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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, ...).

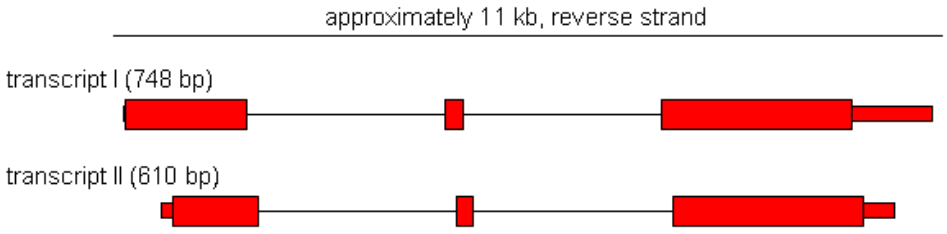

Figure 1. Schematic illustration of the gene structure of human TNFSF18 on chromosome 1. Both published transcript variants are shown. Red boxes represent the mRNA transcript within the gene. The smaller boxes at the beginning and the end of the transcripts indicate untranslated regions, while the larger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

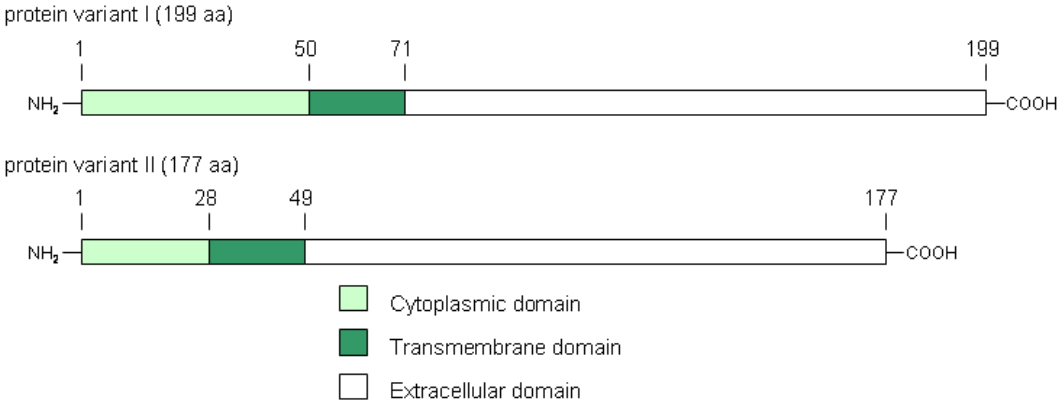

Figure 2. Schematic illustration of the structure of TNFSF18 protein versions, according to the two published transcripts.

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.

References

Nocentini G, Giunchi L, Ronchetti S, Krausz LT, Bartoli A, Moraca R, Migliorati G, Riccardi C. A new member of the tumor necrosis factor/nerve growth factor receptor family inhibits T cell receptor-induced apoptosis. Proc Natl Acad Sci U S A. 1997 Jun 10;94(12):6216-21

Gurney AL, Marsters SA, Huang RM, Pitti RM, Mark DT, Baldwin DT, Gray AM, Dowd AD, Brush AD, Heldens AD, Schow AD, Goddard AD, Wood WI, Baker KP, Godowski PJ, Ashkenazi A. Identification of a new member of the tumor necrosis factor family and its receptor, a human ortholog of mouse GITR. Curr Biol. 1999 Feb 25;9(4):215-8

Kwon B, Yu KY, Ni J, Yu GL, Jang IK, Kim YJ, Xing L, Liu D, Wang SX, Kwon BS. Identification of a novel activation-inducible protein of the tumor necrosis factor receptor superfamily and its ligand. J Biol Chem. 1999 Mar 5;274(10):6056-61

Shimizu J, Yamazaki S, Takahashi T, Ishida Y, Sakaguchi S. Stimulation of CD25(+)CD4(+) regulatory T cells through GITR breaks immunological self-tolerance. Nat Immunol. 2002 Feb;3(2):135-42

Shin HH, Lee MH, Kim SG, Lee YH, Kwon BS, Choi HS. Recombinant glucocorticoid induced tumor necrosis factor receptor (rGITR) induces NOS in murine macrophage. FEBS Lett. 2002 Mar 13;514(2-3):275-80

Spinicelli S, Nocentini G, Ronchetti S, Krausz LT, Bianchini R, Riccardi C. GITR interacts with the pro-apoptotic protein Siva and induces apoptosis. Cell Death Differ. 2002 Dec;9(12):1382-4

Lee HS, Shin HH, Kwon BS, Choi HS. Soluble glucocorticoid-induced tumor necrosis factor receptor (sGITR) increased MMP-9 activity in murine macrophage. J Cell Biochem. 2003 Apr 1;88(5):1048-56

Shin HH, Lee HW, Choi HS. Induction of nitric oxide synthase (NOS) by soluble glucocorticoid induced tumor necrosis factor receptor (sGITR) is modulated by IFN-gamma in murine macrophage. Exp Mol Med. 2003 Jun 30;35(3):175-80

Tone M, Tone Y, Adams E, Yates SF, Frewin MR, Cobbold SP, Waldmann H. Mouse glucocorticoid-induced tumor necrosis factor receptor ligand is costimulatory for T cells. Proc Natl Acad Sci U S A. 2003 Dec 9;100(25):15059-64

Ji HB, Liao G, Faubion WA, Abadía-Molina AC, Cozzo C, Laroux FS, Caton A, Terhorst C. Cutting edge: the natural ligand for glucocorticoid-induced TNF receptor-related protein abrogates regulatory T cell suppression. J Immunol. 2004 May 15;172(10):5823-7

Muriglan SJ, Ramirez-Montagut T, Alpdogan O, Van Huystee TW, Eng JM, Hubbard VM, Kochman AA, Tjoe KH, Riccardi C, Pandolfi PP, Sakaguchi S, Houghton AN, Van Den Brink MR. GITR activation induces an opposite effect on alloreactive CD4(+) and CD8(+) T cells in graft-versus-host disease. J Exp Med. 2004 Jul 19;200(2):149-57

Ronchetti S, Zollo O, Bruscoli S, Agostini M, Bianchini R, Nocentini G, Ayroldi E, Riccardi C. GITR, a member of the TNF

receptor superfamily, is costimulatory to mouse T lymphocyte subpopulations. Eur J Immunol. 2004 Mar;34(3):613-22

Shin HH, Kim SJ, Lee HS, Choi HS. The soluble glucocorticoid-induced tumor necrosis factor receptor causes cell cycle arrest and apoptosis in murine macrophages. Biochem Biophys Res Commun. 2004 Mar 26;316(1):24-32

Calmels B, Paul S, Futin N, Ledoux C, Stoeckel F, Acres B. Bypassing tumor-associated immune suppression with recombinant adenovirus constructs expressing membrane bound or secreted GITR-L. Cancer Gene Ther. 2005 Feb;12(2):198-205

Esparza EM, Arch RH. Glucocorticoid-induced TNF receptor functions as a costimulatory receptor that promotes survival in early phases of T cell activation. J Immunol. 2005 Jun 15;174(12):7869-74

Esparza EM, Arch RH. Glucocorticoid-induced TNF receptor, a costimulatory receptor on naive and activated T cells, uses TNF receptor-associated factor 2 in a novel fashion as an inhibitor of NF-kappa B activation. J Immunol. 2005 Jun 15;174(12):7875-82

Ko K, Yamazaki S, Nakamura K, Nishioka T, Hirota K, Yamaguchi T, Shimizu J, Nomura T, Chiba T, Sakaguchi S. Treatment of advanced tumors with agonistic anti-GITR mAb and its effects on tumor-infiltrating Foxp3+CD25+CD4+ regulatory T cells. J Exp Med. 2005 Oct 3;202(7):885-91

Patel M, Xu D, Kewin P, Choo-Kang B, McSharry C, Thomson NC, Liew FY. Glucocorticoid-induced TNFR family-related protein (GITR) activation exacerbates murine asthma and collagen-induced arthritis. Eur J Immunol. 2005 Dec;35(12):3581-90

Watts TH. TNF/TNFR family members in costimulation of T cell responses. Annu Rev Immunol. 2005;23:23-68

Baumgartner-Nielsen J, Vestergaard C, Thestrup-Pedersen K, Deleuran M, Deleuran B. Glucocorticoid-induced tumour necrosis factor receptor (GITR) and its ligand (GITRL) in atopic dermatitis. Acta Derm Venereol. 2006;86(5):393-8

Cohen AD, Diab A, Perales MA, Wolchok JD, Rizzuto G, Merghoub T, Huggins D, Liu C, Turk MJ, Restifo NP, Sakaguchi S, Houghton AN. Agonist anti-GITR antibody enhances vaccine-induced CD8(+) T-cell responses and tumor immunity. Cancer Res. 2006 May 1;66(9):4904-12

Cuzzocrea S, Nocentini G, Di Paola R, Agostini M, Mazzon E, Ronchetti S, Crisafulli C, Esposito E, Caputi AP, Riccardi C. Proinflammatory role of glucocorticoid-induced TNF receptor-related gene in acute lung inflammation. J Immunol. 2006 Jul 1;177(1):631-41

Hanabuchi S, Watanabe N, Wang YH, Wang YH, Ito T, Shaw J, Cao W, Qin FX, Liu YJ. Human plasmacytoid predendritic cells activate NK cells through glucocorticoid-induced tumor necrosis factor receptor-ligand (GITRL). Blood. 2006 May 1;107(9):3617-23

Kim J, Choi WS, Kim HJ, Kwon B. Prevention of chronic graft-versus-host disease by stimulation with glucocorticoid-induced TNF receptor. Exp Mol Med. 2006 Feb 28;38(1):94-9

Mahesh SP, Li Z, Liu B, Fariss RN, Nussenblatt RB. Expression of GITR ligand abrogates immunosuppressive function of ocular tissue and differentially modulates inflammatory cytokines and chemokines. Eur J Immunol. 2006 Aug;36(8):2128-38

Ramirez-Montagut T, Chow A, Hirschhorn-Cymerman D, Terwey TH, Kochman AA, Lu S, Miles RC, Sakaguchi S, Houghton AN, van den Brink MR. Glucocorticoid-induced TNF receptor family related gene activation overcomes tolerance/ignorance to melanoma differentiation antigens and enhances antitumor immunity. J Immunol. 2006 Jun 1;176(11):6434-42

Baltz KM, Krusch M, Bringmann A, Brossart P, Mayer F, Kloss M, Baessler T, Kumbier I, Peterfi A, Kupka S, Kroeber S, Menzel D, Radsak MP, Rammensee HG, Salih HR. Cancer immunoediting by GITR (glucocorticoid-induced TNF-related protein) ligand in humans: NK cell/tumor cell interactions. FASEB J. 2007 Aug;21(10):2442-54

Cuzzocrea S, Ronchetti S, Genovese T, Mazzon E, Agostini M, Di Paola R, Esposito E, Muià C, Nocentini G, Riccardi C. Genetic and pharmacological inhibition of GITR-GITRL interaction reduces chronic lung injury induced by bleomycin instillation. FASEB J. 2007 Jan;21(1):117-29

Grohmann U, Volpi C, Fallarino F, Bozza S, Bianchi R, Vacca C, Orabona C, Belladonna ML, Ayroldi E, Nocentini G, Boon L, Bistoni F, Fioretti MC, Romani L, Riccardi C, Puccetti P. Reverse signaling through GITR ligand enables dexamethasone to activate IDO in allergy. Nat Med. 2007 May;13(5):579-86

Ronchetti S, Nocentini G, Bianchini R, Krausz LT, Migliorati G, Riccardi C. Glucocorticoid-induced TNFR-related protein lowers the threshold of CD28 costimulation in CD8+ T cells. J Immunol. 2007 Nov 1;179(9):5916-26

Zhou P, L'italien L, Hodges D, Schebye XM. Pivotal roles of CD4+ effector T cells in mediating agonistic anti-GITR mAb-induced-immune activation and tumor immunity in CT26 tumors. J Immunol. 2007 Dec 1;179(11):7365-75

Bae EM, Kim WJ, Suk K, Kang YM, Park JE, Kim WY, Choi EM, Choi BK, Kwon BS, Lee WH. Reverse signaling initiated from GITRL induces NF-kappaB activation through ERK in the inflammatory activation of macrophages. Mol Immunol. 2008 Jan;45(2):523-33

Baltz KM, Krusch M, Baessler T, Schmiedel BJ, Bringmann A, Brossart P, Salih HR. Neutralization of tumor-derived soluble glucocorticoid-induced TNFR-related protein ligand increases NK cell anti-tumor reactivity. Blood. 2008 Nov 1;112(9):3735-43

Igarashi H, Cao Y, Iwai H, Piao J, Kamimura Y, Hashiguchi M, Amagasa T, Azuma M. GITR ligand-costimulation activates effector and regulatory functions of CD4+ T cells. Biochem Biophys Res Commun. 2008 May 16;369(4):1134-8

Liu B, Li Z, Mahesh SP, Pantanelli S, Hwang FS, Siu WO, Nussenblatt RB. Glucocorticoid-induced tumor necrosis factor receptor negatively regulates activation of human primary natural killer (NK) cells by blocking proliferative signals and increasing NK cell apoptosis. J Biol Chem. 2008 Mar 28;283(13):8202-10

Nishikawa H, Kato T, Hirayama M, Orito Y, Sato E, Harada N, Gnjatic S, Old LJ, Shiku H. Regulatory T cell-resistant CD8+ T cells induced by glucocorticoid-induced tumor necrosis factor receptor signaling. Cancer Res. 2008 Jul 15;68(14):5948-54

Baessler T, Krusch M, Schmiedel BJ, Kloss M, Baltz KM, Wacker A, Schmetzer HM, Salih HR. Glucocorticoid-induced tumor necrosis factor receptor-related protein ligand subverts immunosurveillance of acute myeloid leukemia in humans. Cancer Res. 2009 Feb 1;69(3):1037-45

Cho JS, Hsu JV, Morrison SL. Localized expression of GITR-L in the tumor microenvironment promotes CD8+ T cell dependent anti-tumor immunity. Cancer Immunol Immunother. 2009 Jul;58(7):1057-69

Duan F, Lin Y, Liu C, Engelhorn ME, Cohen AD, Curran M, Sakaguchi S, Merghoub T, Terzulli S, Wolchok JD, Houghton AN. Immune rejection of mouse tumors expressing mutated self. Cancer Res. 2009 Apr 15;69(8):3545-53

Piao J, Kamimura Y, Iwai H, Cao Y, Kikuchi K, Hashiguchi M, Masunaga T, Jiang H, Tamura K, Sakaguchi S, Azuma M. Enhancement of T-cell-mediated anti-tumour immunity via the ectopically expressed glucocorticoid-induced tumour necrosis factor receptor-related receptor ligand (GITRL) on tumours. Immunology. 2009 Aug;127(4):489-99

Vecchiarelli A, Pericolini E, Gabrielli E, Agostini M, Bistoni F, Nocentini G, Cenci E, Riccardi C. The GITRL-GITR system alters TLR-4 expression on DC during fungal infection. Cell Immunol. 2009;257(1-2):13-22

You S, Poulton L, Cobbold S, Liu CP, Rosenzweig M, Ringler D, Lee WH, Segovia B, Bach JF, Waldmann H, Chatenoud L. Key role of the GITR/GITRLigand pathway in the development of murine autoimmune diabetes: a potential therapeutic target. PLoS One. 2009 Nov 20;4(11):e7848

Gonçalves-Sousa N, Ribot JC, deBarros A, Correia DV, Caramalho I, Silva-Santos B. Inhibition of murine gammadelta lymphocyte expansion and effector function by regulatory alphabeta T cells is cell-contact-dependent and sensitive to GITR modulation. Eur J Immunol. 2010 Jan;40(1):61-70

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