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# Physiological functions of tumor necrosis factor and the consequences of its pathologic overexpression or blockade: Mouse models

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**Abstract**

TNF is an exciting cytokine which has helped to establish many paradigms in immunology. Although TNF itself has found only very limited use in the clinic, anti-cytokine therapy, which targets this single molecule, has enjoyed astounding success in treatment of a growing number of human diseases. However, since TNF mediates unique physiologic functions, in particular those related to host defense, TNF blockade may result in unwanted consequences. Much of our understanding about TNF intrinsic functions in the body, as well as about consequences of its overexpression and ablation, is based on studying phenotypes of various genetically engineered mice. Here we review mouse studies aimed at understanding TNF physiologic functions using transgenic and knockout models, and we discuss additional mouse models that may be helpful in the future.


*Keywords:* Knockout; Transgenic mice; Disease models; Anti-cytokine therapy

## 1. Introduction

Tumor necrosis factor (TNF, TNFα) was discovered because of its striking anti-tumor activity in mice [1]. Under a different name the same molecule was later purified and cloned by Cerami and co-workers [2]. Today's knowledge puts TNF downstream of many, if not all, pattern-recognition receptors, including Toll-like receptors [3], as well as various cytokine receptors and the T-cell receptor (TCR). Although TNF was initially identified as a product of activated macrophages, and its production was greatly enhanced by challenging mice with the combination of Mycobacteria and bacterial endotoxin [1], it was later found to be produced by many types of leukocytes, as well as by some non-hematopoietic cells (for review see [4]). Since the main signaling receptor, TNFR1 or p55, is expressed on most cell lineages, one can expect that communications between cells via TNF are complex and may have local as well as global consequences.

Pre-knockout studies identified two important opposite functions of TNF in host defense: a seemingly ''deleterious'' one, due to systemic overproduction which resulted in lethal septic shock [5], and an apparent ''beneficial'' effect due to the stimulation of protective granuloma formation during mycobacterial infections [6,7]. Later studies utilizing

*Abbreviations:* TNF, tumor necrosis factor; LTi, lymphoid tissue inducer cells; LPS, lipopolysaccharide; FDC, follicular dendritic cells; MZ, marginal zone; PP, Peyer's patches; LN, lymph node.

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knockout mice uncovered a constellation of beneficial and detrimental effects that TNF may exert in the body. Even before the whole range of intrinsic biological effects of TNF was revealed through mouse studies [8–14], pathologic consequences of TNF production were noticed in humans, and, as a result, anti-TNF therapy was proposed [15]. The underlying concept behind this therapeutic approach is based on the widely publicized notion of "bad TNF" [16], neglecting somewhat the many beneficial and unique functions of TNF identified through knockout studies. However, the successful application of anti-TNF treatment for a growing list of autoimmune and other diseases, where patients remain on continuous TNF blockage for the rest of their lives, reinforced interest in TNF biology [17,18].

In this chapter we review mouse studies aimed at understanding TNF intrinsic physiologic functions – both the seemingly deleterious and the seemingly beneficial – using numerous transgenic and knockout animal models.

## 2. Dissection of multiple TNF functions by gene targeting

### 2.1. Overview of TNF functions revealed in TNF- and TNFR-knockout studies

In the first knockout mice which highlighted critical TNF functions, it was TNF receptor I (TNFR1, p55) rather than the cytokine itself that was ablated by gene targeting [19,20]. Two main functions of TNFR signaling were reported: its protective role in intracellular bacterial infections (Listeria), and its detrimental role in LPS/D-gal mediated liver toxicity [19,20]. Since at that time lymphotoxin-alpha (LTα, formerly known as TNF-β), a TNF-like cytokine produced by activated lymphocytes and NK cells, was considered as the second *in vivo* ligand for TNFR1 [21], the interpretation of TNFR1 KO phenotype in terms of signaling pathways was not straightforward. However, later studies have clarified that the primary *in vivo* functions of lymphotoxin are mediated by a separate

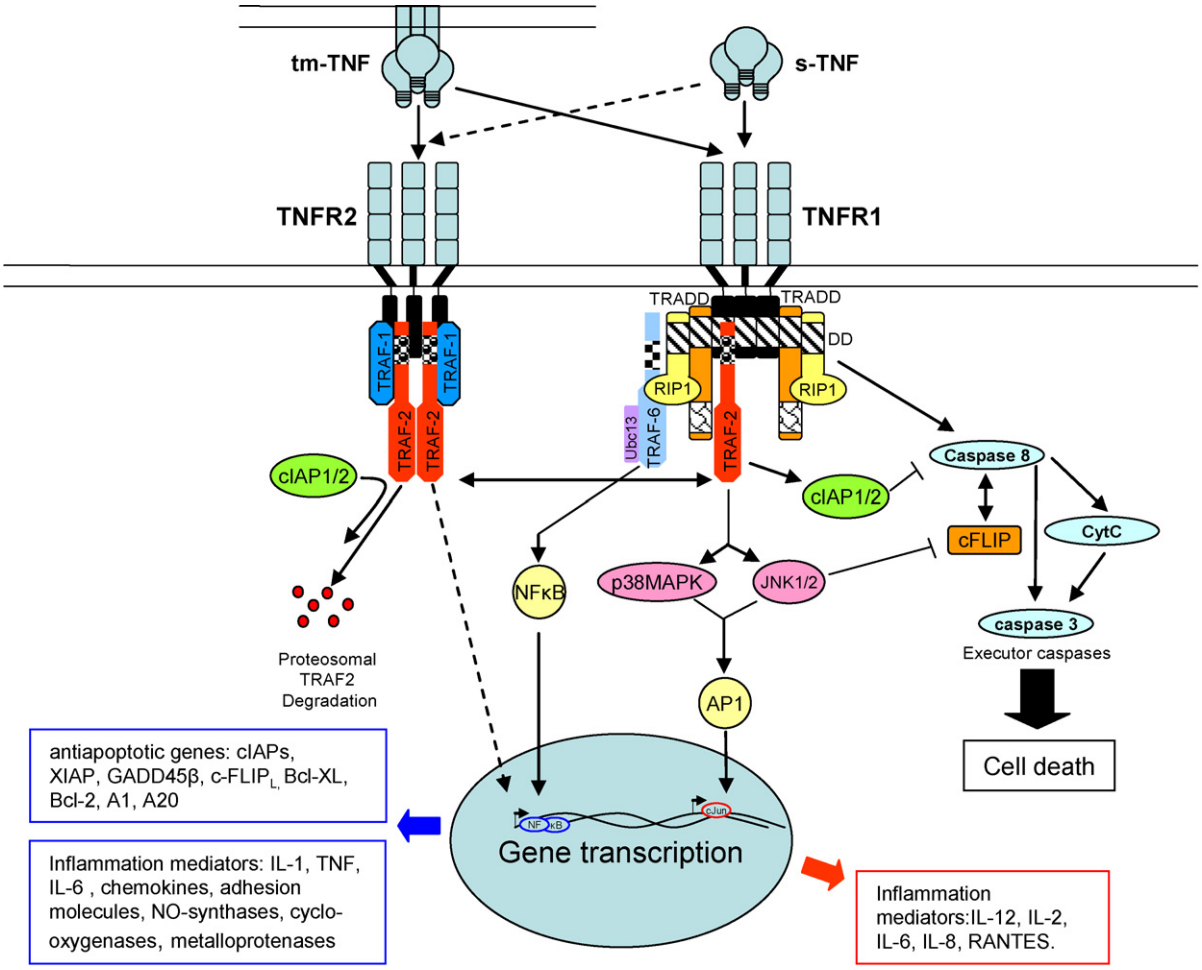


Fig. 1. Tumor necrosis factor receptor 1 (TNFR1) and TNFR2 signaling pathways. TNF activates both survival and proliferation pathways along with apoptotic pathways via TNFR1. According to Micheau and Tschopp (Cell 2003;114:181–90), pro-apoptotic signaling is triggered by a distinct cytoplasmic complex. TNFR2 plays an important role in regulation of apoptosis through TNFR1; however, molecular details of TNFR2 involvement in the regulation of survival-death remain unclear. Abbreviations: cIAP 1/2, cytoplasmic inhibitor of apoptosis 1/2; JNK, cJun N-terminal kinase; p38MAPK, p38 mitogen-activated protein kinase; RIP, receptor interacting protein; ROS, reactive oxygen species; TRADD, TNF receptor-associated DD; TRAF1/2/6, TNF receptor-associated factor 1/2/6, DD, death domain.