# S100A8:S100A9 binds Mn2+

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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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## Literature references

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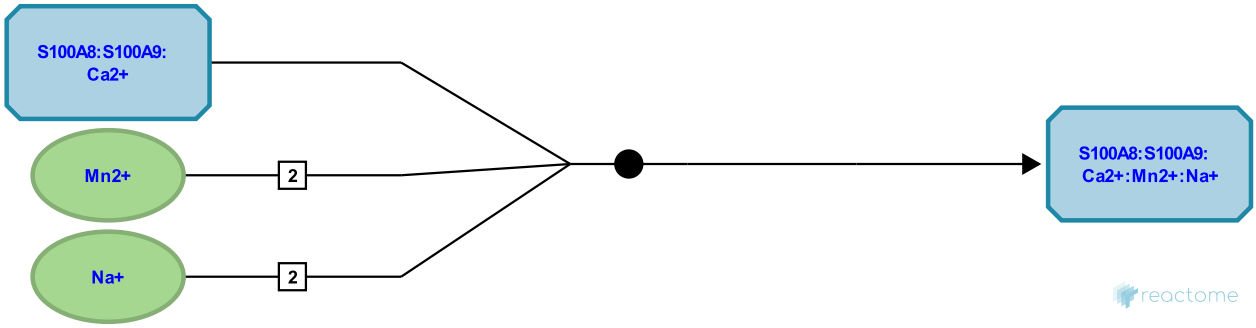
**Stable identifier:** R-HSA-6798528

**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.

## Literature references

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## Editions

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