Molecular Pathways

Targeting TRAIL Agonistic Receptors for Cancer Therapy

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Abstract
Based on preclinical studies demonstrating that tumor necrosis factor – related apoptosis-inducing ligand (TRAIL) exerts a potent and cancer cell – specific proapoptotic activity, recombinant TRAIL as well as agonistic anti – TRAIL-R1 and anti – TRAIL-R2 antibodies recently entered clinical trials. Additionally, gene therapy approaches using TRAIL-encoding adenovirus (Ad-TRAIL) are currently being developed to overcome the limitations inherent to TRAIL receptor targeting, i.e., pharmacokinetic of soluble TRAIL, pattern of receptor expression, and tumor cell resistance. To optimize gene therapy approaches, CD34$^+$ cells transduced with Ad-TRAIL (CD34-TRAIL$^+$) have been investigated as cellular vehicles for TRAIL delivery. Transduced cells exhibit a potent tumor killing activity on a variety of tumor cell types both *in vitro* and *in vivo* and are also cytotoxic against tumor cells resistant to soluble TRAIL. Studies in tumor-bearing nonobese diabetic/severe combined immunodeficient mice suggest that the antitumor effect of CD34-TRAIL$^+$ cells is mediated by both direct tumor cell killing due to apoptosis and indirect tumor cell killing due to vascular-disrupting mechanisms. The clinical translation of cell and gene therapy approaches represent a challenging strategy that might achieve systemic tumor targeting and increased intratumor delivery of the therapeutic agent.

Background

Dysregulated apoptosis plays a key role in the pathogenesis and progression of neoplastic disorders, allowing tumor cells to survive beyond their normal life span and to eventually acquire chemoradioresistance (1, 2). Thus, apoptotic pathways represent attractive therapeutic targets for restoring apoptosis sensitivity of malignant cells or activating agonists of apoptosis. To modulate apoptotic genes and proteins, several strategies can be envisaged that target either the mitochondria-dependent (intrinsic) or the death receptor-dependent (extrinsic) pathways of apoptosis (3). Because of the ability of death receptor ligands to induce death in susceptible cell types, there has been considerable interest in the physiologic roles and therapeutic potential of these cytokines as anticancer agents. Death receptor ligands of the tumor necrosis factor α (TNFα) superfamily are type II transmembrane proteins that signal to target cells on cell-cell contact, or after protease-mediated release to the extracellular space (4). Four members of this family, namely, Fas ligand, TNFα, TL1A (a recently discovered TNF-like ligand), and TNF – related apoptosis-inducing ligand (TRAIL), stand out because of their ability to induce cell death (5, 6).

TRAIL, in its soluble form, is emerging as an attractive anticancer agent because of its cancer cell specificity and potent antitumor activity. *In vitro* several sets of evidence show that TRAIL selectively induces apoptosis in a variety of transformed cell lines (7 – 9); *in vivo* administration of TRAIL to mice exerts a remarkable activity against tumor xenografts of various cancers (10 – 15). Unlike other apoptosis-inducing TNF family members, soluble TRAIL seems to be inactive against normal healthy tissue (10), and reports in which TRAIL induces apoptosis in normal cells could be attributed to the specific preparations of TRAIL used in the experiments (16). The physiologic functions of TRAIL are not yet fully understood, but mouse gene knock-out studies indicate that this agent has an important role in antitumor surveillance by immune cells, mediates thymocyte apoptosis, and is important in the induction of autoimmune diseases (17 – 19). TRAIL signals by interacting with its receptors. Thus far, five receptors have been identified, namely, the two agonistic receptors, TRAIL-R1 (20) and TRAIL-R2 (21), and the three antagonistic receptors (22) TRAIL-R3 (23), TRAIL-R4 (24), and osteoprotegerin (OPG; ref. 25). Both TRAIL-R1 and TRAIL-R2 are type I transmembrane proteins containing a cytoplasmic death domain (DD) motif that engage apoptotic machinery upon ligand binding (7), whereas the other three receptors either act as decoys or transduce antiapoptotic signals (26). TRAIL-R3 and TRAIL-R4 have close homology to the extracellular domains of agonistic receptors. TRAIL-R4 has a truncated, nonfunctional cytoplasmic DD, whereas TRAIL-R3 exists on the plasma membrane as a glycophospholipid-anchored protein lacking the cytosolic tail. The physiologic relevance of OPG as a soluble receptor for TRAIL is unclear, but a recent study suggests that cancer-derived OPG may be an important survival factor in hormone-resistant prostate cancer cells (27).

TRAIL-Induced Apoptosis Signaling

TRAIL forms homotrimers that bind three receptor molecules, each at the interface between two of its subunits. A Zn atom bound to cysteine residues in the trimeric ligand is essential for trimer stability and optimal biological activity. Binding of TRAIL to the extracellular domain of agonistic receptors results in the trimerization of the receptors and clustering of the intracellular DDs, which leads to the recruitment of the adaptor molecule Fas-associated protein with death domain (FADD; Fig. 1). Subsequently, FADD recruits initiator caspase-8 and caspase-10, leading to the formation of the death-inducing signaling complex (DISC), in which initiator caspases autoactivate by proteolysis. Once they become enzymatically active, caspase-8 and/or caspase-10 are released from the DISC and signal through two different proteolytic pathways that converge on caspase-3 and lead to cellular disassembly (28). In type I cells, activation of initiator caspases upon death receptor ligation is sufficient to directly activate downstream effector caspases, such as caspase-3 and/or caspase-7 (29). This extrinsic pathway is independent of the mitochondria and is not blocked by overexpression of Bcl-2. In type II cells, the commitment from death receptor ligation to apoptosis is less direct (29). The amount of initially cleaved caspase-8 and/or caspase-10 is not enough to directly trigger effector caspase activation. Consequently, apoptotic signaling requires an amplification loop by mitochondrial pathway engagement through caspase-8 – mediated cleavage of Bid (BH3 interacting DD agonist), which, in turn, induces the cytosolic Bcl-2 family member Bcl-2 – associated X protein (Bax) and/or the loosely bound mitochondrial homologue Bcl-2 antagonist/killer (Bak) to insert into the mitochondrial membrane, where they contribute to the mitochondrial release of cytochrome *c* (30). In the cytosol, cytochrome *c* binds the adaptor protein apoptotic protease activating factor 1 (Apaf-1) to form an apoptosome with recruitment and activation of the apoptosis-initiating caspase-9, which proteolytically activates additional caspase-3. These events are further amplified by apoptogenic factors released from the mitochondrial space, including Smac/DIABLO [second mitochondrial activator of caspases/direct IAP-binding protein with low isoelectric point (p*I*)], which displaces the X-chromosome – linked inhibitor of apoptosis protein (XIAP) from caspase-3, caspase-7, and caspase-9 (31).

Clinical-Translational Advances

Apoptosis induction in response to most DNA-damaging drugs usually requires the function of the tumor suppressor p53, which engages primarily the intrinsic apoptotic-signaling pathway. In most human cancers, however, tumor progression as well as conventional treatments eventually select for tumor cells in which p53 is inactivated, resulting in resistance to therapy. Activation of the DD-containing TRAIL receptors represents an opportunity to exploit the extrinsic apoptotic pathway to destroy cancer cells, regardless of p53 status, and therefore, it might be a useful therapeutic strategy, particularly in cells in which the p53-response pathway has been inactivated, thus helping to circumvent resistance to chemo- and radiotherapy. Based on promising preclinical observations,
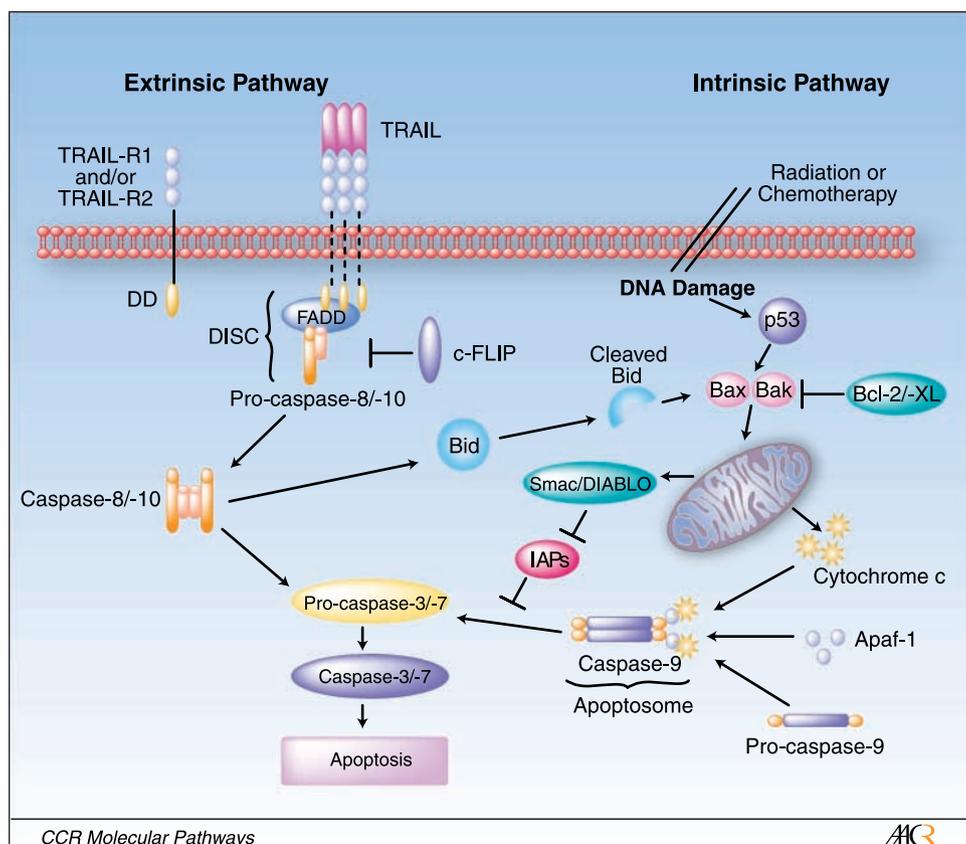

Fig. 1. Crosstalk between apoptosis signaling pathways following activation of death receptors. Death receptors trigger the cell-intrinsic pathway by activation of caspase-8 and caspase-10. Cleaved BID interacts with Bax and Bak, which in turn, activate caspase-9 and caspase-3, resulting in apoptosis induction through the cell-extrinsic pathway. In type I cells, death-receptor engagement of the cell-extrinsic pathway is sufficient for commitment to apoptotic death. In type II cells, commitment to apoptosis requires the amplification of the death-receptor signal by the cell-intrinsic pathway. Because death-receptor targeting and conventional agents induce tumor cell apoptosis through different signaling pathways, combinations of the two approaches might facilitate the killing of tumor cells that resist death induction through either one of the pathways.

Fig. 2. Therapeutic approaches to death receptor activation. TRAIL-R1 and TRAIL-R2 can be engaged by soluble TRAIL as well as the membrane-bound form of the ligand. Agonistic antibodies selectively bind either TRAIL-R1 or TRAIL-R2.
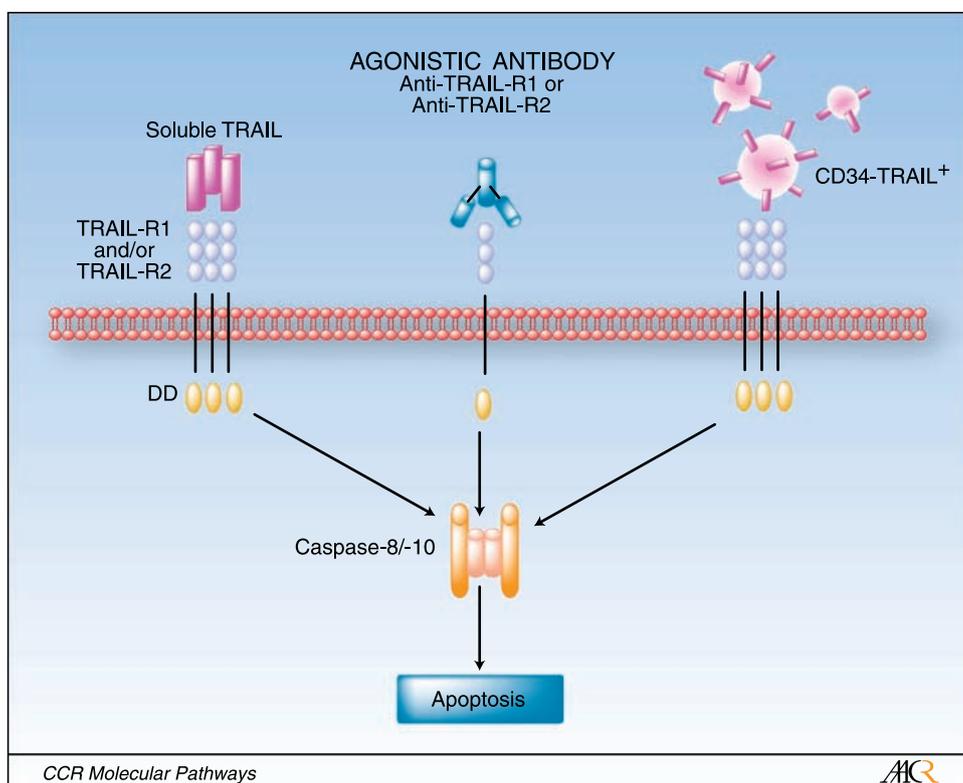
recombinant TRAIL as well as agonistic anti–TRAIL-R1 and anti–TRAIL-R2 antibodies recently entered clinical trials (Fig. 2).

Recombinant TRAIL, a receptor agonist that directly activates both TRAIL-R1 and TRAIL-R2, is currently being codeveloped by Genentech (San Francisco, CA) and Amgen (Thousand Oaks, CA) as a targeted therapy for solid tumors and hematologic malignancies. Phase I studies using recombinant TRAIL have been initiated, but results are not yet available (32). HGS-ETR1 (Mapatumumab; Human Genome Sciences, Rockville, MD) is a fully human agonistic monoclonal antibody that targets TRAIL-R1. HGS-ETR1 is currently in phase II clinical development as a single agent in patients with non–small cell lung cancer and colorectal cancer (reviewed in ref. 33). Clinical activity of HGS-ETR1 is suggested by three partial responses observed in a recently reported multicenter phase II trial in relapsed non-Hodgkin lymphoma receiving either 3 or 10 mg/kg HGS-ETR1 every 3 weeks for six cycles or until disease progression (33). Additional phase Ib trials with HGS-ETR1 in combination with carboplatin/paclitaxel and cisplatin/gemcitabine have been initiated in patients with advanced solid malignancies (33). Fully human antibodies to TRAIL-R2 (HGS-ETR2 and HGS-TR2J; Human Genome Sciences) have also entered the clinic and are currently in phase I clinical development (33). Agonist monoclonal antibodies specifically bind and activate TRAIL-R1 (HGS-ETR1) or TRAIL-R2 (HGSETR2 and HGS-TR2J). Monoclonal antibodies restrict the therapeutic target to tumors with a distinct receptor expression profile, whereas soluble TRAIL interacts with both TRAIL-R1 and TRAIL-R2 as well as the decoy receptors. Therefore, soluble TRAIL may either have a wider therapeutic spectrum or a narrower and more unpredictable therapeutic window compared with the highly specific antibodies. The

biological relevance of the decoy receptors, their ability to inhibit TRAIL signaling, and the expression profile of the decoy receptors have not yet been fully investigated.

Tumor cells may have an impaired apoptotic response to TRAIL because of resistance mechanism(s) occurring at different points along the TRAIL signaling pathway (34). Dysfunctions due to mutations and defects in either the death receptors TRAIL-R1 or TRAIL-R2, as well as the adaptor protein FADD and caspase-8, can lead to TRAIL resistance because of their essential role in the DISC complex assembly (20, 22–24). Overexpression of cellular FADD-like interleukin-1β–converting enzyme-inhibitory protein (cFLIP) correlates with TRAIL resistance in several types of cancer. Overexpression of Bcl-2 or Bcl-XL, loss of Bax or Bak function, high expression of inhibitor of apoptosis proteins, and reduced release of Smac/DIABLO from the mitochondria to the cytosol have all been reported to result in TRAIL resistance in mitochondria-dependent type II cancer cells (11, 12, 34). Finally, activation of different subunits of mitogen-activated protein kinases or nuclear factor-κB can lead to development of either TRAIL resistance or apoptosis in certain types of cancer cells (22, 34).

The mechanism(s) to overcome TRAIL resistance remains largely unclear. A prolonged exposure to the drug or very high doses of TRAIL might be required to overcome resistance (35–38). Because of the short half-life of TRAIL in plasma (10) and rapid elimination (15), however, achieving prolonged exposure at high concentrations is difficult. Despite *in vivo* studies using a trimerized (15) or a nontagged (10, 39) form of TRAIL having shown a good toxicity profile of the molecule, organ toxicity might occur when using high doses of soluble TRAIL. In experimental anticancer treatments, the response to TRAIL-induced apoptosis was significantly increased on coadministration of DNA-damaging chemotherapeutic drugs

because of up-regulation of TRAIL-R1 and/or TRAIL-R2 (40, 41). In addition, irradiation seems to specifically up-regulate TRAIL-R2 receptor expression, and combining irradiation with TRAIL treatment has an additive or synergistic effect (42). Alternatively, up-regulation of TRAIL-R1 or TRAIL-R2 using small molecules, such as the proteasome inhibitor bortezomib (43) or inhibitors of histone deacetylase (44) might allow to overcome TRAIL resistance.

Several gene therapy approaches are currently being developed to specifically target tumor cells and overcome the limitations inherent to death receptor targeting, i.e., pharmacokinetic, toxicity profile, pattern of receptor expression, tumor cell resistance. A TRAIL-expressing adenoviral vector (Ad-TRAIL) has been recently shown to cause direct tumor cell killing, as well as a potent bystander effect through the presentation of TRAIL by transduced normal cells (45). Using Ad-TRAIL might be an alternative to delivery of systemic soluble TRAIL that may lead to better tumor cell targeting and increased tumoricidal activity (45–49). Optimal Ad-TRAIL–based gene therapy, however, requires efficient infection of target tumor cells and avoidance of immune clearance (50). In addition, safety and toxicity issues linked to the systemic vector administration force cancer researchers to adopt an intratumoral injection of Ad-TRAIL, which results in local therapeutic activity with limited value for treating disseminated tumors.

To optimize the use of TRAIL-encoding adenovectors, thereby allowing the systemic delivery of TRAIL, we explored and recently described a cell therapy approach using a replication-deficient Ad-TRAIL encoding a full-length membrane-bound TRAIL (mTRAIL) to transduce CD34^{+} cells (CD34-TRAIL^{+}; ref. 51; Fig. 2). Gene-modified CD34^{+} cells represent optimal vehicles of antitumor molecules. In fact, they can migrate from the bloodstream into tumor tissues because of the expression of adhesion receptors that specifically interact with counter-receptors on endothelial cells in the tumor microenvironment (52–54). Additionally, up-regulation of inflammatory chemoattractants in the tumor microenvironment provides a permissive environment that allows for homing of systemically delivered CD34-TRAIL^{+} cells and efficient tumor targeting (55). *In vitro* CD34-TRAIL^{+} cells exhibited high killing activity on a variety of tumor cell types, including lymphoma, multiple myeloma, as well as epithelial cancers, and most importantly, mTRAIL-armed cells were highly cytotoxic against tumor cells resistant to soluble TRAIL (51). Thus, the membrane-bound form of the ligand is capable of triggering apoptosis more efficiently than soluble TRAIL and overcoming tumor resistance to the soluble ligand. This peculiar functional property of mTRAIL might be due to a differential activation of TRAIL-R1 and TRAIL-R2 by soluble and membrane TRAIL as suggested by studies showing that TRAIL-R1 signals apoptosis on triggering by both the soluble and membrane-bound form of the ligand, whereas TRAIL-R2 becomes only activated by mTRAIL or soluble TRAIL cross-linked by antibodies (56, 57). CD34-TRAIL^{+} cells also showed potent *in vivo* tumoricidal efficacy in nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice xenografted with soluble TRAIL-sensitive and TRAIL-resistant tumors. Repeated dosing with mTRAIL-armed cells resulted in a significantly prolonged survival of tumor-bearing mice (51). Histologic analysis of tumor nodules growing *in vivo* in NOD/SCID mice showed an efficient tumor homing of transduced cells and a high level of expression of the agonistic TRAIL-R2 receptor by tumor endothelial cells (51). Indeed, injection of CD34-TRAIL^{+} cells resulted in extensive damage of the tumor vasculature followed by hemorrhagic necrosis that exhibited a perivascular distribution, suggesting that CD34-TRAIL^{+} cells might be an efficient vehicle for mTRAIL delivery to tumors, where they exert a potent antitumor effect mediated by both direct tumor cell killing due to apoptosis and indirect tumor cell killing due to vascular-disrupting mechanisms.

Because death receptor activation can instruct malignant cells to undergo apoptosis independent of p53, targeting death receptors with TRAIL-targeting therapeutics is a rational therapeutic strategy against cancer. According to experimental data obtained thus far, TRAIL-targeting therapeutics possess considerable and specific antitumor therapeutic activity both when used alone as well as in combination with nonspecific cytotoxic agents, radiation, and other target-based therapeutics. In a way that recapitulates the dilemmas faced with targeted agents in clinical development, the ideal tumor types to select to achieve a proof of principle of clinical activity of TRAIL receptor targeting is not known. TRAIL-targeting therapeutics are highly specific for the TRAIL death receptors. Therefore, the level of receptor expression should be evaluated in clinical specimens as a prerequisite for patient's inclusion in clinical studies. Clinical translation of gene therapy approaches using adenovector-transduced cells for delivery of membrane-bound TRAIL represent a challenging strategy that might achieve systemic tumor targeting and increased intratumor delivery of the therapeutic agent.

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