Gene name: **SOCS3**

External Ids for SOCS3 Gene: HGNC: 19391 NCBI Gene: 9021 Ensembl: ENSG00000184557
OMIM®: 604176 UniProtKB/Swiss-Prot: O14543

NCBI Gene Summary: This gene encodes a member of the STAT-induced STAT inhibitor (SSI), also known as suppressor of cytokine signaling (SOCS), family. SSI family members are cytokine-inducible negative regulators of cytokine signaling. The expression of this gene is induced by various cytokines, including IL6, IL10, and interferon (IFN)-gamma. The protein encoded by this gene can bind to JAK2 kinase, and inhibit the activity of JAK2 kinase. Studies of the mouse counterpart of this gene suggested the roles of this gene in the negative regulation of fetal liver hematopoiesis, and placental development.

GeneCards Summary: SOCS3 (Suppressor Of Cytokine Signaling 3) is a Protein Coding gene. Diseases associated with SOCS3 include Dermatitis, Atopic, 4 and Hematologic Cancer. Among its related pathways are Class I MHC mediated antigen processing and presentation and Gene expression (Transcription). Gene Ontology (GO) annotations related to this gene include *protein kinase inhibitor activity*. An important paralog of this gene is CISH.

UniProtKB/Swiss-Prot Summary: SOCS family proteins form part of a classical negative feedback system that regulates cytokine signal transduction. SOCS3 is involved in negative regulation of cytokines that signal through the JAK/STAT pathway. Inhibits cytokine signal transduction by binding to tyrosine kinase receptors including IL6ST/gp130, LIF, erythropoietin, insulin, IL12, GCSF and leptin receptors. Binding to JAK2 inhibits its kinase activity and regulates IL6 signaling. Suppresses fetal liver erythropoiesis. Regulates onset and maintenance of allergic responses mediated by T-helper type 2 cells (By similarity). Probable substrate recognition component of a SCF-like ECS (Elongin BC-CUL2/5-SOCS-box protein) E3 ubiquitin-protein ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins (PubMed:15601820). (SOCS3_HUMAN,O14543)

Cellular localization: mostly in cytosol and plasma membrane.

Full Name: *Suppressor of Cytokine Signaling 3*
Gene Family: SOCS family (SOCS1–SOCS7 + CIS)
Protein Type: Intracellular protein that negatively regulates cytokine signaling.

🔬 Biological Function of SOCS3

SOCS3 is a key negative feedback regulator in cytokine and immune signaling, especially within the JAK/STAT pathway.

🎯 Key Functions:

Cytokine signaling inhibition: Binds to JAK kinases, preventing STAT phosphorylation.
Signal termination: Prevents overactivation of cytokine responses.
Controls inflammation: Inhibits IL-6, IFN-γ, TNF-α, and others.
Regulates immune cell fate: Affects macrophage polarization, neutrophil survival, and T cell differentiation.

🔗 Major Targets:

- **JAK2**, **TYK2** (Janus kinases)
- **STAT3**, **STAT1**
- Receptors: **IL-6R**, **IFNGR**, **TLR4-associated pathways**

🦠 SOCS3 in Sepsis

Sepsis is characterized by a hyperinflammatory response followed by immunosuppression. SOCS3 plays a dual role:

🩸 1. Early Sepsis – Protective Regulation

- Induced by pro-inflammatory cytokines like IL-6, IL-1β, IFN-γ.
- Acts as a brake to prevent cytokine storm by inhibiting JAK/STAT-mediated signaling.
- Limits IL-6 and IFN-γ signaling, reducing tissue damage.

🧪 2. Later Sepsis – Immunosuppression

- Persistent SOCS3 expression can suppress:
    - Neutrophil function
    - Macrophage cytokine production
    - T cell activation
- May contribute to immune paralysis, reducing the host's ability to clear infection.

📈 Clinical Relevance in Sepsis

Diagnostic Marker

- Upregulated in early sepsis in neutrophils and monocytes
- Detectable at mRNA and protein levels in blood samples

Prognostic Marker

- High expression linked to:
  Worse outcomes in some studies (due to immunosuppression)
  Early resolution of inflammation in others (context-dependent)

📌 Biomarker studies have shown that SOCS3 is upregulated in severe cases and can stratify patients based on their immune activation state.

🔬 SOCS3 and Immune Modulation

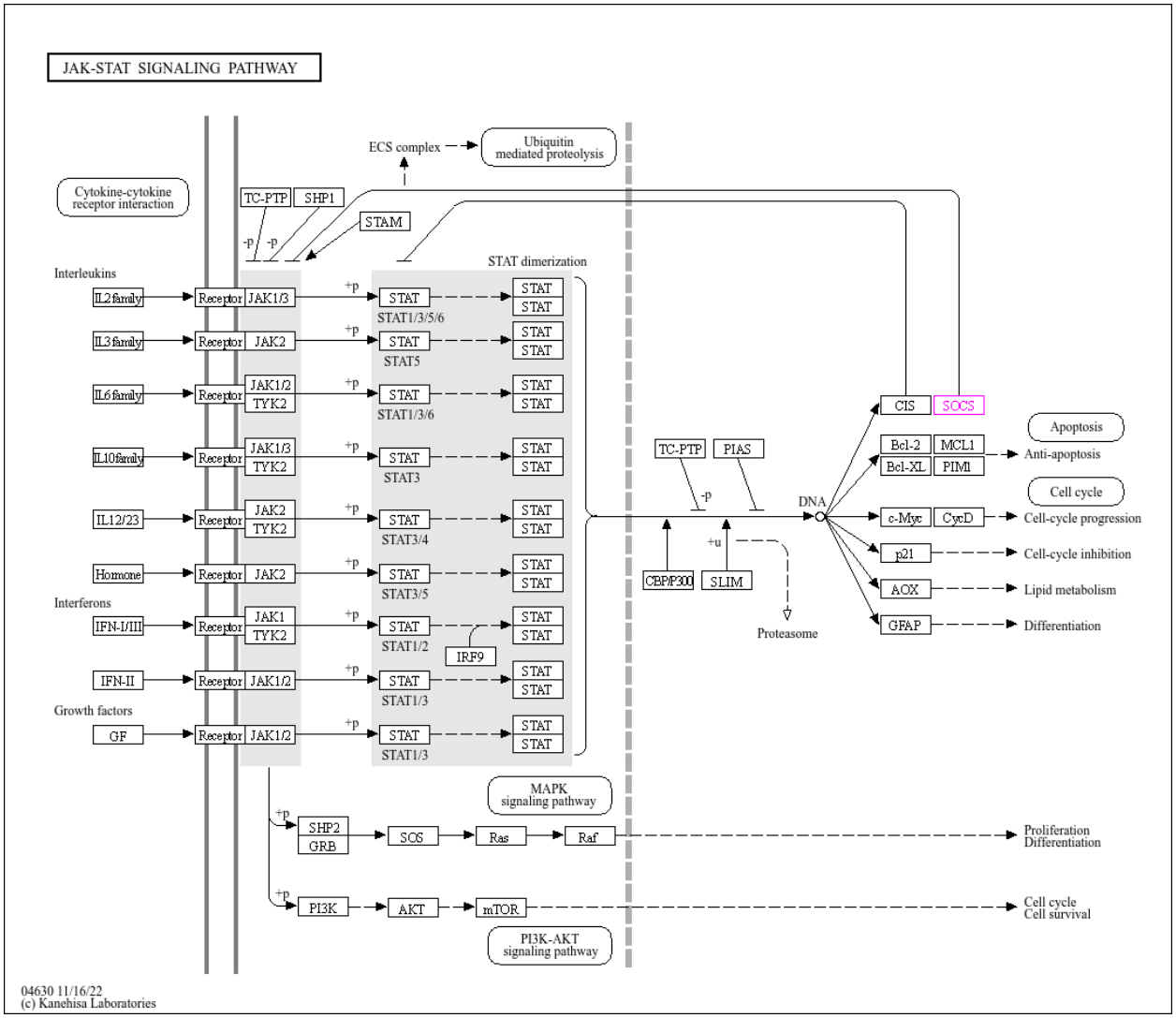
- Promotes M2-like macrophage polarization (anti-inflammatory)
- Suppresses Th17 cell differentiation
- Inhibits neutrophil survival and NET formation

🧠 **Why it matters in sepsis:** The balance between too much and too little SOCS3 determines whether the immune response resolves inflammation or collapses into immunosuppression.

🧪 Supporting Literature

Doi: 10.4049/jimmunol.1201168.
Doi: 10.1096/fasebj.2021.35.S1.01790.
Doi: 10.3389/fimmu.2014.00058.

KEGG:



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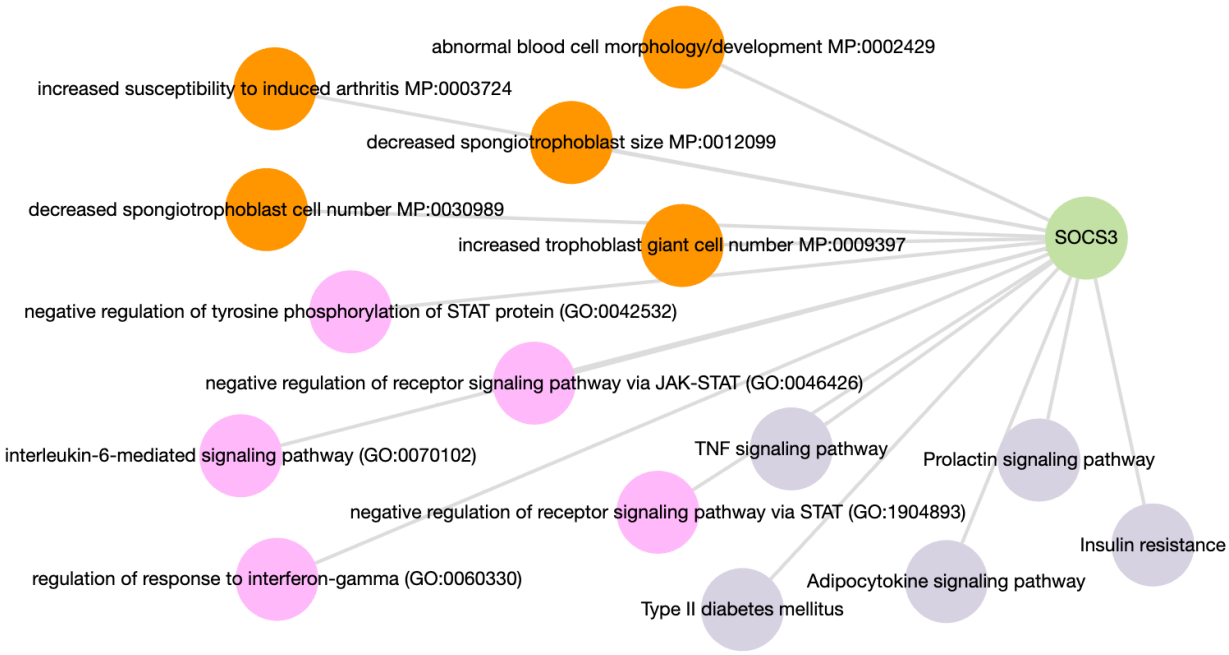
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increased susceptibility to induced arthritis MP:0003724
decreased spongiotrophoblast size MP:0012099
decreased spongiotrophoblast cell number MP:0030989
increased trophoblast giant cell number MP:0009397
SOCS3
negative regulation of tyrosine phosphorylation of STAT protein (GO:0042532)
negative regulation of receptor signaling pathway via JAK-STAT (GO:0046426)
interleukin-6-mediated signaling pathway (GO:0070102)
TNF signaling pathway
Prolactin signaling pathway
negative regulation of receptor signaling pathway via STAT (GO:1904893)
Insulin resistance
regulation of response to interferon-gamma (GO:0060330)
Adipocytokine signaling pathway
Type II diabetes mellitus