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Mini review

Death receptor agonist therapies for cancer, which is the right TRAIL?

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ABSTRACT

The activation of cell-surface death receptors represents an attractive therapeutic strategy to promote apoptosis of tumor cells. Several investigational therapeutics that target this extrinsic pathway, including recombinant human Apo2L/TRAIL and monoclonal agonist antibodies directed against death receptors-4 (DR4) or -5 (DR5), have been evaluated in the clinic. Although Phase 1/1b studies provided encouraging preliminary results, findings from randomized Phase 2 studies failed to demonstrate significant clinical benefit. This has raised multiple questions as to why pre-clinical data were not predictive of clinical response. Results from clinical studies and insight into why current agents have failed to yield robust responses are discussed. In addition, new strategies for the development of next generation death receptor agonists are reviewed.

1. Introduction

Apoptosis is integral to normal, physiological processes that regulate cell number, and results in the removal of unnecessary or damaged cells. Evasion of apoptosis by tumor cells is key to the pathogenesis and progression of cancer, and advancements in our understanding of the regulation of programmed cell death pathways has led to the development of novel agents to reactivate apoptosis in malignant cells. Activation of cell-surface death receptors by tumor necrosis factor-related apoptosis inducing ligand (Apo2L/TRAIL, TNFSF10) and death-receptor agonists is one approach aimed at promoting apoptosis of tumor cells via activation of the extrinsic pathway. The early observation that Apo2L/TRAIL preferentially triggers apoptosis in tumor cells over normal cells highlighted its potential as a candidate therapeutic in cancer. Several investigational therapeutics that target this pathway, including soluble recombinant human Apo2L/TRAIL (dulanermin) and agonist monoclonal antibodies directed against death receptors 4 (DR4) or 5 (DR5), have been developed and evaluated in phase 1 and 2 trials, either as single agents or in combination with cytotoxic chemotherapy or other targeted agents. These studies demonstrated that this class of agents is well tolerated and provided preliminary evidence of activity. However, findings from randomized Phase 2 studies have not demonstrated strong clinical activity, and no death receptor agonist therapies have advanced into Phase 3 [1–6].

Why have death receptor agonist therapies underperformed in the clinic? One possibility is that clinically, tumors are inherently resistant to death receptor agonism, despite showing potent activity in pre-clinical models. In this case, resistance might be attributed to extrinsic pathway-specific issues, and agonists with distinct features with respect to their receptor selectivity, cross-linking requirements or pharmacokinetics, might all be expected to yield poor activity. On the other hand, it is possible that modality-specific issues have contributed to the weak clinical findings. In this case, liabilities associated with the unique characteristics of agonist antibodies or soluble Apo2L/TRAIL may have independently resulted in similarly weak outcomes. It is likely that multiple factors have influenced the clinical findings generated to date, and the feasibility and supporting data for these alternatives is discussed. A greater understanding of these factors should provide insight into why death receptor agonist therapies have not lived up to their potential in the clinic to date, and may provide approaches to reconsider extrinsic pathway activation as a cancer therapeutic.

2. Apo2L/TRAIL and its receptors

Apo2L/TRAIL is a member of the TNF ligand superfamily, and its physiological role is to modulate immune responses. Apo2L/TRAIL is expressed on many cells of the innate and adaptive immune system in a stimulus dependent manner [7,8]. Apo2L/TRAIL has potent anti-viral activity in vitro and in mice can function as a key effector molecule in NK cell mediated cytotoxicity [8]. Apo2L/TRAIL induction on NK cells also plays a critical role in the anti-metastatic effects mediated by IFNγ in vivo [7].

Apo2L/TRAIL was identified based on its sequence homology to the extracellular domains of TNF and CD95/FasL [9,10]. Although the sequence identity across the family is only 25–30%, all ligands

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are type II transmembrane proteins that exist in the membrane or can be shed from the cell surface and are active as self-assembling non-covalent trimers [11]. Like TNF, lymphotoxin, and CD40L, the structure of Apo2L/TRAIL is a homotrimeric jelly roll protein formed by antiparallel β-pleated sheets, that binds the extracellular portion of three cysteine-rich receptors, thereby inducing oligomerization of intracellular death domains [12,13]. Crystallography studies have also highlighted the presence of a unique zinc binding site buried at the trimer interface which is critical for maintaining the native structure, stability and biological activity of Apo2L/TRAIL [14]. Preparations of recombinant Apo2L/TRAIL lacking zinc have been shown to have reduced solubility, and tend to aggregate, potentially explaining the associated toxicity reported by some in early studies [15,16].

Apo2L/TRAIL binds multiple receptors with high affinity, presumably to enhance regulatory flexibility and signaling complexity in the physiological setting. Two of these receptors, DR4 (TR-1, TNFRSF10A) and DR5 (TR-2, TNFRSF10B), recruit adaptor proteins via death domain interactions and initiate the formation of the death inducing signaling complex (DISC), leading to the induction of apoptosis [17] (Fig. 1). Increasing evidence has suggested that optimal signal transduction mediated by DR4 and DR5 occurs when the receptors are clustered and aggregated into lipid rafts, which can be enhanced by multiple agents [18–20]. Therefore, receptor architecture may be an important component of facilitating DISC formation and optimal caspase activation.

Apo2L/TRAIL binds additional receptors that share close homology within the extracellular domain but do not signal cell death. DcR1 (TR-3, TNFRSF10C) lacks a cytoplasmic tail and is membrane anchored via a glycophosphatidylinositol (GPI) moiety, and DcR2 (TR-4, TNFRSF10D) has a truncated, nonfunctional death domain [17]. In some settings DcR1 and DcR2 may use distinct mechanisms to attenuate Apo2L/TRAIL-induced apoptosis. For example, DcR2 can be co-recruited to DR5 in a ligand dependent manner to prevent initiator caspase activation, and may also sequester DR5 through a pre-ligand assembly domain (PLAD) shared by both receptors, independent of ligand engagement [21,22]. A distinct functional role for DcR1 other than competing for Apo2L/TRAIL binding has not been described.

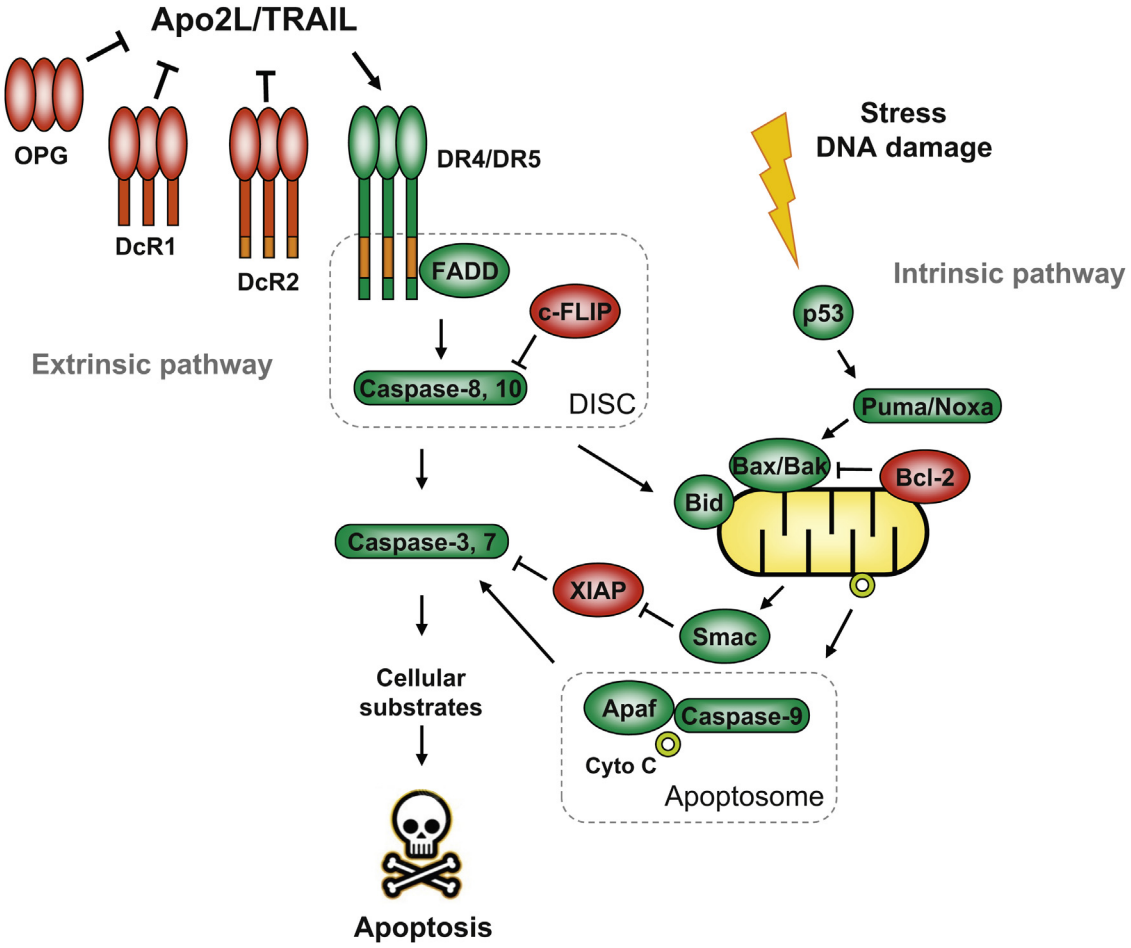

Fig. 1. Apo2L/TRAIL apoptosis signaling. Apo2L/TRAIL-mediated apoptosis is triggered upon binding to pro-apoptotic receptors DR4 and DR5 on the surface of a target cell. Apoptosis may be attenuated by ligand binding to DcR1, DcR2 or OPG, as these receptors do not induce cell death. Binding of death receptor agonists to the receptors DR4 and/or DR5 results in DISC (death-inducing signaling complex) formation. DISC formation involves recruitment of the adaptor protein FADD to the receptor via the death domain (DD) and the inactive pro-caspases 8 and 10. This facilitates activation and self-processing of caspase 8 and 10, leading to their release into the cytoplasm, where they activate effector caspases 3 and 7. c-FLIP is a negative regulator and the ratio of caspase 8 to c-FLIP in the DISC is an important determinant of response to death receptor engagement. Once activated, caspases 3 and 7 cleave intracellular substrates, resulting in cell death. XIAP is another negative regulator of the extrinsic pathway and functions to bind and sequester active caspase 3. The intrinsic, or Bcl-2 regulated mitochondrial pathway, is responsive to a variety of cellular stresses and DNA damaging agents, leading to activation of the tumor suppressor p53 and upregulation of the pro-apoptotic Bcl-2 members Puma and Noxa. These facilitate Bax and Bak activation, and the release of cytochrome C and Smac/DIABLO from the mitochondrion. Cytochrome C complexes with Apaf-1 and caspase 9 to form the apoptosome and further activate caspase-3, -6 and -7, thereby providing signal amplification. Extrinsic and intrinsic pathway cross-talk is mediated by Bid, a caspase-8 substrate that translocates to the mitochondria and activates Bax and Bak upon cleavage.
Figure adapted from Holland, Cancer Letters [118].