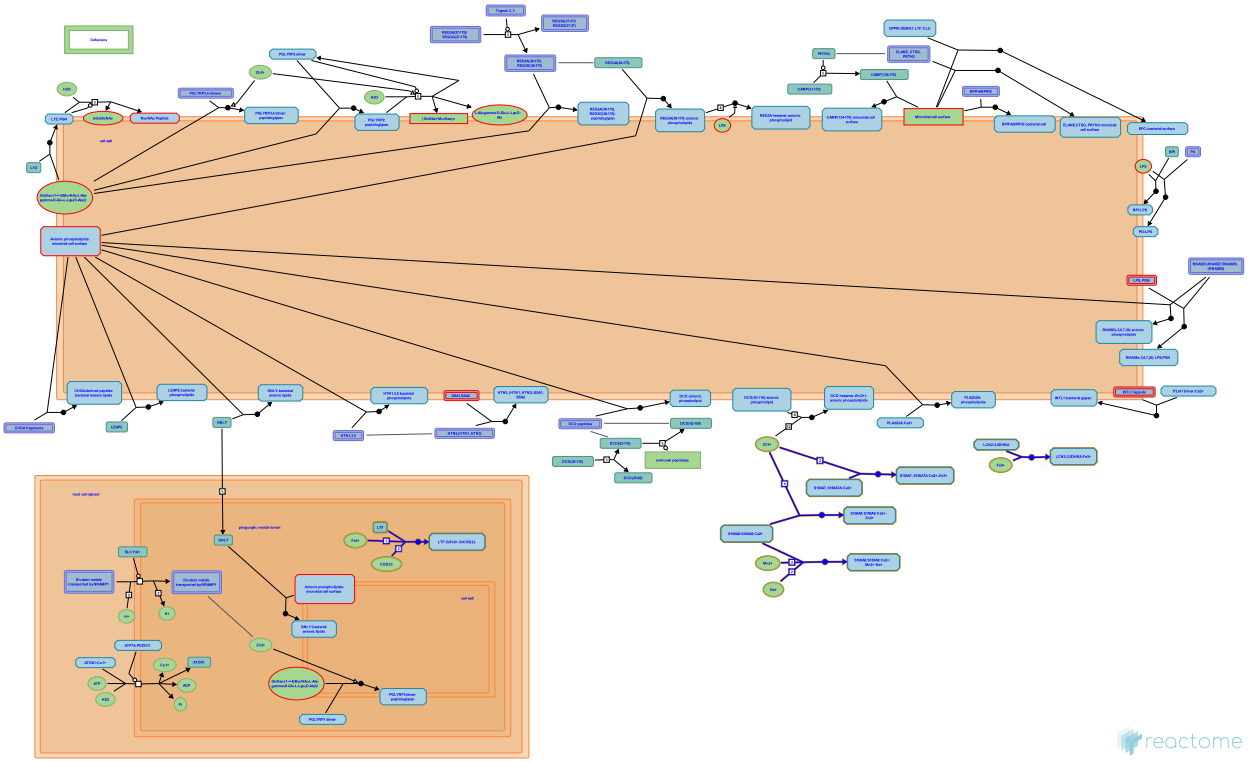
Metal sequestration by antimicrobial proteins



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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. ↗

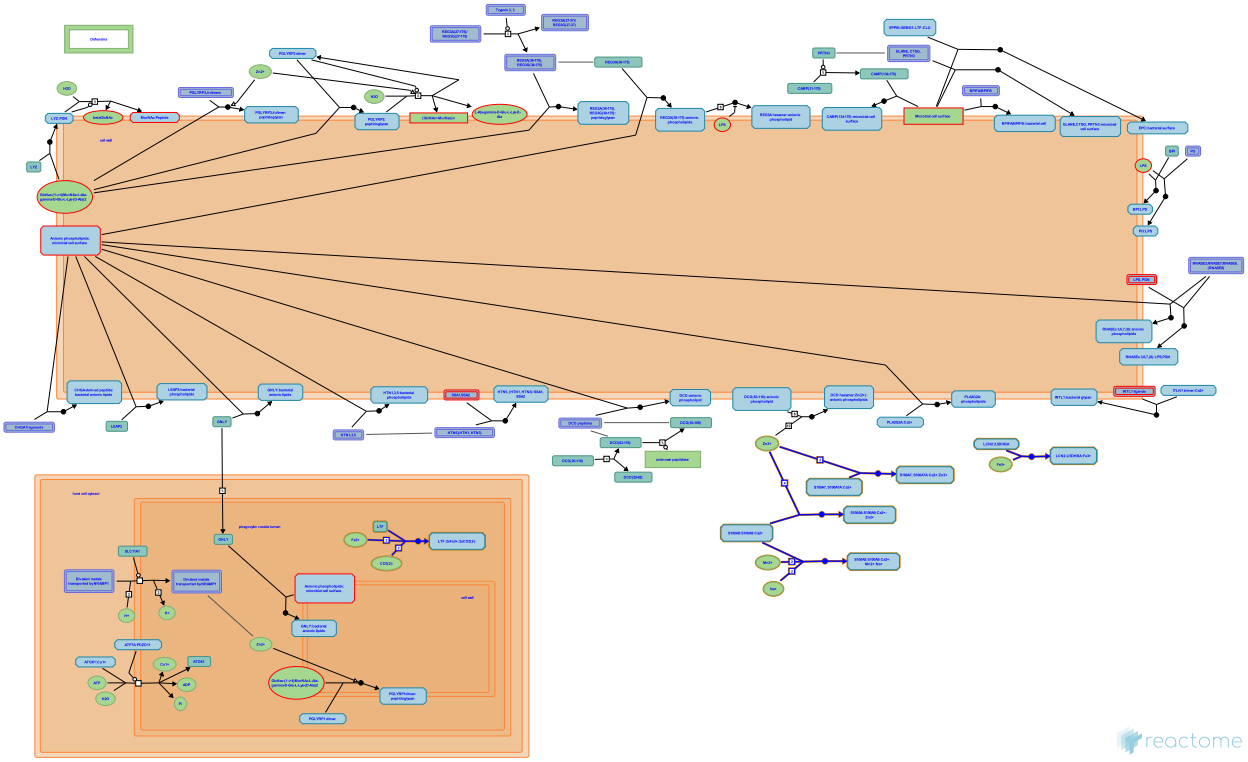
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 90

This document contains 1 pathway and 5 reactions (see Table of Contents)

Metal sequestration by antimicrobial proteins ↗

Stable identifier: R-HSA-6799990



Metals are necessary for all forms of life including microorganisms, evidenced by the fact that metal cations are constituents of approximately 40% of all proteins crystallized to date (Waldron KJ et al. 2009; Foster AW et al. 2014; Guengerich FP 2014, 2015). The ability of microorganisms to maintain the intracellular metal quota is essential and allows microorganisms to adapt to a variety of environments. Accordingly, the ability of the host to control metal quota at inflammation sites can influence host-pathogen interactions. The host may restrict microbial growth either by excluding essential metals from the microbes, by delivery of excess metals to cause toxicity, or by complexing metals in microorganisms (Becker KW & Skaar EP 2014).

Literature references

Guengerich, FP. (2015). Introduction: Metals in Biology: METALS AT THE HOST-PATHOGEN INTERFACE. *J. Biol. Chem., 290*, 18943-4. ↗

Skaar, EP., Becker, KW. (2014). Metal limitation and toxicity at the interface between host and pathogen. *FEMS Microbiol. Rev., 38*, 1235-49. ↗

Editions

2015-10-05	Authored	Shamovsky, V.
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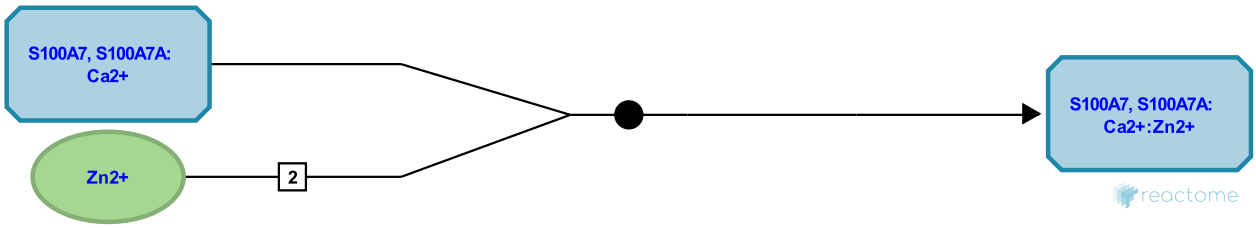
S100A7 or S100A7A binds Zn2+ ↗

Location: Metal sequestration by antimicrobial proteins

Stable identifier: R-HSA-6798489

Type: binding

Compartments: extracellular region



Human S100A7 (known as psoriasin) is expressed in epidermal basal keratinocyte (Martinsson H et al. 2005). During keratinocyte differentiation in epidermis, S100A7 redistributes to the cell periphery suggesting that S100A7 is released from differentiated keratinocytes (Broome AM et al. 2003; Ruse M et al. 2003). Extracellular S100A7 can act as an antibacterial agent restricting growth of E.coli (Glaser R et al. 2005). When purified from human cells the antimicrobial activity of S100A7 can be reversed by the addition of zinc suggesting that S100A7 may inhibit microbial growth through zinc chelation (Glaser R et al. 2005). Additionally, S100A7 has been reported to kill by permeabilizing bacterial membranes (Michalek M et al. 2009). The killing activity of S100A7 showed pH-dependent target specificity (Michalek M et al. 2009). At neutral pH, the Gram-negative bacterium E. coli was killed apparently without compromising its membrane, whereas at low pH exclusively the Gram-positive bacterium B. megaterium was killed by permeabilization of its cytoplasmic membrane (Michalek M et al. 2009).

Structural studies revealed that S100A7 functions as (Ca2+)-bound homodimer, which can load two Zn2+ ions at symmetrically disposed sites across the dimer interface using residues His-86 and His-90 from one subunit and residues His-17 and Asp-24 from the other (Brodersen DE et al. 1999). Binding of Zn2+ is believed to stabilize the dimer and potentially mediate S100A7 function during infection (Brodersen DE et al. 1999).

S100A7 and its paralog, S100A7A (S100A15 or koebnerisin) display 93% sequence identity (Wolf R et al. 2011; Murray JI et al. 2012). Human S100A7A (S100A15) showed antimicrobial activity against E. coli (Büchau AS et al. 2007). Moreover, structural and solution binding studies revealed similar affinities of zinc ion for S100A7 and S100A7A (S100A15) (Murray JI et al. 2012). Though the Reactome project describes psoriasin (S100A7) and koebnerisin (S100A7A) as antimicrobial proteins with the metal-chelating properties, additional studies are needed to more fully define the contribution of S100A7 and S100A7A to nutritional immunity.

Particularly high expression of S100A7 and S100A7A was observed in inflamed psoriatic lesions, which are characterized by disturbed epidermal differentiation and inflammation (Madsen P et al. 1991). Circulating leukocytes (PBMCs) of patients with psoriasis produced increased levels of koebnerisin and psoriasin compared to healthy individuals (Batycka-Baran A et al. 2015). Both S100A proteins further acted as 'alarmins' on PBMC to induce proinflammatory cytokines implicated in the pathogenesis of psoriasis, such as IL-1beta, TNFalpha, IL6 and IL8 (Batycka-Baran A et al. 2015). However, inflammatory activities of S100A7 and S100A7A were found to serve distinct roles in epithelial homeostasis, inflammation, and cancer (Hattinger E et al. 2013; Wolf R et al. 2011; Murray JI et al. 2012). S100A7 signals through the receptor for advanced glycation products (RAGE) in a zinc-dependent manner, while S100A15 signals through a yet unidentified G-protein coupled receptor in a zinc-independent manner (Wolf R et al. 2011; Murray JI et al. 2012). Apart from inflammatory skin diseases an elevated expression of S100A7 was found in several epithelial cancers such as squamous cell carcinoma (SCC) of the skin, bladder, lung as well as in in situ ductal breast carcinoma (Celis JE et al. 1996; Al-Haddad S et al. 1999; Emberley ED et al. 2004; Moubayed N et al. 2007; Qi Z et al. 2015).

Literature references

Farnell, B., Whiting, AL., Boulanger, MJ., Peng, F., Murray, JI., Cullen, JT. et al. (2012). Structural characterization of S100A15 reveals a novel zinc coordination site among S100 proteins and altered surface chemistry with functional implications for receptor binding. *BMC Struct. Biol., 12*, 16. ↗

Brodersen, DE., Kjeldgaard, M., Nyborg, J. (1999). Zinc-binding site of an S100 protein revealed. Two crystal structures of Ca2+-bound human psoriasin (S100A7) in the Zn2+-loaded and Zn2+-free states. *Biochemistry, 38*, 1695-704 . ↗

Cragg, G., Farnell, B., Pace, TC., Watson, PH., Boulanger, MJ., Bohne, C. et al. (2009). Identification and characterization of binding sites on S100A7, a participant in cancer and inflammation pathways. *Biochemistry, 48*, 10591-600. ↗

Editions

2015-10-05	Authored	Shamovsky, V.
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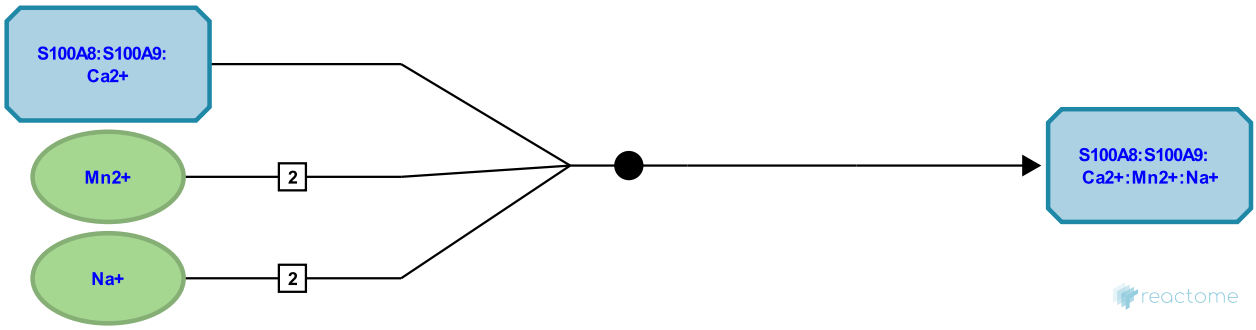
S100A8:S100A9 binds Mn2+ ↗

Location: Metal sequestration by antimicrobial proteins

Stable identifier: R-HSA-6798528

Type: binding

Compartments: extracellular region



S100A8 and S100A9 are calcium-binding regulators of inflammatory processes and immune response (also know as migration inhibitory factor-related proteins 8 (MRP8) and MRP14). S100A8 & S100A9 are constitutively expressed in neutrophils, myeloid-derived dendritic cells, platelets, osteoclasts and hypertrophic chondrocytes (Hessian PA et al. 1993; Kumar A et al. 2003; Healy AM et al. 2006; Schelbergen RF et al 2012). In contrast, these molecules are induced under inflammatory stimuli in monocytes/macrophages, microvascular endothelial cells, keratinocytes and fibroblasts (Hessian PA et al. 1993; Eckert RL et al. 2004; Viemann D et al. 2005; McCormick MM et al. 2005; Hsu K et al. 2005). S100A8 & S100A9 are known to have diverse functions including antimicrobial activities. During infectious processes S100A8 and S100A9 are delivered to the tissue abscess by recruited neutrophils. S100A8 & S100A9 exist mainly as a S100A8:S100A9 heterodimer which is termed calprotectin based on its role in innate immunity (Korndorfer IP et al. 2007). Calprotectin inhibits bacterial growth through chelation of extracellular manganese Mn(2+), zinc Zn(2+) and possibly iron Fe(2+) and thus restricts metal-ion availability during infection (Damo SM et al. 2013; Brophy MB et al. 2012, 2013; Hayden JA et al. 2013; Gagnon DM et al. 2015; Nakashige TG et al. 2015). Calprotectin exhibited antimicrobial activity for a broad range of Gram-positive and Gram-negative bacterial pathogens including Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus lugdunensis, Enterococcus faecalis, Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Shigella flexneri and Acinetobacter baumannii (Damo SM et al. 2013; Kehl-Fie TE et al. 2011; Nakashige TG et al. 2015).

Both S100A8 and S100A9 belong to the S100 family of helix-turn-helix (EF-hand) calcium Ca(2+)-binding proteins. S100 proteins are involved in a wide range of cellular functions (Donato R et al. 2013; Zackular JP et al. 2015; Vogl et al. 2007). Within cells, S100 proteins are involved in aspects of regulation of proliferation, differentiation, apoptosis, Ca(2+) homeostasis, inflammation and migration/invasion (Donato R et al. 2013). During infection, certain S100 proteins can be secreted or released by cells to act as damage-associated molecular patterns (DAMPs) and interact with pattern recognition receptors to modulate inflammatory responses (Foell D et al. 2007; Vogl et al. 2007). In addition, these inflammatory S100 proteins have antimicrobial function by sequestering essential transition metals from bacteria, preventing their growth (Zackular JP et al. 2015). The fundamental structural unit of S100 proteins is a highly integrated antiparallel dimer (Potts BC et al. 1995; Heizmann CW et al. 2002; Brodersen DE et al. 1999; Moroz OV et al. 2009; Gagnon DM et al. 2015). All S100 proteins form this structure as homodimers. S100A8 and S100A9 are unique among all members of the S100 family because they preferentially form a heterodimer. Calprotectin (S100A8:S100A9) and other S100 proteins are Ca(2+)-activated regulators (Brophy MB et al. 2012; Donato R et al. 2013). Inside the cell, where the basal level of Ca(2+) is in the nanomolar range, S100 proteins can serve as a sensor of Ca(2+)-mediated signals. In the extracellular milieu, S100 proteins are perpetually (Ca2+)-bound because Ca(2+) concentration is in the millimolar range. Ca(2+) is also known to stimulate formation of higher order oligomers of S100 proteins, including S100A8/S100A9 tetramers (Leukert N et al. 2006; Korndörfer IP et al. 2007). Upon dimerization S100A8 and S100A9 form two metal binding sites at the dimer interface, both of which can bind to Zn(2+) with high affinity (Kd Zn(2+) about 10e-9 M) (Damo SM et al. 2013; Brophy MB et al. 2013). A chelation of Mn(2+) involves a single binding site (Kd Mn(2+) around 10e-7 - 10e-8 M) (Damo SM et al. 2013; Hayden JA et al. 2013; Gagnon DM et al. 2015).

Thus, calprotectin S100A8:S100A9 inhibits bacterial growth by targeting transition metals and sequestering these metals in a process referred to as nutritional immunity.

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Hench, L., Skaar, EP., Sugitani, N., Fritz, G., Betz, C., Zhang, Y. et al. (2013). Molecular basis for manganese sequestration by calprotectin and roles in the innate immune response to invading bacterial pathogens. *Proc. Natl. Acad. Sci. U.S.A., 110*, 3841-6. ↗

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Nolan, EM., Brophy, MB., Drennan, CL., Gagnon, DM., Britt, RD., Stich, TA. et al. (2015). Manganese binding properties of human calprotectin under conditions of high and low calcium: X-ray crystallographic and advanced electron paramagnetic resonance spectroscopic analysis. *J. Am. Chem. Soc., 137*, 3004-16. ↗

Editions

2015-10-05	Authored	Shamovsky, V.
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2016-08-15	Edited	Shamovsky, V.

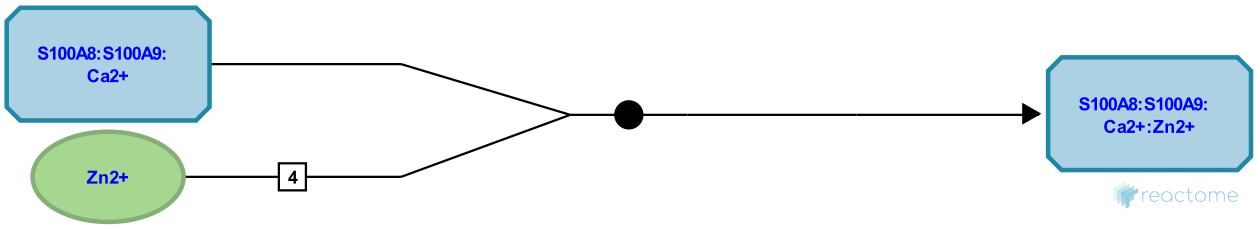
S100A8:S100A9 binds Zn2+ ↗

Location: Metal sequestration by antimicrobial proteins

Stable identifier: R-HSA-6798474

Type: binding

Compartments: extracellular region



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Thus, calprotectin S100A8:S100A9 inhibits bacterial growth by targeting transition metals and sequestering these metals in a process referred to as nutritional immunity.

Literature references

Nolan, EM., Brophy, MB., Drennan, CL., Gagnon, DM., Britt, RD., Stich, TA. et al. (2015). Manganese binding properties of human calprotectin under conditions of high and low calcium: X-ray crystallographic and advanced electron paramagnetic resonance spectroscopic analysis. *J. Am. Chem. Soc., 137*, 3004-16. ↗

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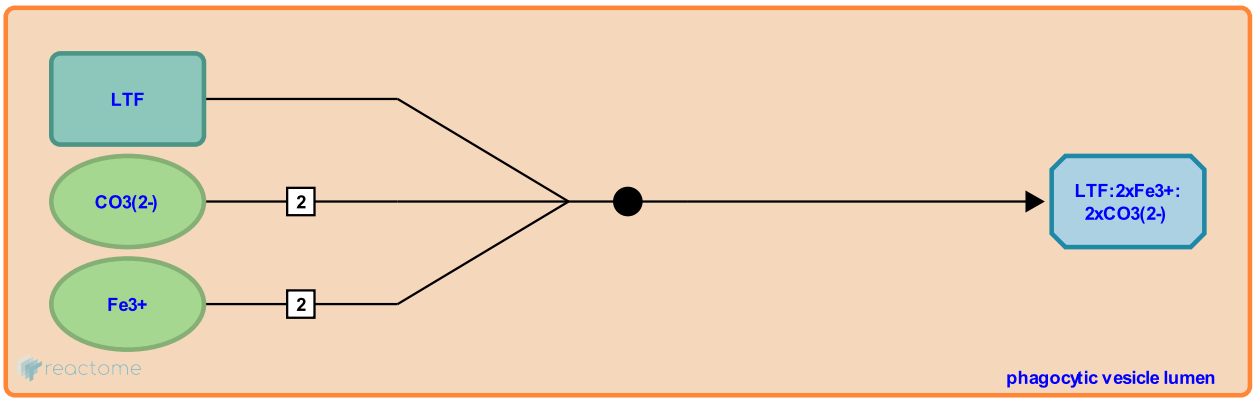
Lactoferrin scavenges iron ions ↗

Location: Metal sequestration by antimicrobial proteins

Stable identifier: R-HSA-1222491

Type: binding

Compartments: phagocytic vesicle lumen



Lactoferrin is secreted from many tissues to collect stray iron ions that can catalyze unwanted reactions, and to starve microorganisms of this important metal. One molecule of lactoferrin can load two ferric (Fe(3+)) ions together with two carbonate (CO3(2-)) anions (Haridas et al. 1995).

Literature references

Haridas, M., Baker, EN., Anderson, BF. (1995). Structure of human diferric lactoferrin refined at 2.2 A resolution. *Acta Crystallogr D Biol Crystallogr, 51*, 629-46. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

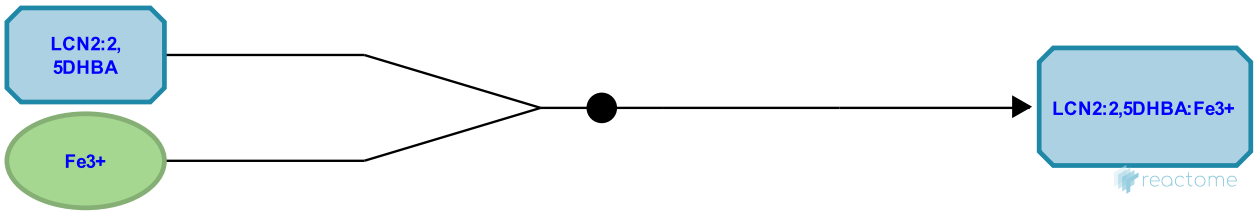
LCN2:2,5DHBA binds Fe3+ ↗

Location: Metal sequestration by antimicrobial proteins

Stable identifier: R-HSA-5229273

Type: binding

Compartments: extracellular region



Neutrophil gelatinase associated lipocalin (LCN2, NGAL) is a member of the lipocalin superfamily that is involved in iron trafficking both in and out of cells. LCN2 binds iron via an association with 2,5 dihydroxybenzoic acid (2,5DHBA), a siderophore that shares structural similarities with bacterial enterobactin, and delivers or removes iron from the cell via interacting with different receptors, depending on cellular requirement (Goetz et al. 2002, Devireddy et al. 2010). LCN2 is a potent bacteriostatic agent in iron limiting conditions therefore it is proposed that LCN2 participates in the antibacterial iron depletion strategy of the innate immune system (Flo et al. 2004).

Literature references

Goetz, DH., Hart, DO., Green, MR., Devireddy, LR. (2010). A mammalian siderophore synthesized by an enzyme with a bacterial homolog involved in enterobactin production. *Cell, 141*, 1006-17. ↗

Raymond, KN., Bluhm, ME., Goetz, DH., Strong, RK., Holmes, MA., Borregaard, N. (2002). The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol. Cell, 10*, 1033-43. ↗

Aderem, A., Rodriguez, DJ., Flo, TH., Sato, S., Strong, RK., Akira, S. et al. (2004). Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. *Nature, 432*, 917-21. ↗

Editions

2014-01-17	Authored, Edited	Jassal, B.
2014-06-09	Reviewed	Chen, C.

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