Gene name: **TNFSF10**

External Ids for TNFSF10 Gene: HGNC: 11925 NCBI Gene: 8743 Ensembl: ENSG00000121858
OMIM®: 603598 UniProtKB/Swiss-Prot: P50591

NCBI Gene Summary: The protein encoded by this gene is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. This protein preferentially induces apoptosis in transformed and tumor cells, but does not appear to kill normal cells although it is expressed at a significant level in most normal tissues. This protein binds to several members of TNF receptor superfamily including TNFRSF10A/TRAILR1, TNFRSF10B/TRAILR2, TNFRSF10C/TRAILR3, TNFRSF10D/TRAILR4, and possibly also to TNFRSF11B/OPG. The activity of this protein may be modulated by binding to the decoy receptors TNFRSF10C/TRAILR3, TNFRSF10D/TRAILR4, and TNFRSF11B/OPG that cannot induce apoptosis. The binding of this protein to its receptors has been shown to trigger the activation of MAPK8/JNK, caspase 8, and caspase 3. Alternatively spliced transcript variants encoding different isoforms have been found for this gene.

GeneCards Summary: TNFSF10 (TNF Superfamily Member 10) is a Protein Coding gene. Diseases associated with TNFSF10 include Anaplastic Thyroid Carcinoma and Colon Adenocarcinoma. Among its related pathways are MIF Mediated Glucocorticoid Regulation and Dimerization of procaspase-8. Gene Ontology (GO) annotations related to this gene include *signaling receptor binding* and *tumor necrosis factor receptor binding*. An important paralog of this gene is TNFSF11.

UniProtKB/Swiss-Prot Summary: Cytokine that binds to TNFRSF10A/TRAILR1, TNFRSF10B/TRAILR2, TNFRSF10C/TRAILR3, TNFRSF10D/TRAILR4 and possibly also to TNFRSF11B/OPG (PubMed:10549288, 26457518). Induces apoptosis. Its activity may be modulated by binding to the decoy receptors TNFRSF10C/TRAILR3, TNFRSF10D/TRAILR4 and TNFRSF11B/OPG that cannot induce apoptosis. (TNF10_HUMAN,P50591)

Cellular localization: mainly extracellular and plasma membrane.

Full Name: *Tumor Necrosis Factor (Ligand) Superfamily Member 10*
Protein Name: TRAIL (TNF-Related Apoptosis-Inducing Ligand)
Protein Type:

- Cytokine
- Member of the **TNF superfamily** (similar to TNF-α and FasL)

Biological Function of TNFSF10 (TRAIL)

- TNFSF10 encodes TRAIL, a cytokine primarily involved in regulating apoptosis.
- Produced by:
    - Activated T cells
    - NK cells
    - Macrophages
    - Dendritic cells

- Key biological actions:
    - Induces apoptosis in target cells by binding death receptors (DR4/TRAIL-R1 and DR5/TRAIL-R2).
    - Maintains immune surveillance by eliminating infected, transformed, or damaged cells.
    - Modulates immune responses by influencing T cell proliferation, dendritic cell maturation, and NK cell activity.

🛠️ How TNFSF10/TRAIL Works:

- Binds to death receptors (DR4 and DR5) on target cells.
- Triggers the extrinsic apoptotic pathway:
    - Recruitment of FADD (Fas-associated death domain).
    - Activation of Caspase-8, leading to downstream activation of Caspase-3 and apoptosis.
- Can also engage decoy receptors (DcR1 and DcR2) that do not signal apoptosis, regulating its activity.

🦠 Role of TNFSF10 in Sepsis

- In early sepsis:
    - TRAIL is upregulated as part of the innate immune response to eliminate infected or dysfunctional host cells.
- In late sepsis:
    - TRAIL-mediated apoptosis contributes to immune cell death, particularly T cell and dendritic cell apoptosis.
    - Leads to immune suppression, inability to clear infections, and increased risk of secondary infections.

🔴 Excessive TRAIL activity is associated with the immunosuppressive phase of sepsis, where too many immune cells are lost.

- TRAIL can also affect:
    - Endothelial cells → promoting vascular dysfunction.
    - Parenchymal tissues → contributing to organ damage.

📈 Clinical Relevance of TNFSF10 in Sepsis

Diagnostic Role:

- Plasma TRAIL levels rise during sepsis and systemic inflammatory conditions.
- Part of multi-marker panels distinguishing infectious sepsis from non-infectious inflammation.

Prognostic Role:

- High TRAIL levels correlate with:
    - More severe immune suppression.
    - Increased susceptibility to secondary infections.
    - Poorer recovery.

- Some studies show that decreased TRAIL activity is associated with better T cell survival and improved outcomes.

Therapeutic Interest:

- TRAIL inhibitors or modulation of death receptor signaling are considered potential strategies to preserve immune function in late sepsis.

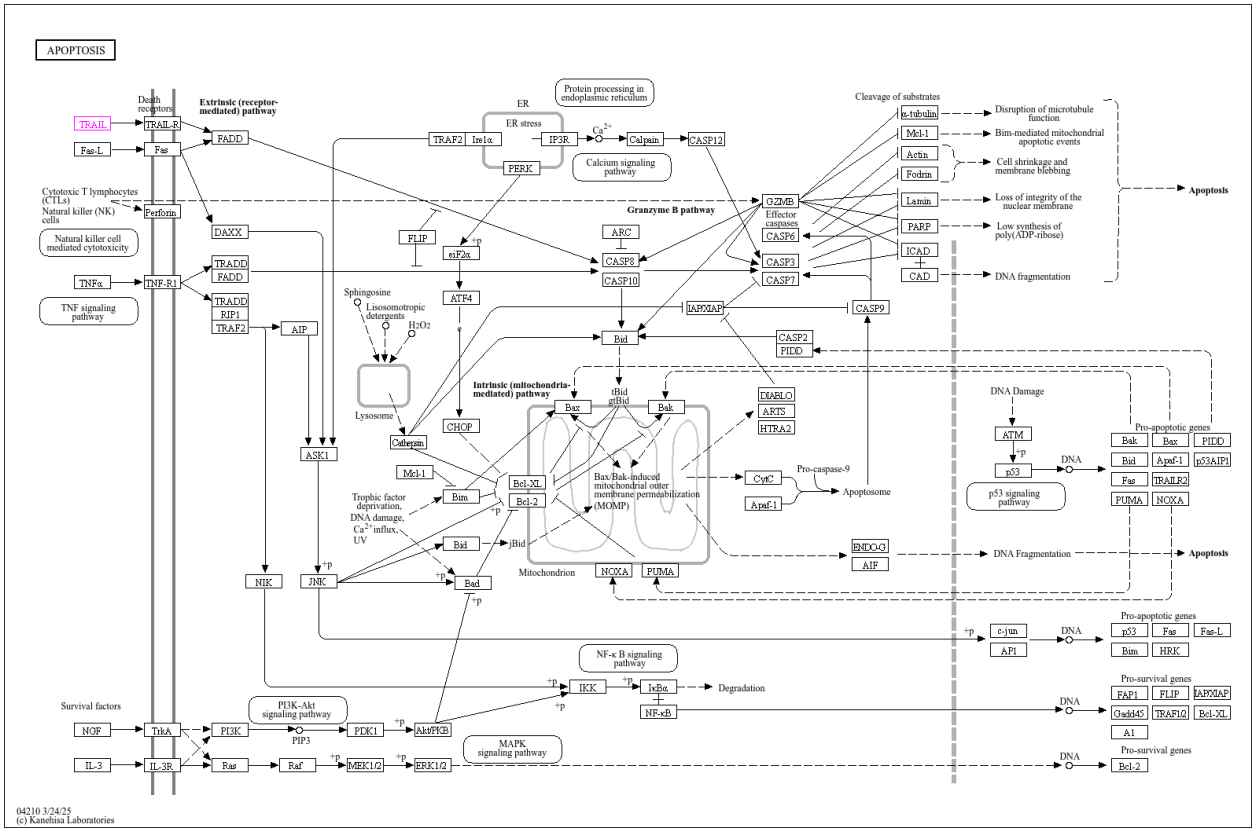
🔬 Pathways Involving TNFSF10

- **Apoptosis pathway (KEGG hsa04210)** → activates extrinsic apoptosis via death receptors.
- **TNF signaling pathway (KEGG hsa04668)** → participates in inflammation and programmed cell death.
- **Immune system regulation** → especially in T cell apoptosis and immune homeostasis.

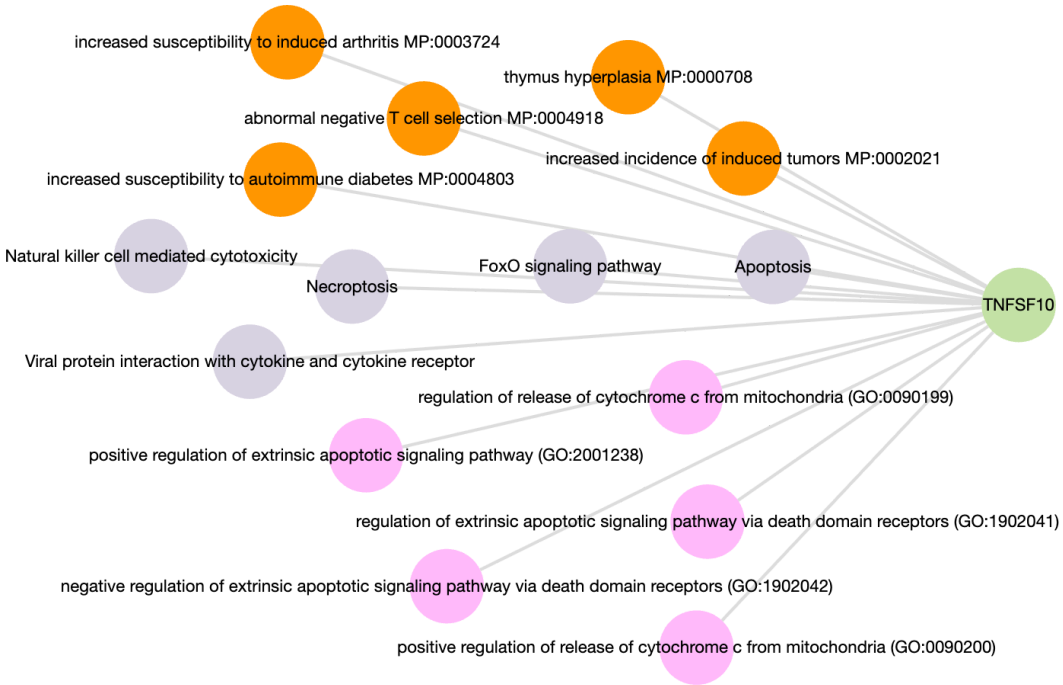
🧪 Supporting Literature

Doi: 10.4049/jimmunol.1101180
Doi: 10.1172/jci.insight.127143
Doi: 10.3390/jcm9061661

KEGG


APOPTOSIS
Death receptors
Extrinsic (receptor-mediated) pathway
TRAIL
Fas-L
TRAIL-R
Fas
FADD
ER
Protein processing in endoplasmic reticulum
ER stress
TRAF2
Ire1α
IP3R
Ca2+
Calpain
CASP12
PERK
Calcium signaling pathway
Cytotoxic T lymphocytes (CTLs)
Natural killer (NK) cells
Perforin
Granzyme B pathway
GZMB
Effector caspases
CASP6
CASP3
CASP7
Natural killer cell mediated cytotoxicity
DAXX
FLIP
eIF2α
ARC
CASP8
CASP10
TNFα
TNF-R1
TRADD
FADD
RIP1
TRAF2
TNF signaling pathway
AIP
ASK1
ATF4
Sphingosine
Lisosomotropic detergents
H2O2
Lysosome
Cathepsin
CHOP
IAPXIAP
CASP9
Bid
CASP2
PIDD
Intrinsic (mitochondria-mediated) pathway
tBid
gtBid
Bax
Bak
DIABLO
ARTS
HTRA2
Mcl-1
Bcl-XL
Bcl-2
Bim
Trophic factor deprivation, DNA damage, Ca2+influx, UV
Bid
jBid
Bad
Bax/Bak-induced mitochondrial outer membrane permeabilization (MOMP)
Mitochondrion
NOXA
PUMA
Cyt C
Pro-caspase-9
Apaf-1
Apoptosome
ENDOG
AIF
DNA Fragmentation
Apoptosis
Cleavage of substrates
α-tubulin
Mcl-1
Actin
Fodrin
Disruption of microtubule function
Bim-mediated mitochondrial apoptotic events
Cell shrinkage and membrane blebbing
Lamin
PARP
ICAD
CAD
Loss of integrity of the nuclear membrane
Low synthesis of poly(ADP-ribose)
DNA fragmentation
DNA Damage
ATM
p53
p53 signaling pathway
DNA
Pro-apoptotic genes
Bak
Bax
PIDD
Bid
Apaf-1
p53AIP1
Fas
TRAILR2
PUMA
NOXA
NF-κ B signaling pathway
IKK
IκBα
NF-κB
Degradation
c-jun
AP1
Pro-apoptotic genes
p53
Fas
Fas-L
Bim
HRK
Survival factors
NGF
TrkA
IL-3
IL-3R
PI3K-Akt signaling pathway
PI3K
PIP3
PDK1
Akt/PKB
Ras
Raf
MEK1/2
ERK1/2
MAPK signaling pathway
Pro-survival genes
FAP1
FLIP
IAPXIAP
Gadd45
TRAF1/2
Bcl-XL
A1
Pro-survival genes
Bcl-2
04210 3/24/25
(c) Kanehisa Laboratories

Enrichr-KG


increased susceptibility to induced arthritis MP:0003724
thymus hyperplasia MP:0000708
abnormal negative T cell selection MP:0004918
increased incidence of induced tumors MP:0002021
increased susceptibility to autoimmune diabetes MP:0004803
Natural killer cell mediated cytotoxicity
FoxO signaling pathway
Apoptosis
Necroptosis
TNFSF10
Viral protein interaction with cytokine and cytokine receptor
regulation of release of cytochrome c from mitochondria (GO:0090199)
positive regulation of extrinsic apoptotic signaling pathway (GO:2001238)
regulation of extrinsic apoptotic signaling pathway via death domain receptors (GO:1902041)
negative regulation of extrinsic apoptotic signaling pathway via death domain receptors (GO:1902042)
positive regulation of release of cytochrome c from mitochondria (GO:0090200)