Gene name: **S100A8** **Previous HGNC Symbols for S100A8 Gene:** CAGA, CFAG

External Ids for S100A8 Gene: HGNC: 10498 NCBI Gene: 6279 Ensembl: ENSG00000143546
OMIM®: 123885 UniProtKB/Swiss-Prot: P05109

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 as a cytokine. Altered expression of this protein is associated with the disease cystic fibrosis. Multiple transcript variants encoding different isoforms have been found for this gene.

GeneCards Summary : S100A8 (S100 Calcium Binding Protein A8) is a Protein Coding gene. Diseases associated with S100A8 include Peptic Ulcer Disease and Duodenal Ulcer. 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 *RAGE receptor binding*. An important paralog of this gene is S100A12.

UniProtKB/Swiss-Prot Summary: S100A8 is a calcium- and zinc-binding protein which plays a prominent role in the regulation of inflammatory processes and immune response. It can induce neutrophil chemotaxis and adhesion. Predominantly found as calprotectin (S100A8/A9) which has a wide plethora of intra- and extracellular functions. 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 neutrophilic NADPH-oxidase. 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. The extracellular functions involve pro-inflammatory, antimicrobial, oxidant-scavenging and apoptosis-inducing activities. Its pro-inflammatory activity includes recruitment of leukocytes, promotion of cytokine and chemokine production, and regulation of leukocyte adhesion and migration. 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). Binding to TLR4 and AGER activates the MAP-kinase and NF-kappa-B signaling pathways resulting in the amplification of the pro-inflammatory cascade. Has antimicrobial activity towards bacteria and fungi and exerts its antimicrobial activity probably via chelation of Zn(2+) which is essential for microbial growth. 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. 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. Its role as an oxidant scavenger has a protective role in preventing exaggerated tissue damage by scavenging oxidants. Can act as a potent amplifier of inflammation in autoimmunity as well as in cancer development and tumor spread. The iNOS-S100A8/A9 transnitrosylase complex directs selective inflammatory stimulus-dependent S-nitrosylation of GAPDH and probably multiple targets such as ANXA5, EZR, MSN and VIM by recognizing a [IL]-x-C-x-x-[DE] motif; S100A8 seems to contribute to S-nitrosylation site selectivity.
Cellular localization: mainly in cytosol, nucleus, cytoskeleton, extracellular, plasma membrane.

Full Name: S100 calcium-binding protein A8
Aliases: Calgranulin A, MRP8, P8…

🧫 Biological Function

S100A8 is a calcium- and zinc-binding protein that forms a heterodimer with S100A9 (called calprotectin). Together, these proteins:

- Regulate inflammatory processes and immune response.
- Are highly expressed in myeloid cells, especially neutrophils and monocytes.
- Function as damage-associated molecular patterns (DAMPs), promoting inflammation via TLR4 and RAGE.

Upon cellular activation or damage, S100A8/A9 is released extracellularly and interacts with receptors on immune cells, triggering:

- **Cytokine production** (e.g., TNF-α, IL-6)
- **Chemotaxis** of leukocytes
- **ROS generation**
- **Amplification of inflammatory signaling**

🦠 S100A8 in Sepsis

In the context of sepsis, S100A8 is considered a *key amplifier* of the innate immune response:

- It is significantly upregulated in sepsis, particularly in neutrophils and monocytes.
  Acts as a potent DAMP, enhancing the systemic inflammatory response through RAGE and TLR4.
- Contributes to endothelial activation, vascular leakage, and organ damage during sepsis progression.

🔗 Pathways implicated:

- **RAGE signaling**
- **TLR4 signaling**
- **Leukocyte extravasation**
- **NF-κB activation**

🧪 Diagnostic/Prognostic Value

- Biomarker: S100A8/A9 (calprotectin) is detectable in blood, urine, and feces and is used as a biomarker of inflammation.

- In sepsis, elevated levels correlate with disease severity, mortality risk, and organ dysfunction (especially in early stages).

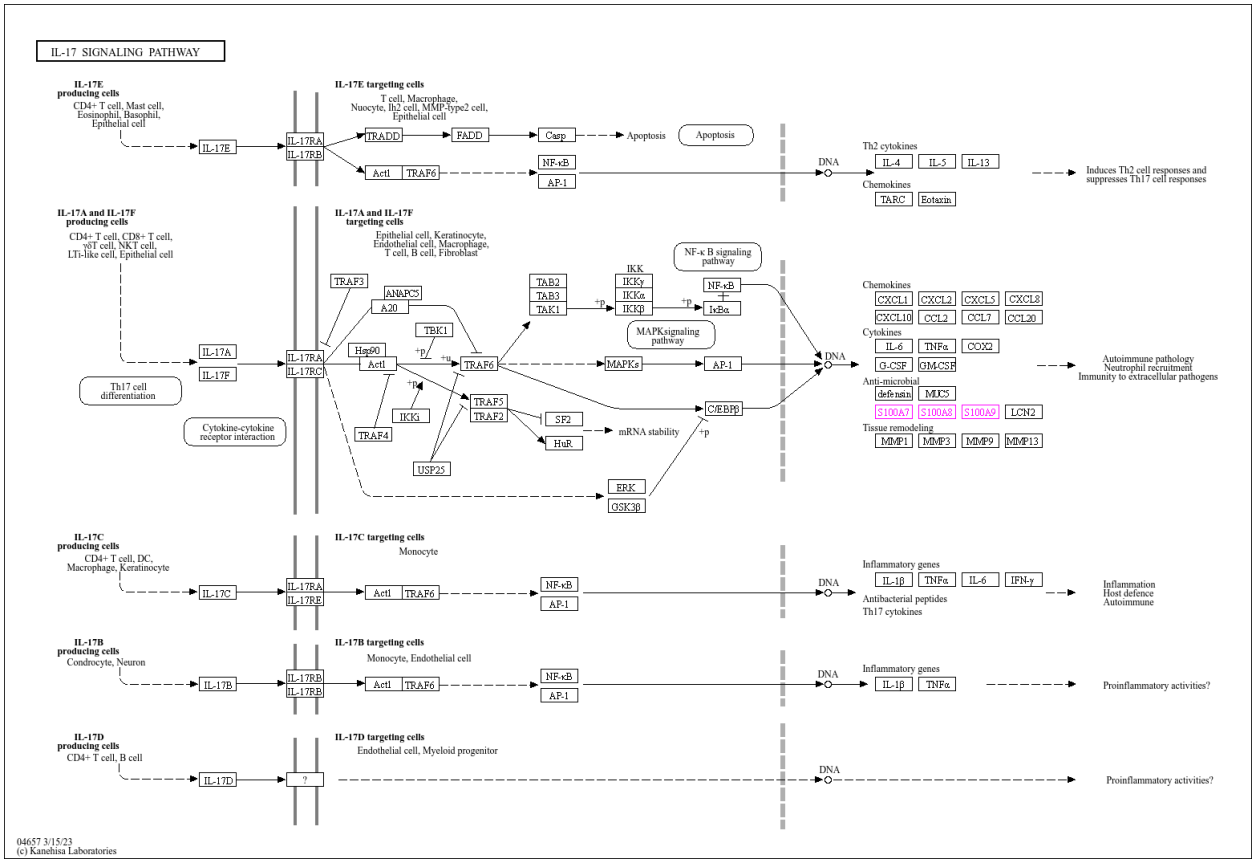
- High S100A8 expression is associated with poor outcomes, making it a potential prognostic biomarker.

📌 *Note:* Calprotectin levels (S100A8/A9) are already in clinical use for **inflammatory bowel disease**, and there's growing interest in its use in **infectious and inflammatory conditions like sepsis**.

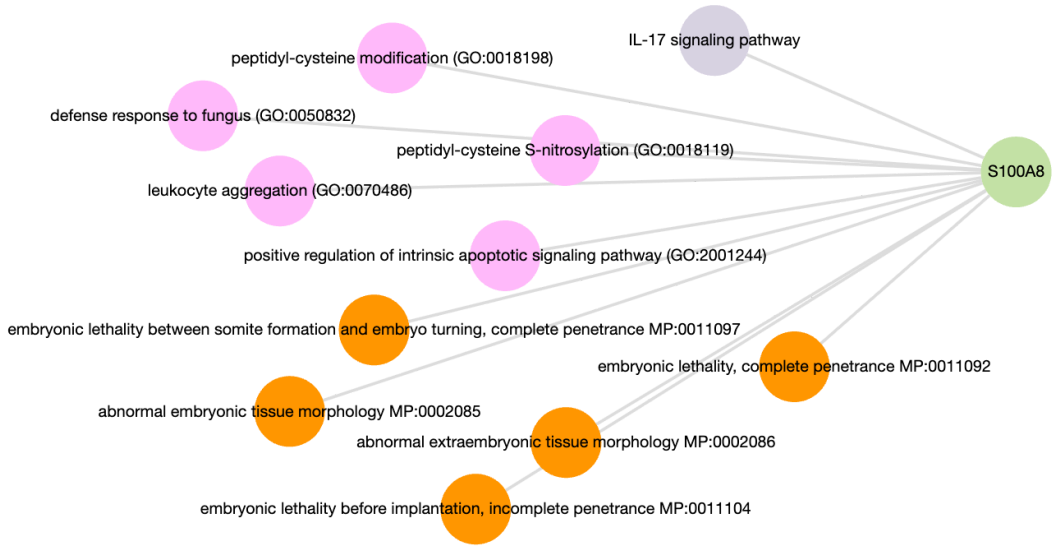
🧪 Supporting Literature

Doi: 10.1186/s13054-023-04652-x
Doi: 10.1021/acs.jproteome.9b00690
Doi: 10.1371/journal.pone.0100909
Doi: 10.1016/j.intimp.2023.109716.

KEGG:



Enrichr-KG


IL-17 signaling pathway
peptidyl-cysteine modification (GO:0018198)
defense response to fungus (GO:0050832)
peptidyl-cysteine S-nitrosylation (GO:0018119)
S100A8
leukocyte aggregation (GO:0070486)
positive regulation of intrinsic apoptotic signaling pathway (GO:2001244)
embryonic lethality between somite formation and embryo turning, complete penetrance MP:0011097
embryonic lethality, complete penetrance MP:0011092
abnormal embryonic tissue morphology MP:0002085
abnormal extraembryonic tissue morphology MP:0002086
embryonic lethality before implantation, incomplete penetrance MP:0011104