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Gene Section

Review

TNFSF18 (tumor necrosis factor (ligand) superfamily, member 18)

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Identity

Other names: AITRL, GITRL, MGC138237, TL6
HGNC (Hugo): TNFSF18
Location: 1q25.1

DNA/RNA

Description

2 transcript versions published:
mRNA 748 bp: 3 exons (1-223, 224-254, 255-748) -> coding for 199 aa (2-601),
mRNA 610 bp: 3 exons (1-176, 177-207, 208-610) -> coding for 177 aa (21-554).

Transcription

Accurate start codon is not clearly defined, 2 transcript versions are published (differing start codons in exon 1).

Pseudogene

Unknown.

Protein

Description

TNFSF18/GITR ligand (GITRL) is a single-pass type II transmembrane protein and contains 2 potential glycosylation sites (predicted at 129 aa and 161 aa). TNFSF18 encompasses 177 or 199 aa and thus has a molecular weight of about 20 kDa. In the 177 aa long version, amino acids 1-28 constitute the cytoplasmic domain, 29-49 the transmembrane domain, and 50-177 the extracellular domain, whereas in the 199 aa long variant the amino acids 1-50 constitute the cytoplasmic domain, 51-71 the transmembrane domain, and 72-199 the extracellular domain.

Expression

TNFSF18 is expressed on DC, monocytes, macrophages, B cells, activated T cells, endothelial cells, osteoclasts and various healthy non-lymphoid tissues (e.g., testis, ...).

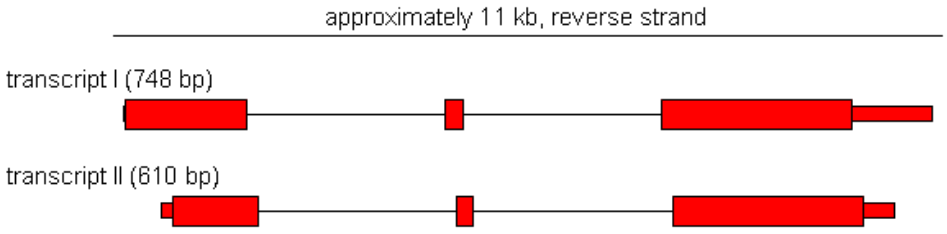

Figure 1. Schematic illustration of the gene structure of human TNFSF18 on chromosome 1. Both published transcript variants are shown. Red boxes represent the mRNA transcript within the gene. The smaller boxes at the beginning and the end of the transcripts indicate untranslated regions, while the larger boxes display the translated parts.

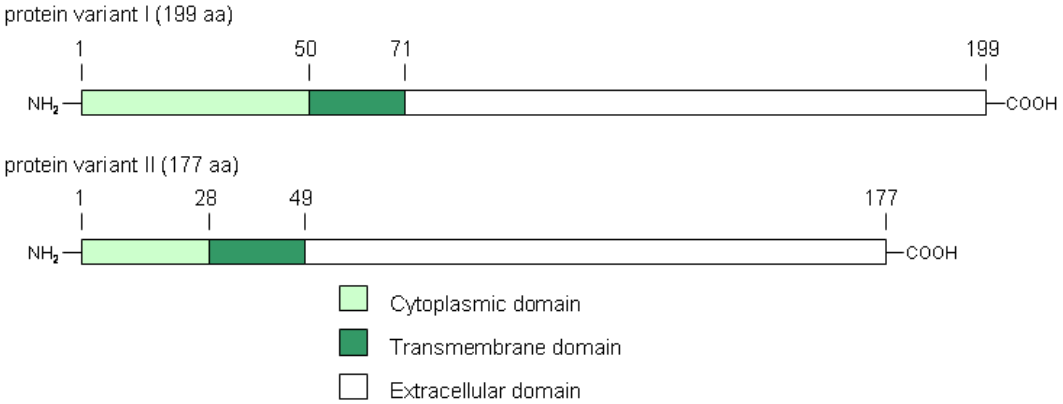

Figure 2. Schematic illustration of the structure of TNFSF18 protein versions, according to the two published transcripts.

The fact that TNFSF18 is constitutively expressed on resting antigen-presenting cells distinguishes it from most other TNF family members, which are not detectable in resting state and are upregulated following activation.
In addition, TNFSF18 is constitutively expressed and released as soluble form by solid tumors of different histological origin and various hematopoietic malignancies.

Localisation

TNFSF18 is a type II transmembrane protein. A soluble form of the molecule has been shown to be released by a yet unknown mechanism e.g. by tumor cells.

Function

TNFSF18 is the only known ligand for GITR (TNFRSF18, AITR), which is mainly expressed by lymphatic cells like T lymphocytes and NK cells. Upon interaction with its receptor, TNFSF18 is, like many other TNF family members, capable to transduce bidirectional signals, i.e. in the receptor and the ligand bearing cell. Transduction of signals into TNFSF18 bearing cells has been shown to cause differentiation of osteoclasts, to activate macrophages and to alter cytokine production of healthy myeloid cells, but also of carcinoma and leukemia cells and influences apoptosis. Activation of macrophages via TNFSF18 results in increased secretion of inflammatory mediators like MMP-9, NO and TNF. In healthy macrophages and myeloid leukemia cells, TNFSF18 signaling has been found to involve the MAP kinase pathway.
Binding to TNFRSF18 may induce signaling through this receptor, which, in mice, has been implicated in the development of autoimmune diseases, graft versus host disease and in the immune response against infectious pathogens and tumors.
Available data suggest that TNFRSF18 may mediate different effects in mice and men, and most functional studies regarding the role of TNFRSF18 in tumor immunology have been performed using agonistic antibodies or injection of adenovirus expressing recombinant TNFSF18 into tumors, which might not reflect the consequences of TNFRSF18 interaction with its natural ligand in vivo. In line, studies evaluating immune responses in GITR$^{-/-}$ mice have so far not led to a clear picture of the role of TNFRSF18 in normal physiology.

Homology

The TNFSF18 gene is conserved in human, chimpanzee, dog, mouse, and rat. The homology among the other TNF family members is highest with OX40L.

Mutations

Note
No published single nucleotide polymorphisms (SNPs).

Implicated in

Host-tumor interaction

Note
In mice, it has been shown that application of the agonistic GITR antibody DTA-1 delays tumor progression and can even lead to complete tumor rejection. Similar results were obtained by using GITRL-Fc fusion protein. Transfection of tumor cells with GITRL causes rejection of the tumor and prolonged survival, while parental cells cannot be rejected. This effect can be reversed by administration of a blocking GITRL antibody. There is evidence that expression of GITRL promotes the development of tumor-specific T cells. Re-challenge of mice which once successfully rejected GITRL-positive tumor results in complete rejection of both transfected and non-transfected tumors. Several studies showed increased infiltration of CD8+ cells in GITRL-expressing tumors. By the use of depletion experiments and athymic nude mice it has been shown that for GITR-GITRL dependent rejection of tumors both CD4+ and CD8+ T cells as well as NK cells are required.

In humans, controversial data regarding the function of GITR and GITRL in tumor immunology were described. Hanabuchi et al. reported that NK cells are activated by engagement of GITRL on plasmacytoid dendritic cells, which can be blocked by anti-GITRL antibody. In contrast, Baltz et al. and Baessler et al. demonstrated substantial GITRL expression on tumor cells and leukemic blasts resulting in diminished NK cell reactivity. Blockade of GITR-GITRL interaction by anti-GITR antibody abrogated the inhibitory effect of GITRL. Furthermore, stimulation of GITRL substantially induced the production of TGF-beta and IL-10 by tumor cells and leukemic blasts. Additionally, they reported that human GITRL is released by tumor cells in a soluble form which impairs NK cell reactivity alike the membrane-bound form. Thus, GITRL expression seems to affect the interaction of human tumor cells with the immune system by influencing tumor cell immunogenity and metastasis and creating an immunosuppressive cytokine microenvironment. The inhibitory effect of GITRL on human NK cells was further supported by Liu et al., who reported inhibition of NK cell proliferation and cytokine production and increased apoptosis after GITR stimulation. These controversial data regarding the function of GITR on human NK cells may be due to the usage of different reagents and different experimental condition.

The results regarding the role of GITR and GITRL in tumor immunology are controversial in mice and humans. Thus, GITR and GITRL may mediate different effects in mice and men, and in line suppression of human regulatory T cells, in contrast to their murine counterparts, is not inhibited by GITR. Many studies employed agonistic antibodies or recombinant protein for GITR stimulation and not constitutively GITRL-expressing cells. Thus, these studies do not involve possible influences of reverse signaling mediated by GITRL, which may change reaction of GITRL-bearing cells and may in turn alter functions of GITR-bearing cells.

Autoimmune disease

Note

The influence of GITR and GITRL was tested in different mouse models of autoimmune disease. Onset of autoimmune diabetes in NOD mice is accelerated if they are treated with agonistic GITR mAb, and activation of CD4+ T cells is increased compared to control treated mice. Likewise, application of a blocking GITRL antibody protected from diabetes. In GITR -/- mice, experimental autoimmune diseases take an attenuated course. GITR -/- mice with collagen-induced arthritis show less joint inflammation and bone erosion than wildtype mice. Furthermore, lower concentrations of inflammatory mediators were reported. In line with these findings, GITR triggering antibody exacerbates collagen-induced arthritis in wildtype mice compared to control-treated siblings.

However, all these studies regarding the function of GITR and its ligand in autoimmune disease were performed in mice. Further investigation is needed to elucidate the relevance of GITR and GITR ligand in human autoimmune disease and to clarify the similarities and differences of these molecules in mice and men.

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