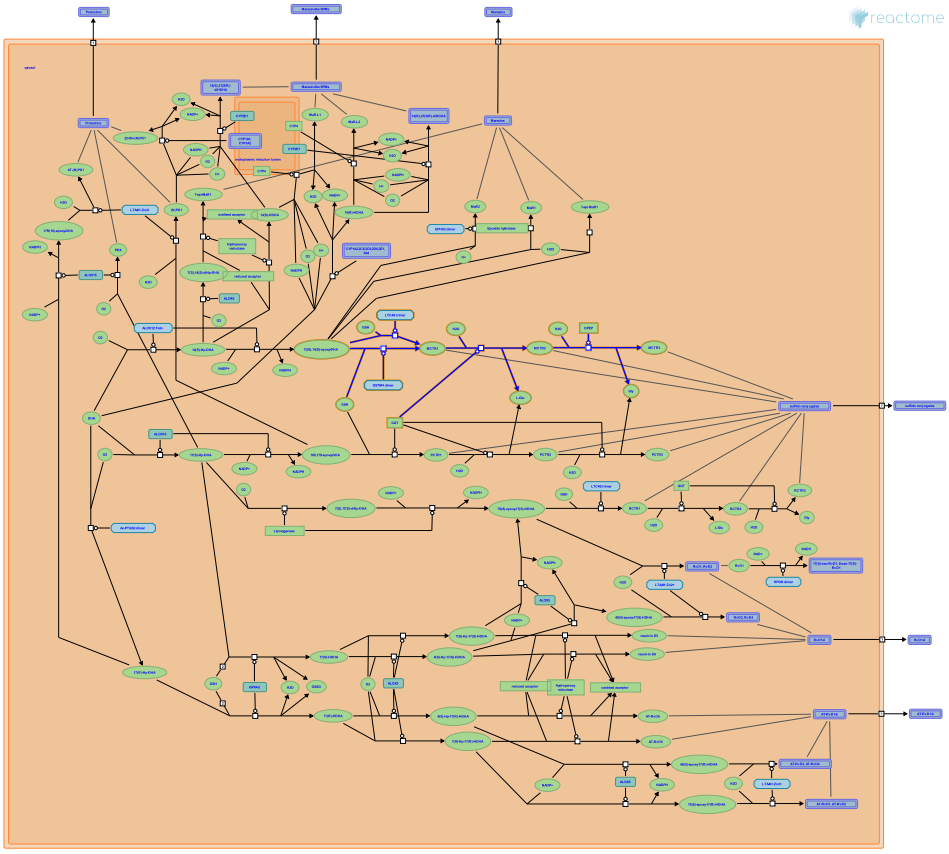
Biosynthesis of maresin conjugates in tissue regeneration (MCTR)



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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.

28/04/2024

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. ↗

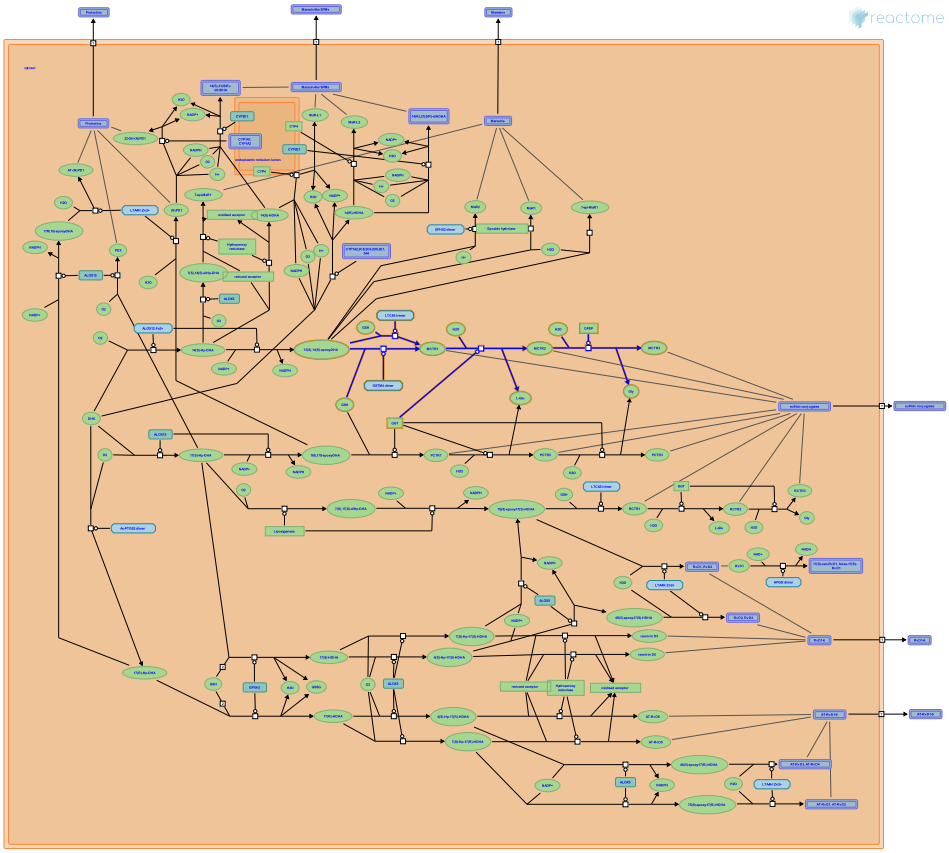
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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 maresin conjugates in tissue regeneration (MCTR) ↗

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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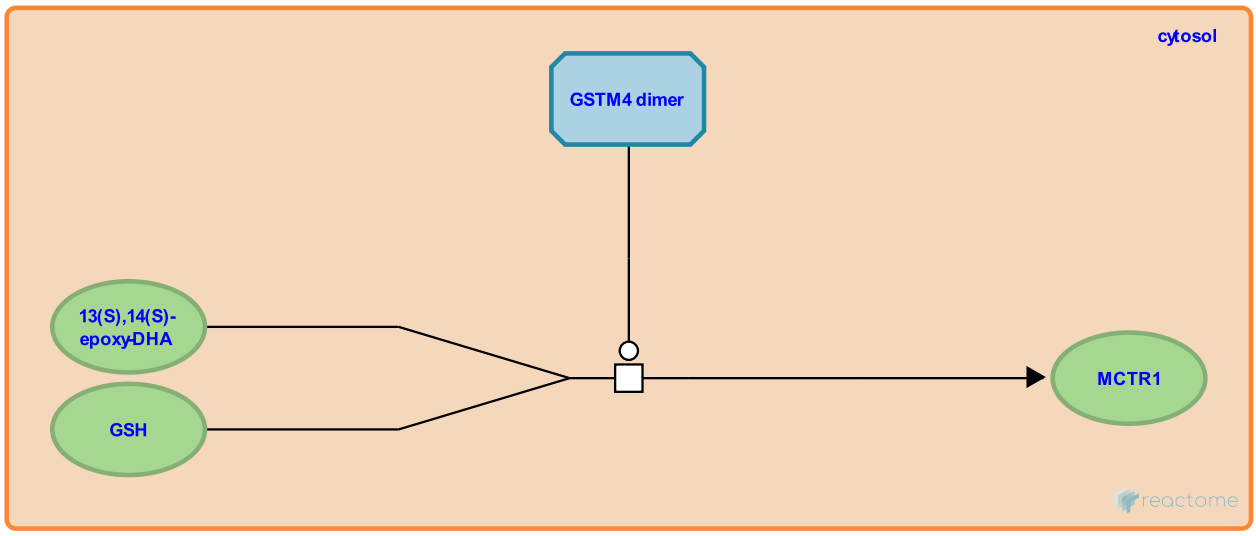
GSTM4 dimer transfers GSH to 13(S),14(S)-epoxy-DHA to form MCTR1 ↗

Location: Biosynthesis of maresin conjugates in tissue regeneration (MCTR)

Stable identifier: R-HSA-9026777

Type: transition

Compartments: cytosol



Cytosolic, dimeric glutathione S-transferase Mu 4 (GSTM4 dimer) can catalyse the transfer of a glutathionyl group from glutathione (GSH) to 13(S),14(S)-epoxy-docosahexaenoic acid (13(S),14(S)-epoxy-DHA) to form maresin conjugate in tissue regeneration 1 (MCTR1) (Dalli et al. 2014, 2016a, 2016b). MCTR1, given to mice with E. coli peritonitis, showed potent proresolving action in inflammation and infections. With human macrophages, MCTR1 stimulated efferocytosis of apoptotic cells (Dalli et al. 2014).

Followed by: GGT hydrolyses MCTR1 to MCTR2

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. ↗

Serhan, CN., Sanger, JM., Rodriguez, AR., Chiang, N., Spur, BW., Dalli, J. (2016). Identification and Actions of a Novel Third Maresin Conjugate in Tissue Regeneration: MCTR3. *PLoS ONE, 11*, e0149319. ↗

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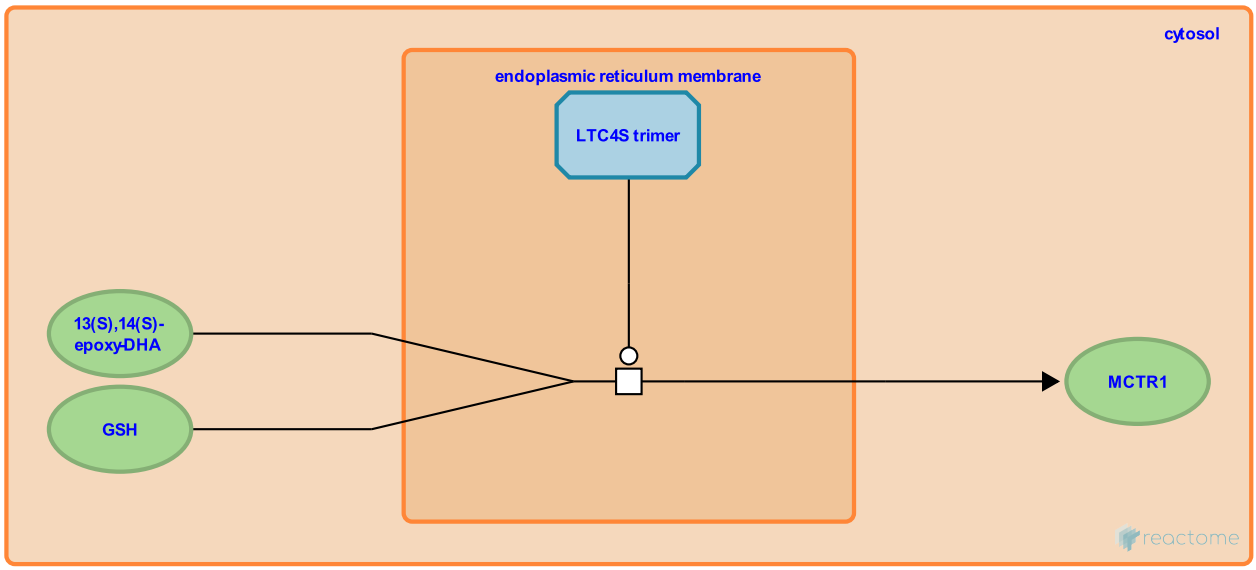
LTC4S trimer transfers GSH to 13(S),14(S)-epoxy-DHA to form MCTR1

Location: Biosynthesis of maresin conjugates in tissue regeneration (MCTR)

Stable identifier: R-HSA-9026780

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Trimeric leukotriene C4 synthase (LTC4S trimer), located on the ER membrane, can catalyse the transfer of a glutathionyl group from glutathione (GSH) to 13(S),14(S)-epoxy-docosahexaenoic acid (13(S),14(S)-epoxy-DHA) to form maresin conjugates in tissue regeneration 1 (MCTR1) (Dalli et al. 2014, 2016a, 2016b). Incubation of human macrophages with LTC4S inhibitors significantly reduces cysteinyl leukotriene production and increases resolvin and lipoxin production (Dalli et al. 2016a). MCTR1, given to mice with E. coli peritonitis, showed potent proresolving action in inflammation and infections. With human macrophages, MCTR1 stimulated efferocytosis of apoptotic cells (Dalli et al. 2014).

Followed by: GGT hydrolyses MCTR1 to MCTR2

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.

Serhan, CN., Sanger, JM., Rodriguez, AR., Chiang, N., Spur, BW., Dalli, J. (2016). Identification and Actions of a Novel Third Maresin Conjugate in Tissue Regeneration: MCTR3. *PLoS ONE, 11,* e0149319.

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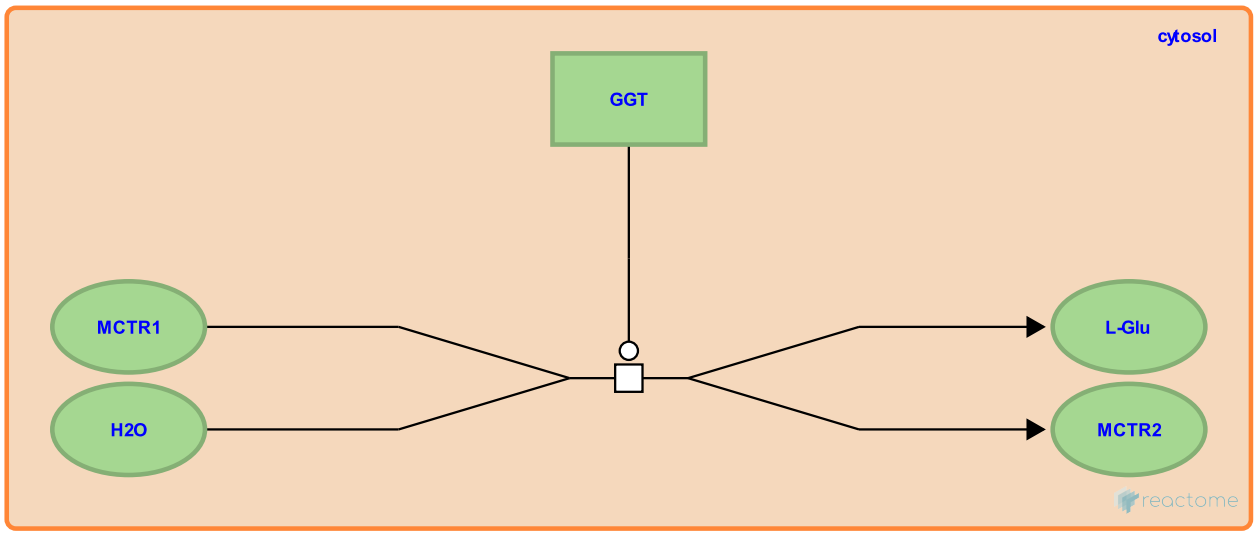
GGT hydrolyses MCTR1 to MCTR2 ↗

Location: Biosynthesis of maresin conjugates in tissue regeneration (MCTR)

Stable identifier: R-HSA-9026757

Type: transition

Compartments: cytosol



In human macrophages, a glutathione hydrolase (GGT) is proposed to cleave the γ-glutamyl moiety of MCTR1 to yield MCTR2, identified as 13(R)-cysteinylglycinyl, 14(S)-hydroxy-docosahexaenoic acid (Dalli et al. 2014, 2016a, 2016b). Incubation of human macrophages with MCTR1 and GGT enzyme inhibitors significantly reduces MCTR2 and MCTR3 production and significantly increases MCTR1 amounts, suggesting a GGT mediates MCTR2 production (Dalli et al. 2016a). In addition, Dalli et al. found the human recombinant GGT used in the experiment has a higher affinity for MCTR1 than leukotriene C4 (Dalli et al. 2016a). MCTR2, given to mice with E. coli peritonitis, showed potent proresolving action in inflammation and infections. With human macrophages, MCTR2 proved to be more potent that MCTR1 in stimulating efferocytosis of apoptotic cells (Dalli et al. 2014).

Preceded by: LTC4S trimer transfers GSH to 13(S),14(S)-epoxy-DHA to form MCTR1, GSTM4 dimer transfers GSH to 13(S),14(S)-epoxy-DHA to form MCTR1

Followed by: DPEP hydrolyses MCTR2 to MCTR3

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. ↗

Serhan, CN., Sanger, JM., Rodriguez, AR., Chiang, N., Spur, BW., Dalli, J. (2016). Identification and Actions of a Novel Third Maresin Conjugate in Tissue Regeneration: MCTR3. *PLoS ONE, 11*, e0149319. ↗

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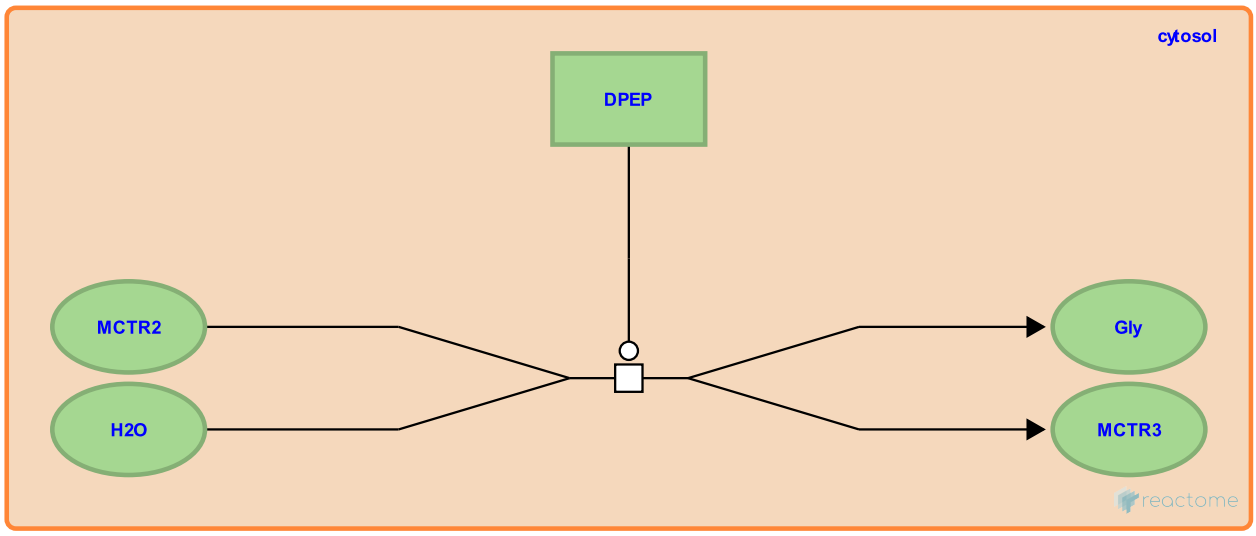
DPEP hydrolyses MCTR2 to MCTR3 ↗

Location: Biosynthesis of maresin conjugates in tissue regeneration (MCTR)

Stable identifier: R-HSA-9026771

Type: transition

Compartments: cytosol



In human macrophages, a dipeptidase (DPEP) is proposed to hydrolyse maresin conjugates in tissue regeneration 2 (MCTR2) to MCTR3, identified as 13(R)-cysteinyl, 14(S)-hydroxy-4Z,7Z,9E,11E,13R,14S,16Z,19Zdocosahexaenoic acid (Dalli et al. 2014, 2016a, 2016b). Incubation of human macrophages with MCTR2 and a DPEP inhibitor demonstrates significantly higher MCTR2 levels and significantly lower MCTR3 levels, suggesting a DPEP mediates MCTR2 hydrolysis (Dalli et al. 2016a). MCTR3 displays potent activity in proresolution of inflammation and tissue regeneration (Dalli et al. 2016b).

Preceded by: GGT hydrolyses MCTR1 to MCTR2

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. ↗

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