S)-diHDHA and 7-epi-MaR1) are released into the exudate of local inflammation sites (Serhan et al. 2015). The mechanism of translocation is unknown.

Preceded by: Non-enzymatic hydrolysis hydrolyses 13(S),14(S)-epoxy-DHA to 7-epi-MaR1, EPHX2 dimer hydrolyses 13(S),14(S)-epoxy-DHA to MaR2, Hydroperoxy reductase reduces 7(S),14(S)-diHp-DHA to 7-epi-MaR1, Epoxide hydrolase hydrolyses 13(S),14(S)-epoxy-DHA to MaR1

Literature references

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

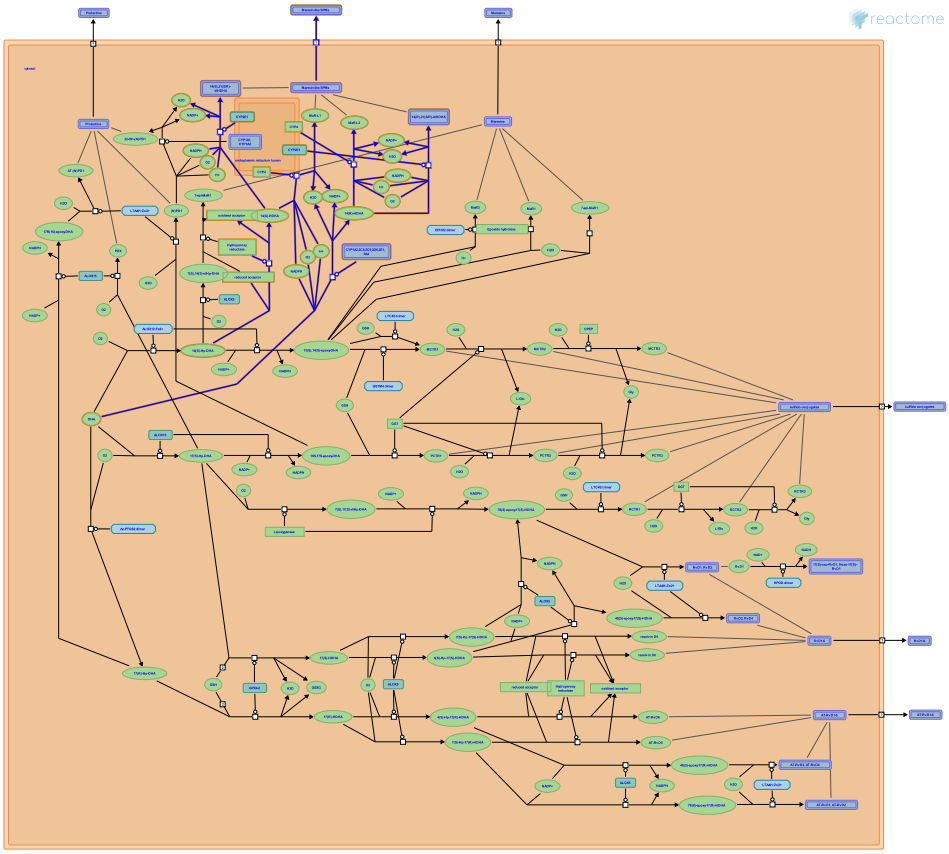
Editions

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

Biosynthesis of maresin-like SPMs ↗

Location: Biosynthesis of maresins

Stable identifier: R-HSA-9027307



Maresin-like mediators MaR-L1, Mar-L2 and 14,21-dihydroxy docosahexaenoic acids are normally synthesized by leukocytes, platelets and macrophages, via the pathways described here. Impaired production of these specialised proresolving mediators (SPMs) in diabetic skin wounds is associated with impaired macrophage function and delayed or absent wound healing (Brem & Tomic-Canic 2007, Boniakowski et al 2017). Macrophages play critical roles in wound healing by mechanisms as yet unknown. They are active in both the initiation (M1 macrophage phenotype) and the resolution (M2 macrophage phenotype) of inflammatory processes. In a pathological state, the switch from the M1 phenotype macrophage to the M2 phenotype macrophage may be delayed or fail to occur, which can result in chronic low-grade inflammation. This macrophage phenotype skewing toward an inflammatory phenotype has been implicated in the pathogenesis of type 2 diabetes (T2D) and the non-healing of diabetic wounds (Boniakowski et al 2017, Pradhan et al. 2009).

Administration of maresin-like SPMs to diabetic mice with induced wounds have been shown to act as autocrine/paracrine factors in restoring reparative functions of macrophages (Hong et al. 2014, Tian et al. 2011a, 2011b, Lu et al. 2010, Hellman et al. 2012).

Literature references

Tang, Y., Spite, M., Hellmann, J. (2012). Proresolving lipid mediators and diabetic wound healing. *Curr Opin Endocrinol Diabetes Obes, 19*, 104-8. ↗

Boniakowski, AE., Kimball, AS., Kunkel, SL., Gallagher, KA., Jacobs, BN. (2017). Macrophage-Mediated Inflammation in Normal and Diabetic Wound Healing. *J. Immunol., 199*, 17-24. ↗

Brem, H., Tomic-Canic, M. (2007). Cellular and molecular basis of wound healing in diabetes. *J. Clin. Invest., 117*, 1219-22. ↗

Editions

2017-10-30	Authored, Edited	Jassal, B.
2018-02-21	Reviewed	Hansen, TV.

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