

Gene Section

Mini Review

TNF (tumor necrosis factor (TNF superfamily, member 2))

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Identity

Other names: TNFa (Tumor Necrosis Factor-a)
Cachectin; TNF superfamily member 2; DIF

HGNC (Hugo): TNF

Location: 6p21.3

DNA/RNA

Description

The human TNFa gene has 4 exons spanning 2,762bp on the region of chromosome 6p21.3. The expression of TNFa gene generates a TNFa mRNA with size of 1,669nt. The 3'-UTR region of TNFa mRNA contains a cluster of "AUUUA" elements that can be seen among many mRNAs with a short half-life, (AUUAUUUAUUUAUUUAUUUAUUU-AUUUAUUUAUUUA). A multiple NF-kB binding elements have been identified in the promoter region of TNFa gene.

Protein

Description

The human TNFa protein contains 233 amino acids with a predicated molecular weight of 25.6 kDa. The TNFa is produced initially in a membrane-associated form, which is then subjected to enzymatic remove of the N-terminal 76 amino acids by TACE/ADAM17, a TNFa converting enzyme, to generate the soluble 17kDa TNFa molecule that forms homotrimer. TNFa is the first prototypic member identified in the TNF superfamily (TNFSF, Fig.1 and Table 1). The human

TNF superfamily currently has 19 well-characterized members. Other members, such as TNFSF19, TNFSF21, and TNFSF22 have not been well-established. Although each member has its own receptor preference, a functional overlapping, such as induction of apoptosis and NF-kB activation, has been observed among the majority of these members. In addition, as indicated in the phylogenetic tree in Figure 1, all of these members exhibit an evolutionary conservation in their amino acid sequences, many of which show characteristics of type II membrane proteins. These features of TNF superfamily suggest that the members in this family may derived from the same ancestral gene. Several members contain a C-terminal conserved domain, named the TNF-homology domain that shares 20-30% of sequence identity. Except TNFSF1 (lymphotoxin a) and TNFSF3 (lymphotoxin b) that can form either homotrimer or heterotrimer, the active form of other members in this family is homotrimer.

Expression

TNFa is expressed virtually in every type of cells in response to inflammatory signals.

Localisation

Membrane (type II membrane protein), extra-cellular soluble form, blood stream, and biological fluids.

Function

The most abundant cellular sources of TNFa are macrophage and monocyte. In response to inflammatory stimulation, macrophage or monocyte secretes TNFa that can induce apoptotic or necrotic cell death of certain tumor cell lines.

Fig.1. The phylogenetic tree of TNF superfamily members.

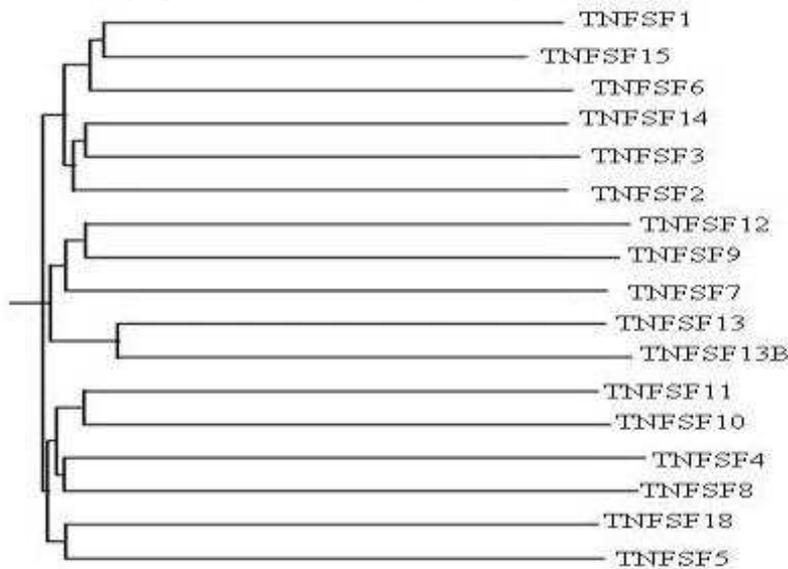


Table 1. TNF superfamily members.

TNF Superfamily Member	Original Name	Other Name	Chromosome	Protein ID
TNFSF1	Lymphotoxin α	TNF β	6p21.3	NP_000586
TNFSF 2	TNF α	Cachectin	6p21.3	NP_000585
TNFSF 3	Lymphotoxin β	TNFC	6p21.3	NP_002332
TNFSF 3L	TAG7	PGRP, P23	19	NP_005082
TNFSF 4	OX40L	GP34, CD134L	1q25	NP_003317
TNFSF 5	CD40L	CD154, TRAP	Xq26	NP_000065
TNFSF 6	FasL	CD95L, CD178	1q23	NP_000630
TNFSF 7	CD27L	CD70	19p13	NP_001243
TNFSF 8	CD30L	CD153	9q33	NP_001235
TNFSF 9	4-1BB-L		19p13.3	NP_003802
TNFSF 10	APO2-L	TRAIL	3q26	NP_003810
TNFSF 11	RANK1	Osteoprotegerin ligand TRANCE	13q14	NP_003692
TNFSF 12	TWEAK		17p13.3	NP_003800
TNFSF 13	APRIL	TALL2	17p13.1	NP_003808
TNFSF 13B	BAFF	TALL1, THANK	13q32-34	NP_006564
TNFSF 14	LIGHT	HVEML	19p13.3	NP_003798
TNFSF 15	TL1	VEGI	9q33	NP_005109
TNFSF 18	AITRL	GITRL	1q23	NP_005083

The phylogenetic tree of TNF superfamily members.

In addition, TNF α is also capable of inducing cell proliferation and differentiation in many types of cells under certain circumstances. TNF α can be a pyrogen that causes fever by its direct action or by stimulation of interleukin 1 secretion. Sustained generation of TNF α in a variety of human diseases, especially cancer and severe infection, can cause cachexia-like syndrome. The increased expression of TNF α in adipose tissue was considered to be responsible for the development of obesity or diabetes due to the induction

of insulin resistance by TNF α . All of above functional characteristics of TNF α are executed through specific members of the TNF receptor (TNFR) superfamily, mainly TNFR1, the primary receptor for soluble TNF α , and TNFR2, the predominant receptor for membrane-associated TNF α . These receptors trigger several intracellular signaling pathways, most importantly, the I κ B kinase (IKK) and mitogen-activated protein kinase (MAPK) cascades, which govern gene expression through NF- κ B and AP-1 transcription factors, respectively.

Implicated in

Disease

Arthritis, asthma, cancer, cardiovascular disorders, diabetes, HIV infection and AIDS, inflammatory bowel disease, lung fibrosis, obesity, septic shock, etc.

Cytogenetics

Mutations or polymorphisms in the promoter or coding region of TNF α gene have been associated with asthma, celiac, septic shock susceptibility, silicosis, Psoriasis, GVHD, Leprosy, etc.

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