Overview of TNF Superfamily: 
A Chest Full of Potential Therapeutic Targets

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Abstract
Since the discovery of tumor necrosis factor TNFα about 25 years ago, TNF superfamily has grown to a large family of related proteins consisting of over 20 members that signal through over 30 receptors. Members of this superfamily have wide tissue distribution and play important roles ranging from regulation of the normal biological processes such as immune responses, hematopoiesis and morphogenesis to their role in tumorigenesis, transplant rejection, septic shock, viral replication, bone resorption and autoimmunity. Thus, many approaches to harness the potency of TNF superfamily members to treat human diseases have been developed. Indeed, TNF and TNF agonistic molecules have been approved for human use in the United States and other countries. Many other TNF family members show promise for several therapeutic applications, including cancer, infectious disease, transplantation and autoimmunity. This chapter will give overview of TNF superfamily for exploitation for therapeutic use in humans.

Introduction
In middle of the nineteenth century, a surprising observation was made that in some cancer patients spontaneous regression of their tumors occurred if they were infected with bacterial infections. This landmark discovery led to the idea of existence of a tumor necrotizing molecule and use of Coley’s toxins (bacterial extracts) for the treatment of human cancers. A century later, a factor from bacterial extracts, lipopolysaccharide (LPS), was isolated that was identified to be responsible for anti-tumor effects. This effect of LPS on tumor regression was later shown to be due to induction of a factor in the serum. This factor was named as tumor-necrotizing factor and later designated as tumor-necrosis factor (TNF). Subsequently TNF was isolated and its gene was cloned and TNF became the prototype of a rapidly growing family of related proteins now called the TNF superfamily.

The TNF superfamily is now composed of over 20 TNF-related ligands all sharing many key structural features. A majority of these ligands are synthesized as type II transmembrane proteins. These ligands contain a relatively long extracellular domain and a short cytoplasmic region. Their extracellular domains can be cleaved by specific metalloproteinases to generate a soluble molecule. In general, cleaved and noncleaved ligands are active as noncovalent homotrimers, although some members can also exist as heterotrimers. Both membrane-bound and secreted ligands are expressed by a variety of normal and malignant cell types. Since most of TNF-superfamily members are expressed as transmembrane cell surface proteins, it is believed they are acting at a local level. Key members of this family include APRIL, BAFF, 4-1BBL, CD30L, CD40L, CD70, CD95L, OX40L, LTα, LTβ, RANKL, NGF, TNFα and TRAIL (Fig. 1). More than 30 receptors for the TNF ligands belonging to the TNF receptor (TNFR) superfamily have been identified in

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humans and in mice. These receptors are type I membrane proteins characterized by the presence of a distinctive cystein-rich domain in their extra-cellular portion. Most of TNF ligands bind to a single receptor, but few of them bind to more than one receptor. For example, TRAIL is known to bind five receptors (DR4, DR5, DcR1, DcR2 and OPG). TNF receptors exert their cellular responses through signaling sequences in their cytoplasmic regions.

Based upon these cytoplasmic sequences and signaling properties, the TNF receptors can be classified into three major groups. The first group includes receptors that contain a death domain (DD) in their cytoplasmic tail. These receptors include CD95, TNFR1, DR3, DR4, DR5 and DR6. Binding of TNF superfamily ligands to their DD containing receptors causes complex signaling through adaptor proteins, such as tumor necrosis factor receptor—associated death domain (TRADD), resulting in activation of the caspase cascade and apoptosis of the cell.

The second group of receptors contains one or more TNF receptor-associated factors (TRAF) interacting motifs (TIM) in their cytoplasmic tails. This group includes TNFR2, CD40, CD30, CD27, LT-βR, OX40, 4-1BB, BAFFR, BCMA, TACI, RANK, NGFR, HVEM, GITR, TROY, EDAR, XEDAR, RELT and Fn14. Ligand binding to TIM containing TNF receptors induces recruitment of TRAF family members and activation of cellular signaling pathways including activation of a nuclear factor-κB (NF-κB), Jun N-terminal kinase (JNK), p38, extracellular signal regulated kinase (ERK) and phosphoinositide-3 kinase. The third group of TNF receptor family members does not contain functional intracellular signaling domains or motifs. These receptors include DcR1, DcR2, DcR3 and OPG. Although this group of receptors lacks the ability to provide intracellular signaling, they can effectively act as decoys to compete for ligand binding and block the signaling through other two groups of receptors.

Signaling events induced by TNFR superfamily members regulate a very broad array of developmental processes and play pivotal roles in numerous biological events in mammals including induction of apoptosis, survival, differentiation and proliferation of cells. The majority of TNF superfamily ligands are predominantly expressed on cells involved in the immune system including B-cells, T-cells, NK cells, monocytes and dendritic cells. In contrast, TNF receptors are expressed by a wide variety of cells that have both hematopoietic and nonhematopoietic