Immunity
Review



# The TNF Receptor Superfamily in Co-stimulating and Co-inhibitory Responses

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Cytokines related to tumor necrosis factor (TNF) provide a communication network essential for coordinating multiple cell types into an effective host defense system against pathogens and malignant cells. The pathways controlled by the TNF superfamily differentiate both innate and adaptive immune cells and modulate stromal cells into microenvironments conducive to host defenses. Members of the TNF receptor superfamily activate diverse cellular functions from the production of type 1 interferons to the modulation of survival of antigen-activated T cells. Here, we focus attention on the subset of TNF superfamily receptors encoded in the immune response locus in chromosomal region 1p36. Recent studies have revealed that these receptors use diverse mechanisms to either co-stimulate or restrict immune responses. Translation of the fundamental mechanisms of TNF superfamily is leading to the design of therapeutics that can alter pathogenic processes in several autoimmune diseases or promote immunity to tumors.

## Introduction

The tumor necrosis factor superfamilies of ligands (TNFSF) and receptors (TNFRSF) provide key communication signals between various cell types during development, especially in the skin, bones, and lymphoid organs, and maintain organ homeostasis and initiate tissue responses (Locksley et al., 2001; Šedý et al., 2015). The TNF-related ligands are defined by structural homology in their ectodomain and assemble into trimers that form a highly efficient receptor-clustering and signal-initiating mechanism (Bodmer et al., 2002). TNF receptors (TNFRs) share a conserved ectodomain defined by a cysteine-rich signature. High-affinity binding of their specific TNFSF ligands induces clustering of receptors expressed in the cognate target cell, which in turn initiates signal-transduction pathways culminating in cellular responses. The cytosolic signaling domain subdivides TNFRSF receptors into those utilizing the death domain, those engaging the TRAF family of ubiquitin E3 ligases (Li et al., 2013), and those lacking a cytosolic domain and functioning as decoy receptors. Depending upon the specific cellular circumstance, the outcome of TNFR signaling can be cellular life, death, or differentiation. However, rational prediction of the cellular and physiologic outcomes initiated by a TNFR remains a skill unperfected. Predictive principles start with the patterns of ligand-receptor specificity and cellular expression profiles to define likely cellular interactions (Figure 1). Both ligands and receptors often show idiosyncratic posttranslational processing mechanisms, e.g., cleavage of membrane ligands into soluble proteins, which dramatically alter the communication loop from a closed cell-to-cell-contact mechanism to a potential systemic impact. The diversity of intracellular signaling cascades set in motion by receptor activation creates dynamic diversity, further lessening the accuracy of our predictive attempts. Predictive capability remains a goal that has important consequences for interpreting results in physiologic models and human clinical trials.

Naive lymphocytes require both engagement with antigen receptors and signals from additional receptors for optimal activation, proliferation, and differentiation. Here, our attention focuses on the subset of TNF superfamily members that provide co-stimulatory or co-inhibitory signals essential for innate and adaptive immunity with an emphasis on T cell responses. The TNFRs with a co-stimulatory reputation are encoded by genes residing within an immune-response locus in chromosomal region 1p36 and include GITR (glucocorticoid-induced tumor necrosis factor), OX40, HVEM (herpesvirus entry mediator), DR3 (death receptor 3), 4-1BB, CD30, and TNFR2 (tumor necrosis factor receptor 2); these are derived from genomic evolution in chromosomal region 12p13, encoding CD27, LTβR, and TNFR1. Their corresponding TNFSF ligands are encoded by genes residing within the major histocompatibility complex (MHC) paralogous regions on chromosomes 1, 6, 9, and 19 (Table 1). However, the extensive shared ligand and receptor usage of TNFSF ligands by several of the receptors creates a communication network among distinct cells and tissues that regulate co-stimulatory and inhibitory pathways, providing mechanisms for initiating immunity and resetting homeostasis (Figure 2A). An emerging feature of several of these TNFRSF members is co-signaling in regulatory T (Treg) cells to suppress immune responses. As a second mechanism of restricting immune responses, the TNFRSF member HVEM activates an IgSF checkpoint receptor. Interestingly, cooperative signaling via TNFRs was first recognized with the CD40 system, which enhanced the proliferation of antigen-activated B cells, driven by expression of CD40 ligand in $CD4^+$ T helper cells (Beiske et al., 1988). Co-signaling in B cells is not limited to CD40, given that critical survival signals for B cells provided by the BAFFR system underscore the essential nature of this TNFRSF member in lymphocyte co-signaling (Mackay and Schneider, 2009). The diversity in expression of the ligands and receptors creates important communication lines between lymphocytes and many other cell types.

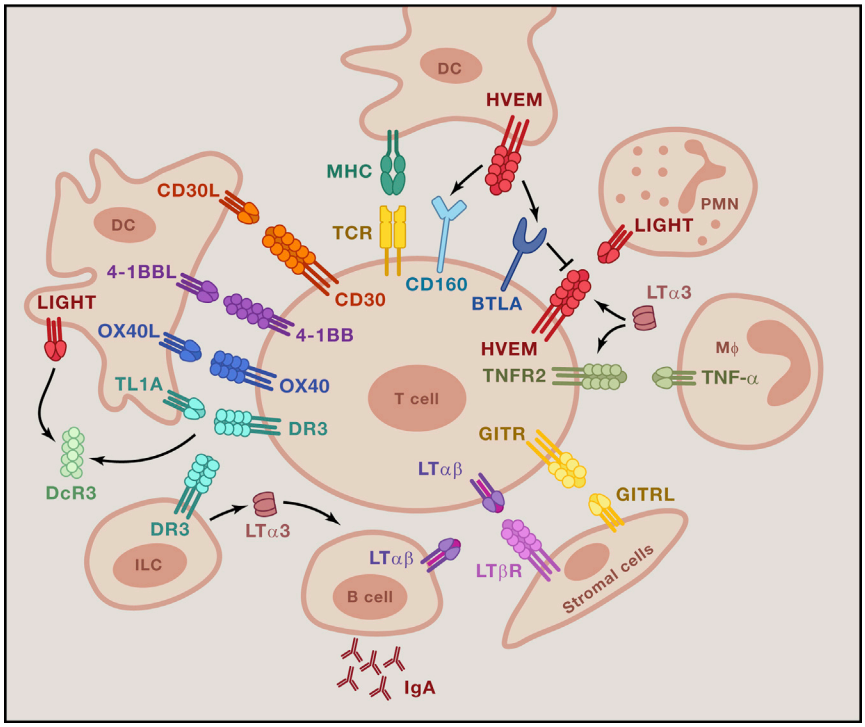


**Figure 1. Intercellular Networks Formed by the Co-signaling TNFRSF**

Many of the co-signaling TNFRSF members are expressed in activated T lymphocytes, and their specific ligands are expressed in professional APCs, neutrophils, macrophages, or stromal cells. The membrane-anchored expression pattern restricts signaling to cell-to-cell contact, whereas some ligands or receptors are shed into soluble forms that can act systemically.

Targeting TNF with antibody or receptor antagonists that block ligand-receptor binding proved enormously effective in treating some but not all human autoimmune diseases, yet not all patients were helped, revealing subsets of clinically defined disease and perhaps reflecting distinct mechanisms (Croft et al., 2013). Members of the co-regulatory TNF superfamily possess the functional and physiologic profiles worthy of consideration as therapeutic targets for intervention in autoimmune diseases or cancer. Both agonists to promote enhanced immune responsiveness in cancer and antagonists to restrict proinflammatory responses in autoimmune diseases are in consideration, and initial clinical trials support this contention but also reveal unexpected results. Applying our understanding of the mechanisms of action of these members of the TNF superfamily could help achieve therapeutic effectiveness in human disease.

## The 1p36 Co-signaling TNFRs

### *TNFR2*

TNFR2 binds the cognate ligand TNF-α (encoded by *TNF*), a type II transmembrane protein, to the secreted ligand lymphotoxin-α (LTα, encoded by *LTA*) (Etemadi et al., 2013), both of which also bind TNFR1. The activation of TNFR2 is primarily considered to trigger the pro-survival NF-κB pathway via E3 ligases TRAF2 and TRAF3, whereas the activation of TNFR1 (TNFRSF1A) recruits TRADD to the cytoplasmic death domain and activates caspase-dependent pathways (Brenner et al., 2015). TNFR2 expression is mainly restricted to immune cells and some other cell types, whereas TNFR1 shows ubiquitous expression. TNF-α is released from the cell surface by the metallopeptidase ADAM17, which is also involved in shedding TNFR2 during activation of effector T cells. Elevated levels of TNF-α and TNFR are often detected in circulation during infection and autoimmune disease (Faustman and Davis, 2013).

TNFR2 in activated T cells provides a co-stimulatory signal required for T cell expansion and effector differentiation. Naive T cells require activation signals to express TNFR2. Several studies have suggested that the immune modulatory role of TNFR2 is primarily in Treg cells because TNFR2 expression is higher in Foxp3$^+$ Treg cells than in naive CD4$^+$ T cells. The activation of TNFR2 is important for proliferation, survival, and lineage stability of Treg cells, as well as the development of thymic Treg cells from Treg precursor cells (Chen et al., 2013; Horwitz et al., 2013; Mahmud et al., 2014). TNFR2 also limits CD8$^+$ T-cell-mediated viral clearance and anti-tumor immunity. Several studies have shown that TNFR2 expression in CD8$^+$ T cells reduces the accumulation of functional CD8$^+$ T cells during viral or tumor challenge (Bertrand et al., 2015; DeBerge et al., 2015; Kim et al., 2009; Wortzman et al., 2013b). During acute influenza infection, the interaction between TNF and TNFR2 leads to rapid contraction of CD8$^+$ T cells and reduces the immunopathology by decreasing the levels of bioactive TNF as a result of increased soluble TNFR2 in the lungs. Similarly, genetic or pharmacologic inactivation of TNF or TNFR2 in mice during tumor challenge reduces the tumor burden linked to increased numbers of functional CD8$^+$ T cells in the tumor microenvironment (Calzascia et al., 2007; Kim et al., 2009).

The adverse recurrence of viral and bacterial infection observed in patients who receive TNF-depleting therapy (Faustman and Davis, 2013) points to TNF as a critical mediator of host defense. In addition, adverse neurologic disease could be due to TNFR2 expression in oligodendrocytes (Arnett et al., 2001; Patel et al., 2012), astrocytes (Patel et al., 2012), and endothelial cells (Venkatesh et al., 2013), and it is important for cell survival and regeneration (Faustman and Davis, 2010). A point mutation in *TNFR2* indicates an important link in patients with T cell lymphoma, including mycosis fungoides and Sézary syndrome (Ungewickell et al., 2015). The identified mutant TNFR2 p.Thr377Ile resides in the TRAF2 binding region, and the mutation leads to enhanced NF-κB activation and increase expression of TNFR2. This mutation implicates the need for caution in utilizing agonists of TNFR2 for treatment of autoimmune diseases.