

Gene Section

Review

TNFSF10 (tumor necrosis factor (ligand) superfamily, member 10)

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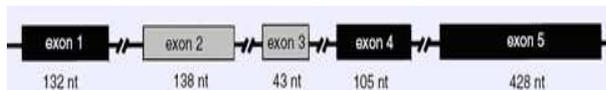
Identity

Hugo: TNFSF10

Other names: APO2L; Apo-2L; CD253; TL2; TRAIL; TRAIL-PEN

Location: 3q26

DNA/RNA



Organization of the human TRAIL gene.

Description

5 exons; DNA size 17805 bp.

Transcription

CDS: 846 nt; Krieg A. et al. (BJC 2003) reported two splice variants in neoplastic and non-neoplastic cells.

Pseudogene

No known pseudogenes.

Protein

Note: 281 AA, 32509 Da; TRAIL (TNF-Related Apoptosis-Inducing Ligand) was originally identified by two independent groups and characterized as a member of the TNF (Tumor Necrosis Factor) family of death-inducing ligands. TRAIL can bind to five different receptors found on a variety of cell types: four membrane-bound and one soluble receptor. Two of

these membrane receptors, TRAIL-R1/death receptor 4 (DR4) and TRAIL-R2/death receptor 5 (DR5), act as agonistic receptors, containing a cytoplasmic death domain through which TRAIL can transmit an apoptotic signal. The other two membrane receptors, TRAIL-R3/decoy receptor 1 (DcR1) and TRAIL-R4/decoy receptor 2 (DcR2), can also bind TRAIL, but act as antagonistic/regulatory receptors, lacking the death domain. In addition to these four transmembrane receptors, a fifth soluble antagonistic receptor, osteoprotegerin (OPG), has been identified (Diagram 1).

Description

The extra-cellular domain of the membrane-bound TRAIL forms a bell shaped homo-trimer, much like other ligands of the TNF family. However, there is a unique insertion loop of about 16-20 amino acids in soluble TRAIL near its amino-terminal end (Diagram 2). Unlike other members of the TNF superfamily, TRAIL carries a zinc ion at the trimer interface, coordinated by the single unpaired cysteine residue (Cys 230) of each monomer (Diagram 2). This zinc ion is essential for structural integrity of TRAIL, and substituting the Cys 230 with alanine or serine strongly affects the capacity of TRAIL to induce apoptosis. Three molecules of TRAIL assemble with three molecules of the transmembrane receptor as a hexameric complex (3:3).

Expression

Membrane-bound TRAIL is expressed on the surface of activated immune cells, such as natural killer (NK)

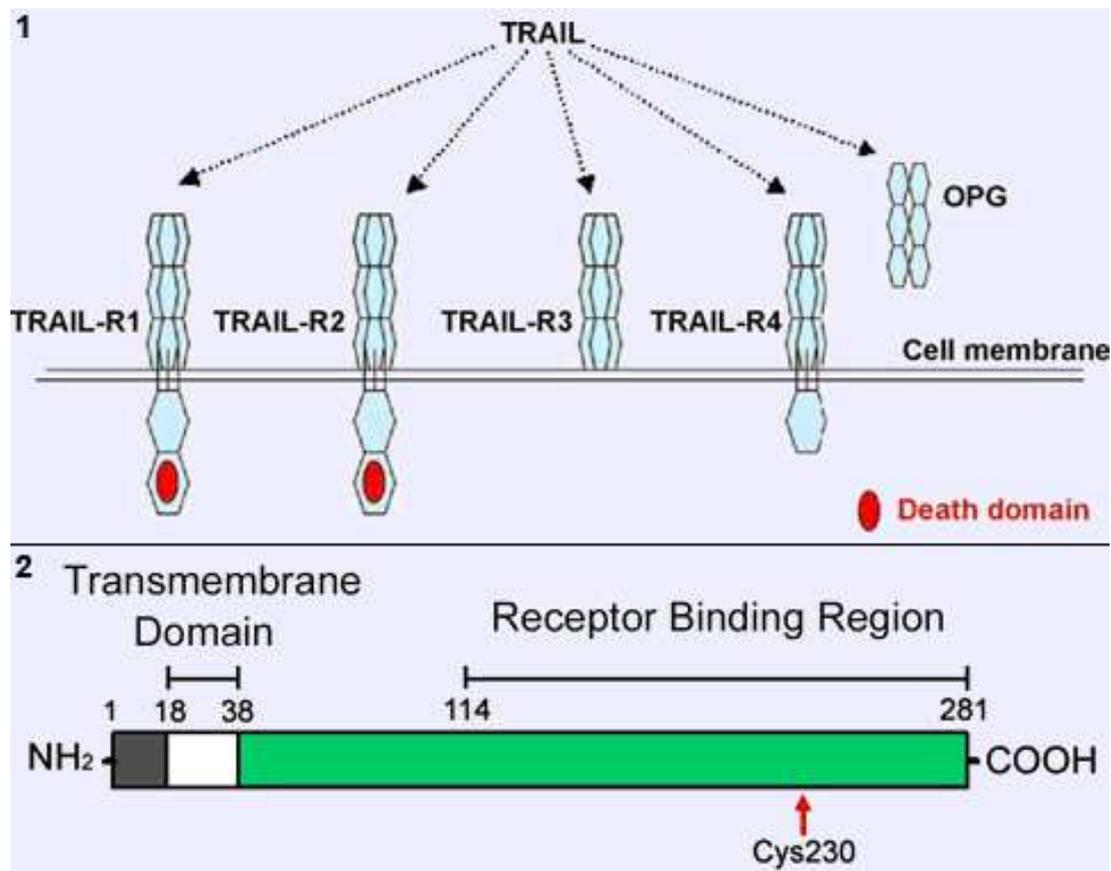


Diagram 1. TRAIL receptor system.

Diagram 2. Schematic representation of the structure of TRAIL protein.

cells, T cells, macrophages and dendritic cells, whereas soluble TRAIL is present in the sera of normal individuals as well as of patients affected by neoplastic disorders. Soluble TRAIL is also released in the culture supernatant of activated peripheral blood mononuclear cells (PBMC) in response to interferon induction, so that it apparently seems to function as an immune effector molecule, mediating antitumor cytotoxicity and immune regulation. Importantly, this biological role of TRAIL is consistent with its tumor selective properties, since it implies that normal tissues are constitutively protected from circulating immune cells bearing TRAIL. Besides, a significant level of TRAIL transcript has been detected in many human tissues including thymus, spleen, PBMC, prostate, ovary, small intestine, colon and placenta, but not in the brain and it is expressed constitutively in some cell lines.

Localisation

TRAIL is a type II membrane protein of about 33-35 kD, which can be cleaved from the cell surface by the aspartic proteinase cathepsin E to form a soluble ligand of about 21 kD that retains biological activity.

Function

The best-characterized biological activity of TRAIL is

to induce apoptotic cell death in a variety of neoplastic cells. Both full-length membrane expressed TRAIL and soluble TRAIL can rapidly induce apoptosis in a wide variety of human cancer cell lines and primary tumors (including hematological malignancies), showing minimal or absent cytotoxicity on normal cells, both in vitro and in vivo; thus TRAIL was identified as a potential tumor-specific cancer therapeutic. The wide expression of TRAIL and TRAIL-Rs in many normal tissues suggests that the physiological role of TRAIL is more complex than the simply induction of apoptosis in cancer cells. In this respect, several studies have demonstrated that the TRAIL-TRAIL receptors system elicit a physiological role in normal hematopoiesis (for example an anti-differentiative effect on erythroid maturation and a pro-maturative effect during megakaryocytopoiesis and in vascular physiology, promoting the survival, migration and proliferation of endothelial cells). It has also been demonstrated that TRAIL significantly counteracts the adhesion of peripheral blood derived monocytes and granulocytes to endothelial cells without inducing apoptosis in response to inflammatory cytokines in vitro, suggesting an anti-inflammatory activity of TRAIL. All these data are reviewed in Secchiero and Zauli, 2008.

Homology

GENE		IDENTITY (%)	
SPECIES	SYMBOL	PROTEIN	DNA
HOMO SAPIENS	TNFSF10		
VS. PAN TROGLODYTES	TNFSF10	98.9	99.3
VS. MUS MUSCULUS	TNFSF10	67.0	75.0
VS. RATTUS NORVEGICUS	TNFSF10	70.3	74.3
VS. GALLUS GALLUS	TNFSF10	59.3	64.2
VS. DANIO RERIO	TNFSF10L2	46.2	54.1

The homology of TRAIL with the other proteins of TNF family is reported below:

GENE		IDENTITY (%)	
SPECIES	SYMBOL	PROTEIN	
HOMO SAPIENS	TNFSF10		
HOMO SAPIENS	TNF	23	
HOMO SAPIENS	RANKL	24	
HOMO SAPIENS	FASL	27	
HOMO SAPIENS	CD40L	23	
HOMO SAPIENS	CD137L	NOT SIGNIFICANT	
HOMO SAPIENS	OX40L	NOT SIGNIFICANT	
HOMO SAPIENS	CD27L	NOT SIGNIFICANT	
HOMO SAPIENS	CD30L	NOT SIGNIFICANT	
HOMO SAPIENS	LTA	22	
HOMO SAPIENS	LTB	21	
HOMO SAPIENS	APO3L	NOT SIGNIFICANT	
HOMO SAPIENS	APRIL	NOT SIGNIFICANT	
HOMO SAPIENS	TNFSF13B	NOT SIGNIFICANT	
HOMO SAPIENS	TNFSF14	25	
HOMO SAPIENS	TNFSF15	34	
HOMO SAPIENS	TNFSF18	NOT SIGNIFICANT	

Mutations

6 esonic variations. For details see: http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=8743

Implicated in

Myelodysplastic Syndromes (MDS)

Note: The myelodysplastic syndromes comprise a heterogeneous group of clonal disorders, usually characterized by a normal or hypercellular marrow with dysplastic features leading to peripheral blood cytopenias and a variable incidence of transformation into acute myeloid leukemia (AML). Ineffective erythropoiesis is a common feature of MDS. One mechanism invoked to explain the apparent discrepancy between cellular marrow and peripheral blood cytopenias in patients with MDS is apoptosis, which occurs with increased frequency in MDS marrow.

Disease

The decrease of mature erythrocytes, the major clinical feature of MDS, has been attributed to the increased expression and release at the bone marrow level of TRAIL, that selectively inhibits erythroid development by specifically targeting immature erythroblasts, impairing erythropoiesis and contributing to the degree of anemia.

B-Chronic Lymphocytic Leukemia (B-CLL)

Note: B-CLL represents a quintessential example of human malignancies that are caused primarily by defects in apoptosis or programmed cell death.

During the early stages of disease, mature B lymphocytes that constitute most B-CLL are largely quiescent G(0) phase cells, which accumulate not because they are dividing more rapidly than normal cells but because they survive longer than their normal counterparts due to defects in the apoptotic pathways. These noncycling CD5+/CD19+ B lymphocytes accumulate in the peripheral blood, marrow, spleen, and lymph nodes. Defects in apoptotic pathways contribute also to chemoresistance, rendering tumor cells less sensitive to the cytotoxic actions of currently available anticancer drugs, and can also promote resistance to cellular immune responses.

Disease

In order to elucidate the expression of TRAIL and its biological potential function in B-CLL, it has been examined the expression of TRAIL in B-CLL PBMC in comparison with PBMC obtained from healthy blood donors as well as the susceptibility of B-CLL cells to soluble recombinant TRAIL and the potential effects of endogenous membrane-bound TRAIL on autologous B-CLL cell survival. It has been shown that TRAIL is overexpressed in B-CLL PBMC in comparison with normal B cells, but B-CLL cells are resistant to TRAIL-mediated apoptosis. Taken together, these findings suggest that an aberrant expression of TRAIL might contribute to the pathogenesis of B-CLL.

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