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Review

TRAIL*ing* death in cancer

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ABSTRACT

The observation that certain types of cancer express death receptors on their cell surface has triggered heightened interest in exploring the potential of receptor ligation as a novel anti-cancer modality, and since the expression is somewhat restricted to cancer cells the therapeutic implications are very promising. One such death receptor ligand belonging to the tumor necrosis receptor (TNF) superfamily, TNF-related apoptosis-inducing ligand (TRAIL), has been in the limelight as a tumor selective molecule that transmits death signal via ligation to its receptors (TRAIL-R1 and TRAIL-R2 or death receptors 4 and 5; DR4 and DR5). Interestingly, TRAIL-induced apoptosis exhibits hallmarks of extrinsic as well as intrinsic death pathways, and, therefore, is subject to regulation both at the cell surface receptor level as well as more downstream at the post-mitochondrial level. Despite the remarkable selectivity of DR expression on cancer cell surface, development of resistance to TRAIL-induced apoptosis remains a major challenge. Therefore, unraveling the cellular and molecular mechanisms of TRAIL resistance as well as identifying strategies to overcome this problem for an effective therapeutic response remains the cornerstone of many research endeavors. This review aims at presenting an overview of the biology, function and translational relevance of TRAIL with a specific view to discussing the various regulatory mechanisms and the current trends in reverting TRAIL resistance of cancer cells with the obvious implication of an improved clinical outcome.

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1. TRAIL and death receptors

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L) was discovered independently by two groups, both groups reported sequence homology with the extracellular domain of CD95 ligand (Fas-L) and TNF (Pitti et al., 1996; Wiley et al., 1995). Located on chromosome 3, the 20 kb gene coding for TRAIL is composed of five exons and four introns. TRAIL mRNA can be detected in most human tissues, with significantly higher expression in prostate and spleen (Wiley et al., 1995). TRAIL, as member of the TNF superfamily of proteins, is expressed as a type II transmembrane protein and consists of 281 amino acids in its human form. Cleavage of its C-terminal part (extracellular domain) allows for a soluble form of TRAIL (Kimberley and Screaton, 2004). As mentioned, TRAIL shares sequence homology with related members of the TNF family such as CD95 and TNF (28% and 23% identity, respectively) (Wiley et al., 1995). Although this level of homology with other members of the family may appear relatively low, analysis of the crystal structure of monomeric TRAIL shows a high similarity with the three-dimensional structures of TNF and CD40 ligand (Cha et al., 1999). TRAIL forms homo-trimers that bind receptors present on the cell surface. This trimerization enhances biological activity of TRAIL as compared to monomeric forms of TRAIL (Wiley et al., 1995).

To date, TRAIL has been shown to interact with five receptors, including the death receptors DR4/TRAIL-R1/TNFRSF10A (Pan et al., 1997a) and DR5/TRAIL-R2/KILLER/TNFRSF10B (Pan et al., 1997b; Sheridan et al., 1997), and the decoy receptors DcR1/TRAIL-R3/TNFRSF10C (Pan et al., 1997b; Sheridan et al., 1997) and DcR2/TRAIL-R4/TNFRSF10D (Marsters et al., 1997). In addition to these four membrane-bound receptors, TRAIL is also able to bind to a soluble receptor called osteoprotegerin (OPG, an inhibitor of RANK ligand) at low affinity (Emery et al., 1998). DR4 and DR5 are type I transmembrane proteins that contain a death domain in their cytoplasmic domain that can bind to other death domains. Upon binding of TRAIL trimer, DR4 and DR5 are oligomerized and can then transduce the apoptotic signal. Inversely, neither decoy receptors (DcR1 and DcR2) can transduce an apoptotic signal. Indeed, DcR1 is bound to the membrane solely via a glycosylphosphatidylinositol (GPI) anchor, hence lacking the entire cytoplasmic domain, and DcR2 contains a truncated and non-functional death domain. Hence, even though TRAIL binds to the decoy receptors, the apoptotic pathway cannot be engaged. This competition for the binding to TRAIL was first thought to be the mechanism behind the resistance of certain tumor cells to TRAIL-mediated apoptosis. However, further investigations showed that other mechanisms were at play (Griffith et al., 1998, 1999) (Fig. 2) as described in more detail later in this review. In mice, only one receptor is able to transduce an apoptotic signal: TRAIL-R (mDR5, MK), which shares 76% and 79% homology with human DR4 and DR5, respectively (Wu et al., 1999). Two others receptors are able to bind to murine TRAIL: mouse decoy receptor TRAIL-R1 and TRAIL-R2 (mDcR1, mDcR2) (Schneider et al., 2003). It has been suggested that the murine decoy receptors perform the same function as their human counterparts.

2. TRAIL signal transduction

2.1. Apoptotic signaling

Binding of specific ligands to death receptors is the first step of the extrinsic apoptotic pathway, also known as the death receptor pathway. Ligation of trimerized TRAIL to the death receptors (DR4 and/or DR5) leads to a conformational change in

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