Gene name: **S100A9** **Previous HGNC Symbols for S100A9 Gene:** CAGB, CFAG

External Ids for S100A9 Gene: HGNC: 10499 NCBI Gene: 6280 Ensembl: ENSG00000163220 OMIM®: 123886 UniProtKB/Swiss-Prot: P06702

NCBI Gene Summary: The protein encoded by this gene is a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation. S100 genes include at least 13 members which are located as a cluster on chromosome 1q21. This protein may function in the inhibition of casein kinase and altered expression of this protein is associated with the disease cystic fibrosis. This antimicrobial protein exhibits antifungal and antibacterial activity.

GeneCards Summary : S100A9 (S100 Calcium Binding Protein A9) is a Protein Coding gene. Diseases associated with S100A9 include Juvenile Rheumatoid Arthritis and Crohn's Disease. Among its related pathways are Toll Like Receptor 7/8 (TLR7/8) Cascade and Diseases of Immune System. Gene Ontology (GO) annotations related to this gene include *calcium ion binding* and *microtubule binding*. An important paralog of this gene is S100A12.

UniProtKB/Swiss-Prot Summary : S100A9 is a calcium- and zinc-binding protein which plays a prominent role in the regulation of inflammatory processes and immune response (PubMed:12626582, 15331440, 16258195, 19122197, 20103766, 21325622, 8423249). It can induce neutrophil chemotaxis, adhesion, can increase the bactericidal activity of neutrophils by promoting phagocytosis via activation of SYK, PI3K/AKT, and ERK1/2 and can induce degranulation of neutrophils by a MAPK-dependent mechanism (PubMed:12626582, 15331440, 20103766). Predominantly found as calprotectin (S100A8/A9) which has a wide plethora of intra- and extracellular functions (PubMed:16258195, 19122197, 8423249). The intracellular functions include: facilitating leukocyte arachidonic acid trafficking and metabolism, modulation of the tubulin-dependent cytoskeleton during migration of phagocytes and activation of the neutrophil NADPH-oxidase (PubMed:15331440, 21325622). Participates also in regulatory T-cell differentiation together with CD69 (PubMed:26296369). Activates NADPH-oxidase by facilitating the enzyme complex assembly at the cell membrane, transferring arachidonic acid, an essential cofactor, to the enzyme complex and S100A8 contributes to the enzyme assembly by directly binding to NCF2/P67PHOX (PubMed:15642721, 22808130). The extracellular functions involve pro-inflammatory, antimicrobial, oxidant-scavenging and apoptosis-inducing activities (PubMed:19534726, 8423249). Its proinflammatory activity includes recruitment of leukocytes, promotion of cytokine and chemokine production, and regulation of leukocyte adhesion and migration (PubMed:15598812, 21487906). Acts as an alarmin or a danger associated molecular pattern (DAMP) molecule and stimulates innate immune cells via binding to pattern recognition receptors such as Toll-like receptor 4 (TLR4) and receptor for advanced glycation endproducts (AGER) (PubMed:19402754). Binding to TLR4 and AGER activates the MAP-kinase and NF-kappa-B signaling pathways resulting in the amplification of the pro-inflammatory cascade (PubMed:19402754, 22804476). Has antimicrobial activity towards bacteria and fungi and exerts its antimicrobial activity probably via chelation of Zn(2+) which is essential for microbial growth (PubMed:19087201). Can induce cell death via autophagy and apoptosis and this occurs through the cross-talk of mitochondria and lysosomes via reactive oxygen species (ROS) and the process involves BNIP3 (PubMed:19935772). Can regulate neutrophil number and apoptosis by an anti-apoptotic effect; regulates cell survival via ITGAM/ITGB and TLR4 and a signaling mechanism involving MEK-ERK (PubMed:22363402). Its role as an oxidant scavenger has a protective role in preventing exaggerated

tissue damage by scavenging oxidants (PubMed:21912088, 22489132). Can act as a potent amplifier of inflammation in autoimmunity as well as in cancer development and tumor spread (PubMed:16258195). Has transglycosylase activity; in oxidatively-modified low-density lipoprotein (LDL(ox))-induced S-nitrosylation of GAPDH on 'Cys-247' proposed to transfer the NO moiety from NOS2/iNOS to GAPDH via its own S-nitrosylated Cys-3 (PubMed:25417112). The iNOS-S100A8/A9 transglycosylase complex is proposed to also direct selective inflammatory stimulus-dependent S-nitrosylation of multiple targets such as ANXA5, EZR, MSN and VIM by recognizing a [IL]-x-C-x-x-[DE] motif .

Cellular localization: mainly in cytosol, nucleus, cytoskeleton, extracellular and plasma membrane.

Full Name: *S100 calcium-binding protein A9*
Aliases: Calgranulin B, MRP14
Protein Type: Small EF-hand calcium-binding protein

🧫 Biological Function

S100A9 is a member of the S100 family, known for its role in:

- **Inflammation**
- **Innate immune responses**
- **Cytoskeletal dynamics**
- **Cell migration and adhesion**

It typically forms a heterodimer with S100A8, called calprotectin, which functions as a damage-associated molecular pattern (DAMP) molecule.

Major Functions:

- Calcium/zinc binding regulates conformational changes and activity.
- Extracellularly, it binds to receptors like TLR4 and RAGE, amplifying the inflammatory response.
- Intracellularly, it modulates cytoskeleton reorganization, ROS generation, and phagocyte function.

🦠 S100A9 in Sepsis

In sepsis, S100A9 plays a critical pro-inflammatory role and is:

- Highly expressed in activated neutrophils and monocytes
- Released upon cell stress or damage
- A potent amplifier of systemic inflammation

Key mechanisms include:

- Binding TLR4 and RAGE, activating NF-κB
- Promoting release of cytokines like IL-6, TNF-α, and IL-1β

- Driving leukocyte recruitment, oxidative burst, and endothelial dysfunction

📈 It contributes to the “cytokine storm” and is associated with:

- Acute respiratory distress syndrome (ARDS)
- Multi-organ failure
- Increased mortality

🧪 Diagnostic/Prognostic Value

S100A9 (often measured as part of S100A8/A9 calprotectin) is a promising biomarker in sepsis:

Diagnostic:

- Elevated in early and severe stages of sepsis
- Distinguishes bacterial infection from viral or sterile inflammation

Prognostic:

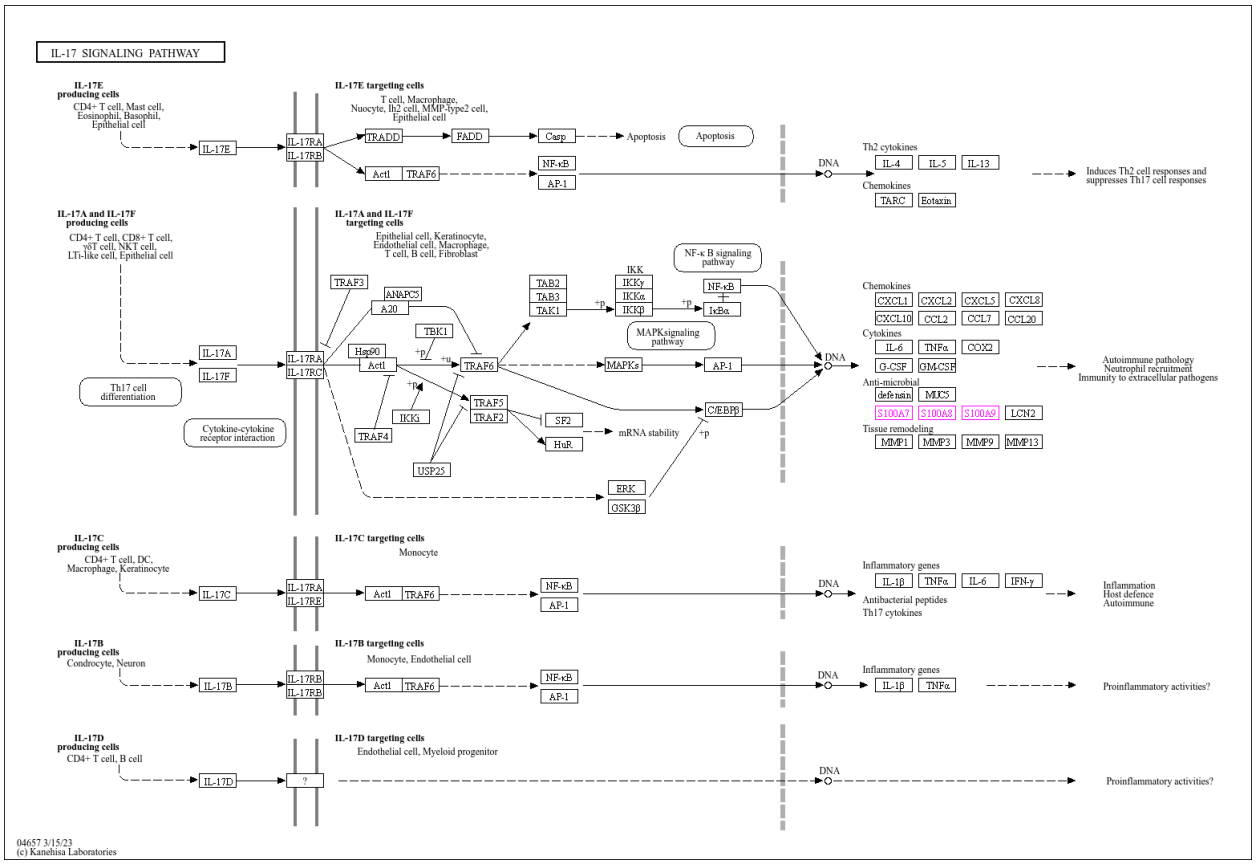
- High S100A9/calprotectin levels correlate with:
    - Increased disease severity (such as, SOFA score)
    - Mortality risk
    - Response to treatment or disease progression

Measured in blood, urine, or feces depending on the context

🧪 Supporting Literature

Doi: 10.3389/fimmu.2018.01298
Doi: 10.3390/ijms222312923
Doi: 10.1007/s10753-024-02161-9
Doi: 10.1186/s12931-023-02594-0

KEGG:



Enrichr-KG