

Tumor necrosis factors

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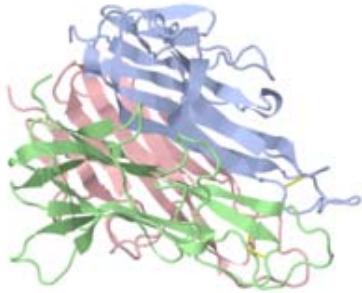


Figure 1
Trimeric structure of TNF alpha, produced by *Mus musculus*, based on PDB structure 2TNF (1.4 Å Resolution). Different colors represent different monomers. Baeyens, KJ et al. (1999).^[1] Figure rendered using FirstGlance Jmol.

Tumor necrosis factors (or the **TNF family**) refer to a group of cytokines that can cause cell death (apoptosis). The first two members of the family to be identified were:

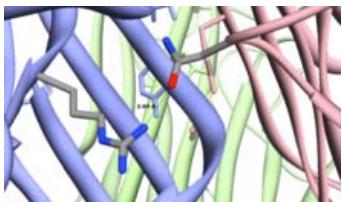
- Tumor necrosis factor (TNF), formerly known as TNF α or TNF alpha, is the best-known member of this class. TNF is a monocyte-derived cytotoxin that has been implicated in tumor regression, septic shock, and cachexia.^{[2][3]} The protein is synthesized as a prohormone with an unusually long and atypical signal sequence, which is absent from the mature secreted cytokine.^[4] A short hydrophobic stretch of amino acids serves to anchor the prohormone in lipid bilayers.^[5] Both the mature protein and a partially processed form of the hormone can be secreted after cleavage of the propeptide.^[5]
- Lymphotoxin-alpha, formerly known as Tumor necrosis factor-beta (TNF- β), is a cytokine that is inhibited by interleukin 10.^[6]

Family members

Nineteen cytokines have been identified as part of the TNF family on the basis of sequence, functional, and structural similarities.^[7] They include:^{[8][9][10]}

- Tumor Necrosis Factor (TNF) (also known as cachectin^[11] or TNF alpha)^{[12][13]} is a cytokine that has a wide variety of functions. It can cause cytolysis of certain tumor cell lines; it is involved in the induction of cachexia; it is a potent pyrogen, causing fever by direct action or by stimulation of interleukin-1 secretion; it can stimulate cell proliferation and induce cell differentiation under certain conditions.
- Lymphotoxin-alpha (LT-alpha) and lymphotoxin-beta (LT-beta), two related cytokines produced by lymphocytes that are cytotoxic for a wide range of tumor cells in vitro and in vivo.^[14]

- T cell antigen gp39 (CD40L), a cytokine that seems to be important in B-cell development and activation.
- CD27L, a cytokine that plays a role in T-cell activation. It induces the proliferation of co-stimulated T cells and enhances the generation of cytolytic T cells.
- CD30L, a cytokine that induces proliferation of T cells.
- FASL, a cytokine involved in cell death.^[15]
- 4-1BBL, an inducible T cell surface molecule that contributes to T-cell stimulation.
- OX40L, a cytokine that co-stimulates T cell proliferation and cytokine production.^[16]
- TNF-related apoptosis inducing ligand (TRAIL), a cytokine that induces apoptosis.^[17]



Model of hydrogen bond between Asn34 of subunit A and Arg82 of subunit C, produced by *M. musculus*, based on PDB structure 2TNF. The residues participating the hydrogen bond are shown in stick. The short bond length, 2.84Å, highly suggests a strong hydrogen bond that supports the tertiary structure. Baeyens, KJ et al. (1999).^[11] Generated in Chimera.

All these cytokines seem to form homotrimeric (or heterotrimeric in the case of LT-alpha/beta) complexes that are recognized by their specific receptors. Strong hydrogen bonds between the monomers stabilize the tertiary structure. One such example is the Asn34-Arg82 hydrogen bond in the *M. musculus* TNF alpha.^[11] The PROSITE pattern for this family is located in a beta-strand in the central section of the protein that is conserved across all members.

All members of the TNF family, with the exception of the secreted lymphotoxin and a proliferation-inducing ligand (APRIL), are type II transmembrane proteins that protrude from immune cells. Such membrane-bound TNF ligands frequently signal back to the immune cells when they contact and bind their cognate receptors on other cells.^[17]

Cytokines can be grouped into a family on the basis of sequence, functional and structural similarities.^{[8][9][10]} Tumor necrosis factor (TNF) (also known as TNF alpha or cachectin) is a monocyte-derived cytotoxin that has been implicated in tumour regression, septic shock and cachexia.^{[2][3]} The protein is synthesised as a prohormone with an unusually long and atypical signal sequence, which is absent from the mature secreted cytokine.^[4] A short hydrophobic stretch of amino acids serves to anchor the prohormone in lipid bilayers.^[5] Both the mature protein and a partially processed form of the hormone are secreted after cleavage of the propeptide.^[5]