Gene name: **TNF** **Previous HGNC Symbols for TNF Gene:** TNFA

External Ids for TNF Gene: HGNC: 11892 NCBI Gene: 7124 Ensembl: ENSG00000232810
OMIM®: 191160 UniProtKB/Swiss-Prot: P01375

NCBI Gene Summary: This gene encodes a multifunctional proinflammatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily. This cytokine is mainly secreted by macrophages. It can bind to, and thus functions through its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. This cytokine is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation. This cytokine has been implicated in a variety of diseases, including autoimmune diseases, insulin resistance, psoriasis, rheumatoid arthritis ankylosing spondylitis, tuberculosis, autosomal dominant polycystic kidney disease, and cancer. Mutations in this gene affect susceptibility to cerebral malaria, septic shock, and Alzheimer disease. Knockout studies in mice also suggested the neuroprotective function of this cytokine. [provided by RefSeq, Aug 2020]
GeneCards Summary: TNF (Tumor Necrosis Factor) is a Protein Coding gene. Diseases associated with TNF include Immunodeficiency 127 and Asthma. Among its related pathways are MIF Mediated Glucocorticoid Regulation and TNFR1 Pathway. Gene Ontology (GO) annotations related to this gene include *identical protein binding* and *cytokine activity*. An important paralog of this gene is TNFSF15.

UniProtKB/Swiss-Prot Summary: Cytokine that binds to TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. It is mainly secreted by macrophages and can induce cell death of certain tumor cell lines. It is potent pyrogen-causing fever by direct action or by stimulation of interleukin-1 secretion and is implicated in the induction of cachexia, Under certain conditions it can stimulate cell proliferation and induce cell differentiation. Impairs regulatory T-cells (Treg) function in individuals with rheumatoid arthritis via FOXP3 dephosphorylation. Up-regulates the expression of protein phosphatase 1 (PP1), which dephosphorylates the key 'Ser-418' residue of FOXP3, thereby inactivating FOXP3 and rendering Treg cells functionally defective (PubMed:23396208). Key mediator of cell death in the anticancer action of BCG-stimulated neutrophils in combination with DIABLO/SMAC mimetic in the RT4v6 bladder cancer cell line (PubMed:16829952, 22517918, 23396208). Induces insulin resistance in adipocytes via inhibition of insulin-induced IRS1 tyrosine phosphorylation and insulin-induced glucose uptake. Induces GKAP42 protein degradation in adipocytes which is partially responsible for TNF-induced insulin resistance (By similarity). Plays a role in angiogenesis by inducing VEGF production synergistically with IL1B and IL6 (PubMed:12794819). Promotes osteoclastogenesis and therefore mediates bone resorption (By similarity). (TNFA_HUMAN,P01375) The TNF intracellular domain (ICD) form induces IL12 production in dendritic cells. (TNFA_HUMAN,P01375).

Cellular localization: mostly extracellular and plasma membrane, Single-pass type II membrane protein.

Full Name: Tumor Necrosis Factor (commonly referred to as TNF-α)
Protein Type: Pro-inflammatory cytokine
Primary Producers: Macrophages, monocytes, T cells, and natural killer (NK) cells.
TNF-α is a key mediator in the inflammatory response, playing a pivotal role in immune system regulation. It exists in both membrane-bound and soluble forms, exerting its effects by binding to TNF receptors (TNFR1 and TNFR2) on various cell types.

🔬 **Biological Function of TNF-α:** TNF-α is involved in several critical physiological and pathological processes:

- **Inflammation:** Induces the expression of adhesion molecules on endothelial cells, facilitating leukocyte migration to sites of infection.
- **Apoptosis:** Can trigger programmed cell death in certain cell types, contributing to the elimination of infected or malignant cells.
- **Fever Induction:** Acts as a pyrogen, stimulating the hypothalamus to raise body temperature during infection.
- **Cachexia:** In chronic diseases, elevated TNF-α levels are associated with muscle wasting and weight loss.
- **Immune Regulation:** Modulates the activity of various immune cells, including macrophages and T lymphocytes.

🦠 **Role of TNF-α in Sepsis:** In the context of sepsis, TNF-α is one of the earliest cytokines released in response to pathogenic invasion, particularly following recognition of lipopolysaccharides (LPS) from Gram-negative bacteria. Its role in sepsis includes:

- **Cytokine Storm Initiation:** TNF-α stimulates the production of other pro-inflammatory cytokines such as IL-1β and IL-6, amplifying the inflammatory response.
- **Endothelial Activation:** Promotes increased vascular permeability, leading to hypotension and edema.
- **Coagulation Cascade Activation:** Enhances the expression of tissue factor on endothelial cells, contributing to disseminated intravascular coagulation (DIC).
- **Organ Dysfunction:** Excessive TNF-α levels can lead to multiple organ failure due to sustained inflammation and impaired perfusion.

While TNF-α is essential for mounting an effective immune response, its overproduction during sepsis can be detrimental, leading to systemic inflammation and tissue damage.

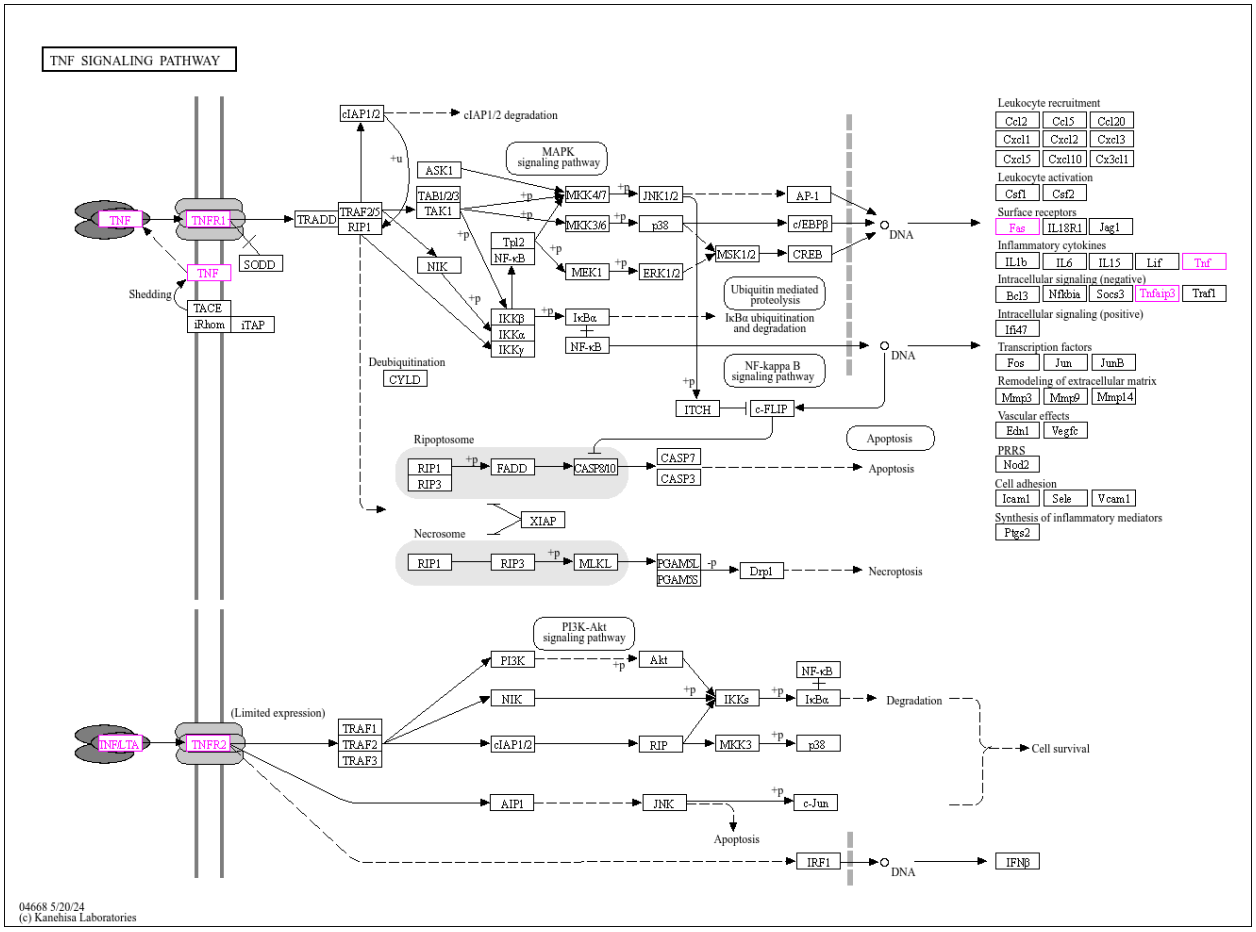
📈 **Diagnostic and Prognostic Value:** Elevated serum TNF-α levels have been associated with the severity and outcome of sepsis:

- **Diagnostic Marker:** Higher TNF-α concentrations can aid in distinguishing septic patients from those with non-infectious inflammatory conditions.
- **Prognostic Indicator:** Increased TNF-α levels on admission correlate with higher mortality rates in sepsis patients.
- **Combined Biomarker Panels:** When measured alongside other markers like soluble interleukin-2 receptor (sIL-2R) and procalcitonin (PCT), TNF-α enhances the diagnostic accuracy for sepsis. For instance, a study evaluating the diagnostic value of sIL-2R, TNF-α, and PCT found that the combination of these markers had a higher area under the ROC curve (AUC) compared to each marker alone, indicating improved diagnostic performance .

🧪 Supporting Literature

doi: 10.1016/0090-1229(92)90036-n - doi: 10.3389/fimmu.2021.741268 - doi:10.1186/s13054-021-03862-5

KEGG:



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