Tumor necrosis factor (TNF) is a potent cytokine that mediates many biological events, including proliferation of fibroblasts and T-cells, induction of NF-κB, cytotoxicity, tumor necrosis as well as antiviral, inflammatory, and immunoregulatory responses. TNF has been implicated as a central mediator of septic shock as well as graft-vs-host disease, arthritis, and several autoimmune disorders. There are two related TNF molecules, TNFα (tumor necrosis factor or cachectin) and TNFβ (lymphotoxin). TNFα is produced mainly by T-cells, macrophages, and mast cells, whereas TNFβ is produced by activated lymphocytes. TNFα and β mediate their actions by binding to two distinct cell surface receptors, TNF-R1 (55 kDa also known as TNFRβ and TNF-R55) and TNF-R2 (75 kDa, also known as TNFRα, and TNFR-75). Both receptors are found on most cell types.

Both TNF receptors are members of a receptor superfamily whose members include the type 1 membrane proteins CD30, CD40, NGFR, OX40, 4-1BB, PV-T2, TNFR-RP, CD27, and Fas (1). They are activated by ligand binding leading to receptor oligomerization, similar to tyrosine kinases (2). Their extracellular domains consist of highly conserved cysteine-rich pseudorepeats.
The highly conserved placement of the cysteine residues suggests a common structural pattern. The cytoplasmic domains are usually small with little sequence homology among members. Consistent with their family members, TNF-R1 and TNF-R2 are most homologous in their extracellular domains, made up of highly conserved cysteine-rich domains. In contrast, their intracellular domains do not show extensive sequence homology suggesting that the receptors may activate different signaling pathways (2). Although the cytoplasmic domains of TNF-R1 and R2 are not homologous, the cytoplasmic domain of TNF-R1 is homologous to another family member, Fas (reviewed in ref. 1). TNF-R1 and Fas share homology in a 65-residue region, known as the death domain, that has been shown to be important in the process of apoptosis (programmed cell death). The death domain of TNF-R1 has been identified as an 80 amino acid domain within the intracellular region (3). Mutations within this region not only alter cell death signaling, but also interfere with the antiviral activity of TNF-R1 and are thought to be important in mediating many of the cellular responses induced by activation of TNF-R1.

Several studies have sought to elucidate the individual roles of each receptor. Studies using antibodies have indicated that TNFR-1 is involved in cell death, antiviral activity, and cytokine production, whereas TNFR-2 is involved in T-cell development and the proliferation of cytotoxic lymphocytes (3–6). Although only TNF-R1 contains a death domain, some reports have suggested both receptors are involved in the process of apoptosis (7). However, the precise function of the two receptor types is largely unknown. Since the intracellular domains of TNF-R1 and R2 are not homologous, it is predicted that they activate different signaling pathways. This is supported by recent reports identifying specific intracellular proteins that bind to either TNF-R1 or R2. One such protein, TNF-R1-associated death domain protein (TRADD) has been shown to interact specifically with an intracellular domain of TNF-R1, but not TNF-R2 (8). Overexpression of TRADD induces cellular responses attributed to TNF-R1, such as apoptosis and NF-κB activation. Proteins that specifically interact with TNF-R2 have also been found. Two related proteins, TNF receptor associated factor 1 and 2 (TRAF1 and TRAF2) have been shown to associate with sequences in the cytoplasmic domain of TNF-R2 (9). The characterization of