Genes, Transcripts and Proteins of CD137 Receptor and Ligand

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CD137 and CD137L belong to the tumor necrosis factor (TNF) superfamily, a group of cysteine-rich cell surface molecules. With a few exceptions, both CD137 and its ligand, CD137L, are activation induced. CD137 activates CD8+ T cells more strongly than CD4+ T cells, and is a potent inducer of IFN-γ. Stimulation through CD137L also relays activation signals to B cells and monocytes. These signals elicit activation of NF-κB via the TRAF-NIK pathway and lead to the induction of a plethora of immune modulators that accentuate the ongoing immune reaction. CD137 and CD137L-deficient mice develop normally, have normal numbers of T and B cells and only demonstrate modest immune malfunction. However, in vivo administration of agonistic anti-CD137 mAb protects strongly against a variety of autoimmune and non-autoimmune diseases. The basis of this protection is unclear; however, it seems to involve an indoleamine dioxygenase (IDO)-dependent process in which pathogenic T cells are killed/suppressed by “regulatory CD11c+CD8+ T cells.” In this review, the origins and functional features of CD137 and CD137L are discussed.

1. Overview

Co-stimulation, an integral component of immune regulation, is required for progressive T cell activation. T cell activation without co-stimulation induces anergy in which subsequent stimulation inhibits T cell responsiveness (Schwartz, 1990). Since the description of the two-signal model for T cell activation by Bretscher and Cohn (1970), understanding of the activation requirements of T cells has progressed rapidly and attained further prominence with the emergence of the CD28-B7 pathway. Several immunological ideas have since been refined, and a clearer picture of the events is slowly emerging.
CD137 and CD137L are an important receptor–ligand pair that belong to the tumor necrosis factor (TNF) superfamily (Vinay and Kwon, 1998; Figure 1.1). This family includes proteins that have cytoplasmic death domains and can induce apoptosis, as well as others with no apparent homology in their cytoplasmic tails. The latter group of receptors is involved in gene activation and anti-apoptotic signaling. Signal transduction by members of this family occurs through TNF receptor-associated factors (TRAFs) which counteract apoptosis via inhibition of apoptosis proteins (IAPs) and/or nuclear factor kappa B (NF-κB) (Croft, 2003).

CD137 exists as both a 30-kDa monomer and a 55-kDa homodimer (Pollok et al., 1993). It is inducible (Kwon and Weisman, 1989; Pollok et al., 1993) and is primarily expressed on activated CD4+ and CD8+ T cells, activated dendritic cells (Pollok et al., 1993) and activated NK and NKT cells (Melero et al., 1998). It is constitutively expressed on primary human monocytes, blood vessel endothelial cells, and human follicular dendritic, and CD4+CD25+ regulatory T cells (Broll et al., 2001; Kienzel and von Kempis, 2000; Lindsted et al., 2003; McHugh et al., 2002). CD137 binds CD137 ligand (CD137L), a member of the TNF superfamily, and exists as a disulfide-linked homodimer (Goodwin et al., 1993). It is expressed