TRAIL AND ITS RECEPTORS

In 1995, tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) was identified based on its sequence homology to other TNF family members (1). Among members of the TNF family, TRAIL shares the highest sequence homology with Fas ligand (FasL, CD95L). However, unlike FasL, TRAIL appears to induce apoptosis of tumor cells but not most normal cells (2). To date, five receptors for TRAIL have been cloned: TRAIL-R1 (DR4, Apo2A) (3), TRAIL-R2 (DR5, TRICK, Killer) (3–8), TRAIL-R3 (DcR1, TRID, LIT) (6–9), TRAIL-R4 (DcR2, TRUNDD) (10), and osteoprotegerin (OPG) (11). Unlike other TRAIL receptors, which bind only to TRAIL, osteoprotegerin also binds to osteoprotegerin ligand (OPGL), TRANCE, and RANK ligand (RANKL). TRAIL-R1 and TRAIL-R2 contain intracellular death domains and induce, via coupling with intracellular adaptor proteins, the proteolytic cleavage of caspase-8 (12). Caspase-8 activation initiates the extrinsic and intrinsic apoptotic pathways, resulting in caspase-3 cleavage, which is an irreversible step in a cell’s commitment to apoptosis. Other TRAIL receptors do not generate death signals because TRAIL-R3 does not contain a death domain and is attached to the membrane by a glycolipid anchor (6,9), whereas the death domain of TRAIL-R4 is not functional (10) and OPG exists only in a soluble form (11). Therefore, TRAIL-R3 and TRAIL-R4 might act as decoy receptors by competing with other TRAIL receptors for TRAIL. The expression pattern of TRAIL receptors on certain cell lines might determine their sensitivity to TRAIL. However, the expression of TRAIL decoy receptors is not always related to a cell’s resistance to TRAIL-induced apoptosis (13). Other factors may, therefore, play more decisive roles in determining a cell’s sensitivity to TRAIL. In this review, we will focus on NF-κB and PPAR-γ, two transcription factors that were recently found to play important roles in TRAIL-induced apoptosis.
ROLES OF NF-κB IN TRAIL-INDUCED APOPTOSIS

The Rel/NF-κB family of transcription factors regulates a number of biological processes, including cell proliferation and differentiation, apoptosis, immune response, and inflammation (14–16). Rel/NF-κB are normally present in the cytoplasm in association with a family of inhibitors (IκBs) that mask their nuclear localization sequences (17,18). Activation of IκB kinase (IKK) leads to phosphorylation and degradation of IκBs. As a result, Rel/NF-κB are released and translocated to the nucleus, where they bind to DNA and induce the transcription of target genes (15).

Rel/NF-κB induce the expression of a number of anti-apoptotic genes, including cellular inhibitors of apoptosis (cIAPs), mitochondrial proteins of the Bcl-2 family such as Bfl-1/A1 and Bcl-XL, A20, manganese superoxide dismutase (MnSOD), IEX-1L, caspase 8/FADD-like IL-1β-converting enzyme (FLICE)-inhibitory protein (c-FLIP), TNF receptor-associated factor 1 (TRAF1) and 2 (TRAF2), and TRAIL receptor 3 (16,19–30). Numerous studies exist which demonstrate that Rel/NF-κB inhibit programmed cell death induced by TNF-α, anticancer drugs, and ionizing radiation (16,31–33).

Recently, it has also become clear that Rel/NF-κB regulate TRAIL-induced apoptosis. Thus, treatment of TRAIL-resistant pancreatic cancer cell line L3.6 with TRAIL and the NF-κB inhibitor NBD (NEMO-binding domain) peptide significantly decreased cell viability and increased apoptosis (34). This effect was most likely due to decreased FLIP levels in L3.6 cells as a result of NF-κB inhibition. Prostate cancer cell lines PC3AR and PC3Neo show different TRAIL sensitivities, which are associated with a difference in NF-κB levels in these cells (35). Blocking NF-κB function by adenoviral transfer of mutated IκB increased apoptotic responses, suggesting a direct role for NF-κB in this system.

Multiple myeloma (MM) is an incurable disease. TRAIL might represent a new treatment option, since it kills most MM cell lines and MM cells freshly isolated from patients. Treatment with the NF-κB inhibitor SN50 enhanced TRAIL-induced apoptosis in sensitive cells and reversed resistance of ARH-77 and IM-9 MM cells (36). Interestingly, treatment with SN50 did not sensitize normal B-lymphocytes towards TRAIL-induced apoptosis. Insulin-like growth factor-1 (IGF-1) promotes proliferation of MM cells and protects them against TRAIL-induced apoptosis. In a recent study, IGF-1 was shown to activate NF-κB and upregulate the expression of survival factors FLIP, survivin, cIAP-2, A1/Bfl-1, and XIAP (37). Overexpression of Akt decreased TRAIL sensitivity of MM cells. Interestingly, treatment of cells with an Akt inhibitor abrogated NF-κB activation and prevented the protective effect. These data show that besides NF-κB, the PI-3K/Akt pathway is also involved in the regulation of TRAIL sensitivity. An important role for NF-κB in TRAIL-induced apoptosis has also been demonstrated in lymphoid cell lines. Thus, acute T-cell leukemia cells (CEM, Jurkat) and BJAB cells (Burkitt lymphoma) treated with NF-κB inhibitors showed a significantly increased sensitivity towards TRAIL (38,39).

It has been previously reported that TRAIL, but not other TNF family members, induces apoptosis in the majority of melanoma cell lines (40–44). The mechanisms of TRAIL resistance of some melanoma cells are not well understood. Lack of response to TRAIL was partially due to a loss of TRAIL receptor expression (41). However, a clear correlation between expression of TRAIL decoy receptors and TRAIL resistance could