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REVIEW ARTICLE

TRAIL AND CANCER THERAPY

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ABSTRACT

Programmed cell death, or apoptosis, is a key regulator of tissue homeostasis. Accordingly, imbalances between cell death and proliferation promote tumor formation. TNF-related apoptosis-inducing ligand (TRAIL) is a member of the TNF superfamily that induces apoptosis upon binding to its receptors on the cell surface. Because it preferentially kills cancer cells, TRAIL is of special interest for application in cancer therapy. In combination with anticancer drugs or gamma radiation, TRAIL synergistically induced apoptosis in various tumor cell lines and also suppressed in vivo tumor growth in cancer models. Since defects in apoptosis programs may result in tumor resistance towards TRAIL, a better understanding of the molecular events regulating TRAIL-induced apoptosis in resistant forms of cancer may provide novel opportunities for cancer therapy. The approach to exploit the TRAIL pathway for therapeutic purposes has already been translated into clinical application. Several proapoptotic TRAIL receptor agonists are currently being evaluated in early clinical trials, e.g., recombinant human TRAIL (dulanermin), a proapoptotic receptor agonist that activates both proapoptotic TRAIL receptors TRAIL-R1 and TRAIL-R2.

INTRODUCTION

Programmed cell death, or apoptosis, plays an important role in the regulation of tissue homeostasis (1). It is characterized by morphological and biochemical hallmarks such as cell shrinkage, nuclear DNA fragmentation and membrane blebbing. Numerous stimuli can trigger an apoptotic response, e.g., withdrawal of growth factors and stimulation of cell-surface receptors (2). Additionally, diverse cytotoxic strategies such as anticancer drugs, gamma radiation and immunotherapy have been shown to involve induction of tumor cell death (3). Interestingly, T or natural killer (NK) cells may release cytotoxic compounds such as granzyme B, which can directly initiate apoptosis effector pathways inside the cell (2). The apoptotic pathways involve proteolytic enzymes called caspases as important effector molecules (4), and are tightly controlled by a number of inhibitory and promoting factors (5). Importantly, anticancer agents and death-inducing ligands were shown to synergistically trigger apoptosis in cancer cells and may even overcome some forms of drug resistance (3). Further insight into the mechanisms controlling tumor cell death in response to death receptor ligation will provide a molecular basis for novel strategies to target death pathways in apoptosis-resistant cancer forms.

THE CORE APOPTOTIC MACHINERY

Most anticancer therapies eventually result in activation of caspases, a family of cysteine proteases that act as common death effector molecules in various forms of cell death (4). Synthesized as inactive proforms, caspases cleave next to aspartate residues upon activation. The proteases can activate each other by cleavage at identical sequences, resulting in amplification of caspase activity in what is called a protease cascade. Caspases cleave a number of different substrates in the cytoplasm and nucleus, leading to many of the morphological features of apoptotic cell death (2). For example, cleavage of DNA fragmentation factor subunit alpha (inhibitor of caspase-activated DNase, ICAD), the inhibitor of the endonuclease DNA fragmentation subunit beta (caspase-activated DNase, CAD), mediates polynucleosomal DNA fragmentation (6). Likewise, proteolysis of several cytoskeletal proteins such as actin or fodrin leads to loss of overall cell shape, while degradation of lamin results in nuclear shrinking (2).

Caspase activation can be initiated at different locations, e.g., at the plasma membrane upon death receptor ligation (receptor pathway) or at the mitochondria (mitochondrial pathway) (3) (Fig. 1). Stimulation of death receptors of the TNF receptor superfamily, e.g., FASLG (FAS/Apo-1/CD95) or TRAIL (TNF-related apoptosis-inducing ligand), results in activation of initiator caspase-8. In turn, caspase-8 can propagate the apoptosis signal by directly cleaving downstream effector caspases such as caspase-3 (7). The mitochondrial pathway is initiated by release of apoptogenic factors such as cytochrome *c*, apoptosis-inducing factor 1, Smac/Diablo, serine protease HTRA2/OMI, endonuclease G, caspase-2 or caspase-9 from the mitochondrial intermembrane space (8). The release of

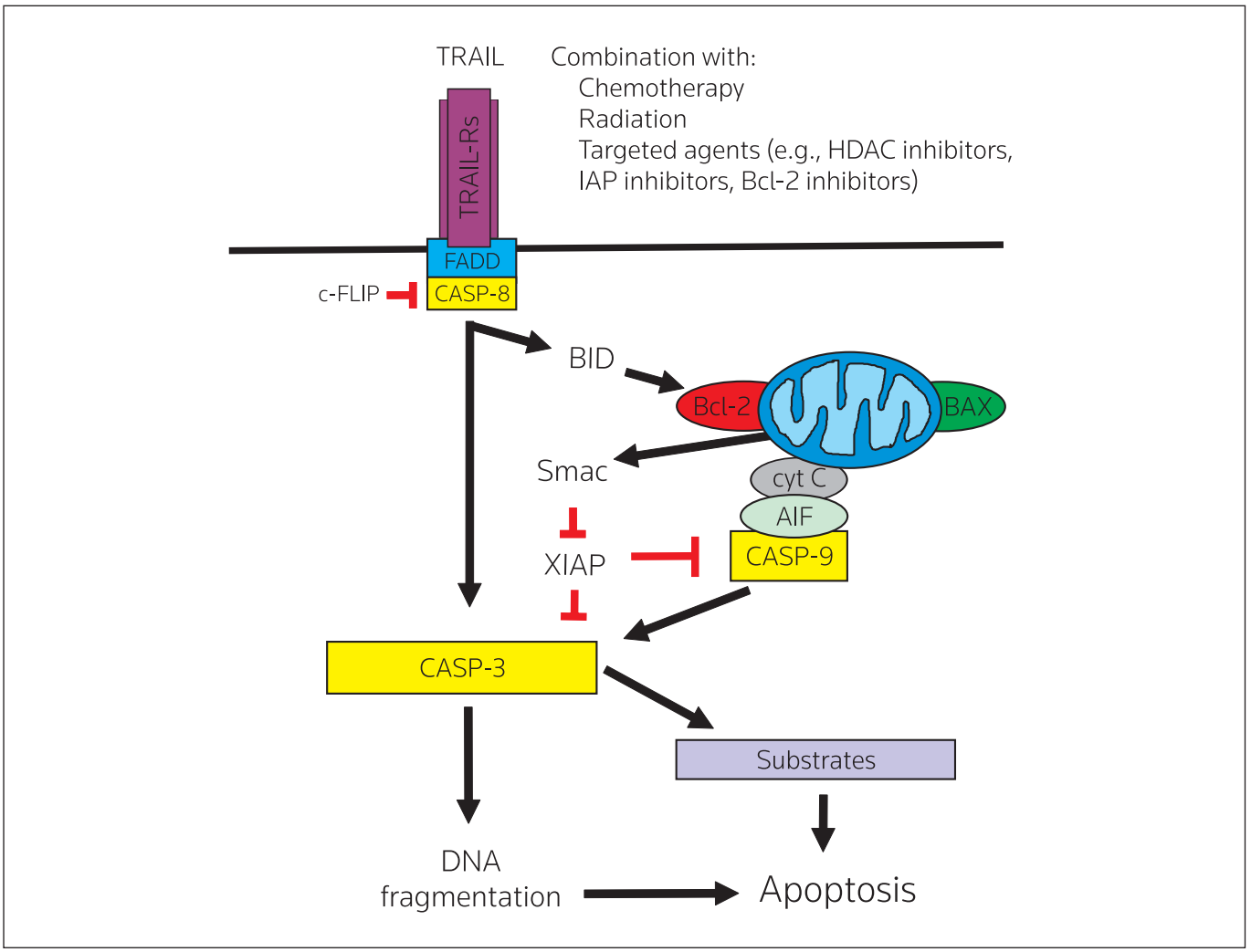

Figure 1. Apoptosis pathways. Apoptosis pathways can be initiated by ligation of one of the two agonistic TRAIL receptors by TRAIL, which triggers receptor trimerization, recruitment of adaptor molecules such as FADD and activation of caspase-8, or CASP-8 (receptor pathway). CASP-8 either directly cleaves caspase-3 (CASP-3) or, alternatively, initiates activation of the mitochondrial pathway by cleaving BID. Once cleaved, BID translocates to the mitochondria to trigger the release of cytochrome *c* (cyt C) and Smac from the mitochondria into the cytosol. In turn, cyt C promotes the formation of the cyt C/apoptosis-inducing factor 1 (AIF)/caspase-9 (CASP-9)-containing apoptosome complex, while Smac neutralizes IAP-mediated inhibition of CASP-3 and -9. Apoptosis can be inhibited by Bcl-2, CASP8 and FADD-like apoptosis regulator/c-FLIP or baculoviral IAP repeat-containing protein 4 (E3 ubiquitin-protein ligase XIAP). TRAIL can be combined with chemotherapy, radiation or targeted agents to maximize its antitumor activity. See text for more details.

cytochrome *c* into the cytosol results in the formation of the cytochrome *c*/apoptosis-inducing factor 1/caspase-9-containing apoptosome complex, which triggers caspase-3 activation (9). Smac/Diablo and HTRA2/OMI promote caspase activation by neutralizing the effects of inhibitor of apoptosis proteins (IAP) (8), endogenous caspase inhibitors that block apoptosis by binding to and inhibiting caspase-3, -7 and -9 (9).

Proteins belonging to the Bcl-2 family play an important role in the regulation of the mitochondrial pathway of apoptosis, since they are involved in the control of mitochondrial outer membrane permeabilization. The Bcl-2 protein family comprises not only antiapoptotic members such as Bcl-2, Bcl-X_L and Mcl-1, but also proapoptotic molecules. The latter group contains multidomain proteins such as BAX, Bcl-2 homologous antagonist/killer (BAK) and Bcl-2 antagonist of cell death (BAD), and also BH3-only proteins like Bcl-2-like protein 11 (Bcl2-L-11, Bim), BH3-interacting domain death agonist (BID), Bcl-2-modifying factor (Bmf), phorbol-12-myristate-13-acetate-induced protein 1 (NOXA) and Bcl-2-binding component 3 (Puma) (10).

TRAIL AND ITS RECEPTORS

Identified in 1995 in a search for proteins homologous to other members of the TNF superfamily, TRAIL/Apo-2L is a type II transmembrane protein that is widely expressed in various tissues. The system comprises five different TRAIL receptors: TRAIL-R1 and TRAIL-R2 are agonistic receptors, whereas TRAIL-R3, -R4 and -R5 are referred to as antagonistic decoy receptors because they bind TRAIL without transmitting a death signal. TRAIL-R1 and TRAIL-R2 possess an evolutionarily conserved cytoplasmic death domain that enables them

to activate the apoptosis signaling cascade upon ligand binding. TRAIL-R3 is a glycosylphosphatidylinositol GPI-anchored cell-surface protein lacking a cytoplasmic tail, while TRAIL-R4 harbors a substantially truncated cytoplasmic death domain. Finally, TRAIL-R5 (osteoprotegerin) is a soluble decoy receptor involved in the regulation of osteoclastogenesis (7).

Similar to TNF ligand superfamily member 6 (Fas ligand, CD95L), TRAIL rapidly induces apoptosis in many tumor cells (11). However, because it was shown to predominantly kill malignant versus nonmalignant cells, TRAIL is an especially interesting candidate cancer therapeutic among the death receptor ligands. Why malignant and nonmalignant cells display differential sensitivity to TRAIL is not fully understood. One proposed mechanism underlying the protection of normal tissue was based on competition between the antagonistic decoy receptors and TRAIL-R1 and -R2 for binding to TRAIL (12). However, screening of normal cells and several different tumor cell types did not reveal a consistent association between TRAIL receptor expression and sensitivity. Therefore, susceptibility to TRAIL-induced cytotoxicity was suggested to be regulated by distinct intracellular patterns of pro- and antiapoptotic molecules.

TRAIL SIGNALING

Binding of TRAIL or agonistic antibodies to the agonistic TRAIL receptors TRAIL-R1 and -R2 leads to receptor trimerization, clustering of the receptors' death domains and recruitment of adaptor molecules such as FADD (Fas-associated death domain protein) through a homophilic interaction mediated by the death domain (13) (Fig. 1). In turn, FADD recruits caspase-8 to the activated TRAIL receptor complex. Oligomerization of caspase-8 at the activated TRAIL receptor complex drives its activation through self-cleavage. Caspase-8 then cleaves and activates downstream effector caspases such as caspase-3. Activated caspase-8 can also cleave BID, which subsequently translocates to mitochondria to induce cytochrome *c* release. The relevance of caspase-10 recruitment to the TRAIL death-inducing signaling complex (DISC) for apoptosis induction is controversial (14, 15).

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Safety of TRAIL

The concept of targeting death receptors to induce apoptosis in cancer cells is attractive for cancer therapy given the direct link of death receptors to the cell's death machinery (16). In this respect, TRAIL is considered a relatively safe and promising candidate for clinical application, particularly in its nontagged, zinc-bound homotrimeric form (17). Studies in nonhuman primates such as chimpanzees and cynomolgus monkeys showed no toxicity upon intravenous infusion even at high doses (11). In addition, no cytotoxic TRAIL activity was reported in a variety of normal human cell types, including fibroblasts, endothelial cells, smooth muscle cells, epithelial cells and astrocytes (18). However, some concerns have been raised about potential toxic side effects on human hepatocytes and brain tissue (19, 20). The loss of tumor selectivity may be related to the TRAIL preparations used in these studies. Indeed, preparations that have not been optimized for zinc content or preparations crosslinked to antibodies have been reported to form multimeric aggregates and may thereby overpass the sensitivity threshold of normal cells (17).

Antitumor activity of TRAIL

Recombinant soluble TRAIL induced apoptosis in a broad spectrum of cancer cell lines and also exhibited potent tumoricidal activity in vivo in several xenograft models. Furthermore, monoclonal antibodies targeting the TRAIL-R1 and -R2 receptors also demonstrated potent antitumor activity against tumor cell lines and in preclinical cancer models (11).

Combination therapy with TRAIL

In recent years, various approaches have been developed to enhance the antitumor activity of TRAIL in combination protocols. For example, TRAIL was shown to synergize with cytotoxic drugs or gamma radiation to suppress tumor growth in various types of cancers both in vitro and in vivo (21-26) (Fig. 1). Synergy for TRAIL and DNA-damaging agents has been linked to transcriptional upregulation of the apoptosis-inducing TRAIL receptors TRAIL-R1 and -R2, which may occur via p53-dependent and -independent mechanisms (27, 28). It is also possible that the synergy results from downregulation of antiapoptotic proteins such as Bcl-2, Bcl-X_L or CASP8 and FADD-like apoptosis regulator (c-FLIP) in response to DNA-damaging anticancer agents (11). In addition, cancer cells may be sensitized to TRAIL due to increased expression of proapoptotic molecules such as caspases or FADD caused by DNA damage (29).

Tumor cell resistance to TRAIL could be specifically targeted using small molecules as therapeutics. For instance, Smac mimetics that antagonize IAPs have been reported to enhance the antitumor activity of TRAIL (30-32). Moreover, a significant increase in TRAIL-induced apoptosis was observed after administration of ABT-737, a small-molecule inhibitor of the antiapoptotic Bcl-2 family proteins Bcl-2, Bcl-X_L and Bcl-2-like protein 2 (Bcl2-L-2, Bcl-W) (33, 34).

Furthermore, histone deacetylase inhibitors, which modulate the aberrant chromatin architecture of cancers, have been reported to enhance TRAIL efficacy in a variety of human cancers. Several mechanisms mediating this sensitization to TRAIL have been implicated, including upregulation of agonistic TRAIL receptors, redistribution of TRAIL receptors to membrane lipid rafts, increased efficacy of TRAIL-induced DISC formation, enhanced mitochondrial damage, upregulation of proapoptotic molecules or downregulation of antiapoptotic proteins (35).

CLINICAL TRIALS WITH TRAIL RECEPTOR AGONISTS

Agents directed at agonistic TRAIL receptors are currently being evaluated in early clinical studies, i.e., recombinant soluble TRAIL and fully human monoclonal antibodies targeting TRAIL-R1 or -R2. While trials in patients with advanced solid tumors defined the maximal tolerated dose of monoclonal TRAIL-R2 antibodies, no major dose-limiting toxicities of recombinant TRAIL or fully human monoclonal TRAIL-R1 antibodies were revealed (36-38). Fully human monoclonal antibodies against TRAIL-R1 (mapatumumab; Human Genome Sciences) were reported to elicit tumor responses in 3 of 40 patients (8%) with non-Hodgkin's lymphoma (NHL) in a phase II trial (39). Furthermore, clinical trials combining TRAIL receptor agonists

with other cytotoxic treatments were also launched based on preclinical studies demonstrating a cooperative interaction of TRAIL with agents such as chemotherapeutic drugs. Monoclonal TRAIL-R1 antibodies are currently being evaluated in combination with carboplatin, paclitaxel, gemcitabine or cisplatin (40, 41). Recombinant human Apo-2L/TRAIL (dulanermin), a proapoptotic receptor agonist that activates both proapoptotic TRAIL receptors TRAIL-R1 and -R2, is currently undergoing phase II trials combined with rituximab in relapsed NHL patients (42), and with chemotherapy (i.e., carboplatin, paclitaxel) and antiangiogenic agents such as bevacizumab in patients with metastatic non-small cell lung cancer (43). Finally, combinations of Apo-2L/TRAIL and irinotecan and cetuximab are currently in phase I of trials in metastatic colorectal cancer patients (17).

TUMOR SURVEILLANCE

TRAIL may play an important role in tumor surveillance, as suggested by mounting evidence obtained from studies in TRAIL knockout mice (44, 45). Although the biology of the TRAIL system may differ significantly between mice and humans, since mice have only one TRAIL receptor homologous to both TRAIL-R1 and -R2, the phenotype of these knockout mice is informative with respect to the physiological function of TRAIL in vivo. Importantly, mice deficient in TRAIL or its receptor were more susceptible to tumor metastasis than wild-type animals (45-47). These data are in accordance with studies showing that NK cells, which constitutively express TRAIL, play an important role in the control of tumor metastasis (48, 49). In addition, tumor formation induced by carcinogens was found to be enhanced in the presence of antagonistic TRAIL antibodies or in TRAIL receptor-deficient mice (47, 49). Thus, TRAIL may play an essential role as an innate effector molecule in immune surveillance during tumor formation and progression.

CONCLUSIONS

The death receptor ligand TRAIL is considered a promising candidate for cancer therapy because of its preferential toxicity to malignant versus nonmalignant cells. Of special interest for translation into therapeutic application is the cooperative interaction of TRAIL with conventional anticancer therapies, including various chemotherapeutic drugs and radiation. However, the tumor-selective toxicity of TRAIL is not yet fully understood. For this reason, attention should be paid to the potential toxicity of TRAIL or agonistic TRAIL receptor antibodies to nonmalignant tissues, particularly in combination with anticancer agents or radiation. Moreover, TRAIL remains to be tested in clinical settings, alone or in combination protocols. Monitoring biomarkers of response to TRAIL in individual patients, e.g., by DNA microarrays or proteomics, may provide the basis for "tailored" TRAIL therapy and may identify new targets for therapeutic intervention.

DISCLOSURE

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