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Therapeutic applications of TRAIL receptor agonists in cancer and beyond

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Abstract

TRAIL/Apo-2L is a member of the TNF superfamily first described as an apoptosis-inducing cytokine in 1995. Similar to TNF and Fas ligand, TRAIL induces apoptosis in caspase-dependent manner following TRAIL death receptor trimerization. Because tumor cells were shown to be particularly sensitive to this cytokine while normal cells/tissues proved to be resistant along with being able to synthesize and release TRAIL, it was rapidly appreciated that TRAIL likely served as one of our major physiologic weapons against cancer. In line with this, a number of research laboratories and pharmaceutical companies have attempted to exploit the ability of TRAIL to kill cancer cells by developing recombinant forms of TRAIL or TRAIL receptor agonists (e.g., receptor-specific mAb) for therapeutic purposes. In this review article we will describe the biochemical pathways used by TRAIL to induce different cell death programs. We will also summarize the clinical trials related to this pathway and discuss possible novel uses of TRAIL-related therapies. In recent years, the physiological importance of TRAIL has expanded beyond being a tumoricidal molecule to one critical for a number of clinical settings — ranging from infectious disease and autoimmunity to cardiovascular anomalies. We will also highlight some of these conditions where modulation of the TRAIL/TRAIL receptor system may be targeted in the future.

Keywords

TRAIL; Apoptosis; Cell death; Immune therapy; Cancer

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Conflict of interest

"The authors declare that there are not conflicts of interest."

1. Introduction

The quest for the so-called “magic bullet” of cancer therapy can be considered one of the oldest and foremost aspirations of the scientific community. During this long and fierce journey, scientists have struggled with financial, ethical, as well as biological obstacles. The work completed over the years has generated a lavish amount of information, including the discovery of novel biochemical pathways that regulate tumor cell growth and anti-tumor molecules, thereby improving considerably the way we currently treat cancer. Strikingly, much of this knowledge has also contributed to the development of strategies for fighting other diseases not related to cancer. No “magic bullet” has emerged so far, and the scientific community agrees that combined therapies are the best strategy to fight cancer and many other diseases.

The discovery of *T*NF-*r*elated *a*poptosis-*i*nducing *l*igand (TRAIL/Apo-2L) was well preceded by the description of *t*umor *n*ecrosis *f*actor (TNF)/Lymphotoxin (LT) in the late 1960’s and early 1970’s (Carswell et al., 1975; Granger & Kolb, 1968; Kolb & Granger, 1968) and cloning of TNF/LT in 1985 (Pennica et al., 1984; Aggarwal & Kohr, 1985). TNF-α is the prototype of a superfamily of proteins that are bioactive as a transmembrane protein and/or in soluble form. Initially, TNF-α was considered by many to be the first “magic bullet” against cancer, since it induced tumor cell death, as its name implies. Soon enough, however, it was realized that the major physiological property of TNF-α was to mediate immune/inflammatory responses, and pharmacological concentrations of TNF-α resulted in dramatic hepatotoxicity and a systemic inflammatory response syndrome (Kimura et al., 1987; Ciesielski & Modzelewski, 1995). The discovery and cloning of Fas (CD95) (Trauth et al., 1989; Yonehara et al., 1989; Itoh et al., 1991) and Fas Ligand (FasL/CD178) (Suda et al., 1993) led to the description of the pro-apoptotic Fas/FasL pathway and rekindled the expectations of finding a physiological “magic bullet” against tumor cells. But once again, disappointment emerged with the findings that the introduction of Fas agonists in mouse models rapidly resulted in acute lethal hepatotoxicity (Ogasawara et al., 1993). In mid-1990’s two groups independently described a third member of the TNF family with potent tumoricidal activity, which soon proved to be relatively non-toxic to normal cells and tissues in vivo (Ashkenazi et al., 1999; Walczak et al., 1999). A group at Immunex, led by Raymond Goodwin and Craig Smith, named this protein TNF-related apoptosis-inducing ligand, or TRAIL (Wiley et al., 1995), while the group at Genentech, led by Avi Ashkenazi, called their molecule Apo-2 ligand, or Apo-2L (Pitti et al., 1996).

Since its discovery, numerous reports have provided strong evidence showing that TRAIL plays a major role as a tumor suppressor protein. First, a variety of tumor cell lines exhibit exquisite sensitivity to TRAIL, compared to primary cells (Wiley et al., 1995; Griffith & Lynch, 1998; Walczak et al., 1999). Second, administration of recombinant TRAIL protein (or TRAIL cDNA using a recombinant adenovirus) was extremely effective in eliminating tumor cells in vivo (Walczak et al., 1997, 1999; Ashkenazi et al., 1999; Griffith & Broghammer, 2001). Third, stimulation of a variety of hematopoietic cells, including T cells, NK cells, B cells and monocytes, with types I and II IFN induces TRAIL expression and endows these cells with a potent anti-tumor activity (Zamai et al., 1998; Fanger et al., 1999; Griffith et al., 1999; Kayagaki et al., 1999; Sedger et al., 1999; Smyth et al., 2001; Takeda et

al., 2001; Kemp et al., 2003a; Kemp et al., 2004). In addition, neutrophils can release bioactive TRAIL from granule stores upon proper stimulation (Kamohara et al., 2004; Ludwig et al., 2004; Tecchio et al., 2004; Kemp et al., 2005; Cassatella et al., 2006; Simons et al., 2007, 2008). Forth, TRAIL deficiency in mice was associated with increased carcinogen-induced tumorigenesis and metastasis, particularly to the liver (Cretney et al., 2002; Sedger et al., 2002). Fifth, TRAIL expression is down regulated in a variety of human cancers and restoration of TRAIL expression enhances in vitro tumor sensitivity to chemotherapeutic drugs (De Carvalho et al., 2011, 2013).

2. TRAIL and TRAIL receptor signaling to apoptosis

TRAIL is a 281 amino acid type II transmembrane protein that shares homology with other members of the TNF superfamily via the so-called *T*NF *h*omology *d*omain (THD), a conserved sequence of approximately 150 residues located at the extracellular, carboxy terminal end of the molecules (Wiley et al., 1995; Pitti et al., 1996). Unlike FasL and TNF-α, TRAIL is widely distributed and constitutively expressed in many tissues, such as small intestine, colon, placenta, and in most cells of the hematopoietic tissue (Wiley et al., 1995). Interestingly enough, murine and human forms of TRAIL are 65% identical at the amino acid level and completely cross-reactive. TRAIL interacts with five different receptors (Fig. 1) that may act as transducers of signaling information into the target cells to induce cell death, or as regulators/decoys to preventing the signaling events that lead to death (Wajant et al., 2002). The TRAIL death receptors (DRs), DR4/TRAIL-R1 and DR5/TRAIL-R2, have an intracellular *death domain* (DD), a homodimerization module responsible for the aggregation of proteins that promote signaling transduction. DR4/TRAIL-R1 (Pan et al., 1997b) and DR5/TRAIL-R2 (Chaudhary et al., 1997; MacFarlane et al., 1997; Pan et al., 1997a; Schneider et al., 1997a; Screaton et al., 1997; Sheridan et al., 1997; Walczak et al., 1997; Wu et al., 1997) are Type I transmembrane proteins with 58% identity. Tissue distribution of DR4/TRAIL-R1 and DR5/TRAIL-R2 mRNA by Northern blot analysis is broad, with expression in most normal human tissues (colon, esophagus, heart, kidney, liver, lung, ovary, pancreas, placenta, prostate, skeletal muscle, small intestine, spleen, stomach, testis, thymus, uterus) (Pan et al., 1997a,b; Walczak et al., 1997). Interestingly, all vertebrates, with the exception of human and chimpanzees, present only one TRAIL death receptor. Thus, the question whether DR4/TRAIL-R1 and DR5/TRAIL-R2 in humans and chimpanzees serve redundant function or have arisen in the need for fundamentally distinct signal transduction pathways and/or biological consequences may ultimately have implications for future development of receptor-specific targeting reagents (van Roosmalen et al., 2014).

In contrast to the TRAIL DRs, DcR1/TRAIL-R3 completely lacks an intracellular tail (suggesting it has no intracellular signaling ability) and is expressed on the cell surface via glycosyl-phosphatidylinositol linkage (Degli-Esposti et al., 1997b; MacFarlane et al., 1997; Pan et al., 1997a; Schneider et al., 1997a; Sheridan et al., 1997; Mongkolsapaya et al., 1998). DcR2/TRAIL-R4, on the other hand, has a truncated intracellular domain missing 52 of the 76 amino acids found in the DDs of DR4/TRAIL-R1 and DR5/TRAIL-R2 (Degli-Esposti et al., 1997a; Marsters et al., 1997; Pan et al., 1998). These two TRAIL-binding proteins are unable to transduce signaling events that lead to cell death, and have

subsequently been defined as TRAIL decoy receptors (DcR). Despite being unable to signal for apoptosis, TRAIL ligation of DcR2/TRAIL-R4 does activate NF-κB (Degli-Esposti et al., 1997a). As NF-κB activation has been linked to increased resistance to apoptosis-inducing cytokines, including TRAIL (Beg & Baltimore, 1996; Van Antwerp et al., 1996; Keane et al., 2000; Ravi et al., 2001; Karacay et al., 2004), it is possible that DcR2/TRAIL-R4 protects against TRAIL-induced apoptosis through ligand sequestration and induction of proteins with anti-apoptotic activity. Tissue distribution of DcR1/TRAIL-R3 is much more restricted than DR4/TRAIL-R1 and DR5/TRAIL-R2, with mRNA found only in the heart, kidney, liver, lung, placenta, peripheral blood leukocytes, and spleen (Degli-Esposti et al., 1997a,b; Pan et al., 1997a). DcR2/TRAIL-R4 mRNA, in contrast to DcR1/TRAIL-R3, is found in a much broader range of human tissues, with it expressed in most of the same tissues as DR4/TRAIL-R1 and DR5/TRAIL-R2 (Degli-Esposti et al., 1997a,b; Pan et al., 1998). The tissues where DcR1/TRAIL-R3 mRNA was detected are heavily vascularized, suggesting the possibility the mRNA present was coming from “blood contamination” and the actual organ tissue does not normally express DcR1/TRAIL-R3 mRNA. Interestingly, the genes for all four human TRAIL receptors map to chromosome 8p21 (Degli-Esposti et al., 1997a, b; Walczak et al., 1997), suggesting that they are the result of recent gene duplications. A fifth receptor, osteoprotegerin (OPG), is a soluble protein that interacts with TRAIL with low affinity (Emery et al., 1998), but the in vivo functional relevance of this event remains unclear.

In general terms, the signaling cascade initiated by TRAIL binding to its death receptors is similar to the signal generated after Fas/FasL interaction, and is known as the extrinsic pathway of apoptosis (Fig. 1) (Schulze-Osthoff et al., 1998; Amarante-Mendes & Green, 1999; Barnhart et al., 2003). Binding of TRAIL to either DR4/TRAIL-R1 or DR5/TRAIL-R2 results in receptor trimerization and further aggregation, allowing the recruitment of the death domain-containing protein *F*AS-*a*ssociated *d*eath *d*omain (FADD) to the receptors. FADD has a second domain called *death effector domain* (DED) capable of binding to the DED domains present on caspases-8 or -10. Recruitment of caspase-8 and/or -10 results in the formation of the *d*eath-*i*nducing *s*ignaling *c*omplex (DISC) and activation a proteolytic signaling cascade. Depending on the cell type, high or low amount of caspase activation may result from the TRAIL death receptor engagement. In addition, the relative expression of *X*-linked *i*nhibitor of *a*poptosis *p*rotein (XIAP), an endogenous inhibitor of caspases, greatly impacts the outcome of caspase activation at the DISC. In Type I cells, the balance between caspase-8/10 activation and XIAP expression results in high levels of caspase activation and favors the direct activation of the executioner/effector caspases-3, 6- and -7 (Jost et al., 2009). On the other hand, in Type II cells, the balance between DISC-induced caspases-8/10 activation and XIAP expression allows only the formation of low levels of caspase activity and supports an amplification loop mediated by the activation of the BH3-only protein BID (BCL-2 inhibitory BH3-domain containing protein), which in turn engages the mitochondrial (intrinsic) pathway of apoptosis (Jost et al., 2009) (Fig. 1). The truncated form of BID migrates to the mitochondria where it activates BAX (*B*cl-2 *a*ssociated *X* protein) and BAK (*B*cl-2 *a*ntagonist *k*iller 1) to induce *M*itochondrial *O*uter *M*embrane *P*ermeabilization (MOMP) and the consequent release of pro-apoptotic factors, such as cytochrome c, *S*econd *M*itochondria-derived *A*ctivator of *C*aspases/*D*irect *I*AP *B*inding

protein with *lo*w pI (SMAC/DIABLO) [34, 35], and HtrA serine peptidase 2/serine protease OMI (HTRA2/Omi). In the cytosol, cytochrome c initiates the formation of a multimolecular complex called the *Apoptosome*, which is composed of cytochrome c, APAF-1 (*Ap*optosis *A*ctivating *F*actor-*1*) and caspase-9. Caspase-9 is activated by an "induced-proximity" mechanism and triggers the activity of caspases-3, -6 and -7 (Muzio et al., 1998; Boatright et al., 2003). The multiple active caspases go on to systematically disassemble the cell through cleavage of a range of intracellular proteins vital to cell structure and integrity.

3. TRAIL-induced necroptosis

Besides apoptosis, and specifically in situations where caspase activity is artificially precluded through the use of caspase inhibitors, TRAIL (as well as FasL and TNF-α) can induce an alternative, *R*eceptor-*I*nteracting *P*rotein *K*inase (RIPK)-mediated form of cell death termed *regulated necrosis* or *necroptosis* (Holler et al., 2000; Kemp et al., 2003b; Galluzzi et al., 2014; Linkermann & Green, 2014; Vanden Berghe et al., 2014). This type of cell death depends on the activation of an amyloid-like molecular complex known as the *necrosome* (J. Li et al., 2012). Downstream of TRAIL death receptor engagement, particularly when either caspase-8 or cellular FLICE-inhibitory protein (cFLIP) is absent or inactivated, the necrosome is formed by the association of RIPK1 and RIPK3 via their *R*IP *h*omotypic *i*nteraction *m*otif (RHIM) domain (Cho et al., 2009; He et al., 2009; Orozco et al., 2014; X. N. Wu et al., 2014). At the necrosome complex, RIPK3 is activated by autophosphorylation and recruits and phosphorylates *m*ixed *l*ineage *k*inase-*l*ike (MLKL), a pseudokinase associated with the effector phase of necroptosis (Cai et al., 2014; X. Chen et al., 2014). At the necrosome, MLKL undergoes conformational change leading to the exposure of its 4-helical bundle domain (Murphy et al., 2013; Su et al., 2014). The molecular mechanism responsible for MLKL induction of necroptosis is still not completely understood, but recent data suggest MLKL may destabilize and mediate deformation of pores at the plasma membrane (Dondelinger et al., 2014; H. Wang et al., 2014; Su et al., 2014).

Historically, apoptosis has been considered to be tolerogenic cell death while necroptosis is a highly immunogenic form of cell death that can activate both the innate and adaptive immune responses (Kaczmarek et al., 2013). While this general difference is largely accurate, inflammatory cytokines and chemokines are produced during TNF- and Fas-induced apoptosis (Cullen et al., 2013; Kearney et al., 2013; Kearney et al., 2015). It remains to be determined whether there is a similar production of proinflammatory cytokines and chemokines during TRAIL-induced apoptosis or necroptosis. Thus, the type of cell death induced by TRAIL-related therapies should be carefully evaluated depending on the disease context. Although we will briefly touch on this point again below, the characteristics and consequences of immunogenic versus non-immunogenic forms of cell death are outside the scope of this manuscript. Therefore, we suggest the following articles as a supplementary literature (Ullrich et al., 2008; Green et al., 2009; Griffith & Ferguson, 2011).

4. Resistance to TRAIL—mediated cell death

One of the most important aspects considered when designing therapeutic approaches using TRAIL receptor agonists is the diversity of mechanisms that can award resistance to TRAIL-mediated cell death (So et al., 2015; Trivedi & Mishra, 2015; Twomey et al., 2015). We have already mentioned the existence of the Decoy Receptors (DcR1/TRAIL-R3, DcR2/TRAIL-R4 and OPG), which can bind to TRAIL but are unable to activate either the apoptotic or necroptotic signaling cascade. Increased expression of DcR1/TRAIL-R3, DcR2/TRAIL-R4, or OPG can interfere with the action of TRAIL (Degli-Esposti et al., 1997a, b; Pan et al., 1997a; Pan et al., 1998), leading to the hypothesis that expression of these receptors governs which cells are sensitive to TRAIL. The “decoy hypothesis” has received support from a number of studies correlating increased DcR1/TRAIL-R3 and/or DcR2/TRAIL-R4 expression in human tumor samples to increased disease staging and decreased survival. Targeted DcR1/TRAIL-R3 or DcR2/TRAIL-R4 downregulation, in some settings, has proven to increase tumor cell sensitivity to TRAIL — lending some credence to the possibility that these receptors truly function as “decoys” and compete with DR4/TRAIL-R1 and DR5/TRAIL-R2 for TRAIL. However, the vast majority of these studies have been conducted in vitro using easily manipulated established tumor cell lines. When staying at the cell surface, DR4/TRAIL-R1 or DR5/TRAIL-R2 downregulation has been associated with TRAIL resistance in human tumors (Horak et al., 2005a, b; Kurbanov et al., 2007; Jung et al., 2012; Yoon et al., 2013). In these cases, the use of drugs that increase DR4/TRAIL-R1 and/or DR5/TRAIL-R2 expression has proven to be an important supporting strategy. However, mutation or methylation of the promoter region of these two genes in some circumstances may impose an extra level of complexity to the problem (Arai et al., 1998; Pai et al., 1998; Lee et al., 1999; Ozoren et al., 2000). In addition to the transcriptional regulation of DR4/TRAIL-R1 and DR5/TRAIL-R2, post-translation modifications, such as glycosylation and palmitoylation, receptor trafficking to the cell membrane, and receptor internalization, can modulate DR4/TRAIL-R1 and DR5/TRAIL-R2 activity (Wagner et al., 2007; Yoshida et al., 2007; Rossin et al., 2009; Twomey et al., 2015). Moreover, the localization of DR4/TRAIL-R1 and DR5/TRAIL-R2 in lipid rafts within the cell membrane serves as another mechanism for efficient signaling after trimerization (Delmas et al., 2004; VanOosten et al., 2005b; Ouyang et al., 2013).

The likelihood that tumor cell sensitivity to TRAIL is *solely* regulated by TRAIL death and/or “decoy” receptor expression has been debated since the identification of the TRAIL receptor family in the late 1990’s. The next logical location to look for cellular regulation against TRAIL-induced death is within the cell. TRAIL-induced apoptosis combines many aspects of the extrinsic and intrinsic pathways (Fig. 1). One of the first suggestions that tumor resistance to TRAIL can be regulated within a cell came from the observation that treatment with transcription or translation inhibitors (e.g., actinomycin D or cycloheximide, respectively) increased TRAIL-induced death (Griffith et al., 1998; Thomas & Hersey, 1998; Mori et al., 1999; Wajant et al., 2000). These data suggested constitutively produced, but labile, proteins were inhibiting the intracellular signaling processes required for TRAIL-mediated killing. TRAIL death receptor signaling can be inhibited at the level of the DISC by cFLIP (Schneider et al., 1997b; Thome et al., 1997; Griffith et al., 1998). As with

differential TRAIL receptor expression, cFLIP expression (or lackthereof) also does not appear to be the sole regulator of TRAIL sensitivity. A variety of reports have identified other anti-apoptotic molecules, including (but not limited to) anti-apoptotic members of the Bcl-2 family of proteins (e.g., Bcl-2 or Bcl-xL), inhibitors of apoptosis (IAP) proteins (e.g. cIAP, survivin, or XIAP), and Akt, with the potenital to protect against TRAIL-induced death (Hinz et al., 2000; Deng et al., 2002; Fulda et al., 2002; Griffith et al., 2002; Mitsiades et al., 2002; Ng & Bonavida, 2002; L. Li et al., 2004; Xu et al., 2010; Azijli et al., 2012; Finlay et al., 2014). When these pieces of information are taken into consideration, it is unlikely that a single mechanism for TRAIL sensitivity will be applicable for all tumor cell types, or even explain the profound TRAIL resistance possessed by normal cells throughout the body.

Based on the prevalence of multiple TRAIL resistance mechanisms, considerable effort has been spent identifying chemicals and natural compounds that can overcome these resistance mechanisms (Fulda, 2008, 2014; Dai et al., 2015). Among the thousands of compounds demonstrated to increase tumor cell susceptibility to TRAIL receptor agonists, some of the most striking effects have come from natural compounds mostly derived from plants. Many of these compounds (often called ‘nutraceuticals’) increase DR4/TRAIL-R1 and/or DR5/TRAIL-R2 expression, but they can also interfere with a variety of cell survival pathways (e.g., NF-kB, MAPKs, p38, ERK1/2, PI3K/AKT, and STATs) that increase resistance to TRAIL. A recent review elegantly covers a number of natural compounds that can sensitize tumor cells to TRAIL receptor agonists (Dai et al., 2015). Of the drugs currently approved for cancer treatment, proteasome inhibitors have been investigated as possible combinatorial agents with TRAIL receptor agonists. Proteasome inhibition leads to decreased cFLIP expression, increased pro-apoptotic protein expression, and cell cycle inhibition — all of which can increase TRAIL sensitivity (Bonvini et al., 2007; Shanker et al., 2008; Seki et al., 2010). Proteasome inhibitors, such as Bortezomib, also increase tumor cell sensitivity to TRAIL receptor agonists via TRAIL-R1/-R2 upregulation (Smith et al., 2007; Voortman et al., 2007). Histone deacetylase inhibitors (HDACi) are another class of attractive candidates for sensitizing tumor cells to TRAIL receptor agonists (Fulda & Debatin, 2005; Fulda, 2008). HDACi increase histone acetylation, which epigenetically alters gene expression (Johnstone, 2002). Treatment of tumor cells with HDACi increase TRAIL-R1/-R2 expression, but it also increases the signaling efficiency after TRAIL death receptor ligation (VanOosten et al., 2005a; VanOosten et al., 2005b; VanOosten et al., 2006, 2007). In addition, the expression of pro- and anti-apoptotic proteins that regulate the TRAIL-induced death pathway is modulated after HDACi treatment. Increased expression/activation of caspase-8, Bid and Bax has been reported after HDACi treatment (Rosato et al., 2003; Inoue et al., 2004; Hacker et al., 2009; Fulda, 2012; Riley et al., 2013), as well as downregulation of cFLIP and anti-apoptotic Bcl-2 family proteins (Zhang et al., 2003; Watanabe et al., 2005; Gillespie et al., 2006). Besides proteasome inhibitors and HDACi, numerous studies have demonstrated the ability of standard chemotherapeutic drugs to increase tumor cell sensitivity to TRAIL receptor agonists (Mom et al., 2009; Newsom-Davis et al., 2009; Rajeshkumar et al., 2010; Cohn et al., 2013). It is also important not to discount the importance of the relationship between TRAIL resistance and the function of the endoplasmic reticulum, heat shock proteins, and other metabolic pathways commonly

deregulated in tumor cells (Samali & Orrenius, 1998; Zhuang et al., 2013; Trivedi & Mishra, 2015). For examples, an exciting recent study by So et al. used RNA interference and cDNA overexpression to identify kinases that influenced TRAIL-induced apoptosis in DLD-1 colorectal carcinoma cells (So et al., 2015). By assessing the kinome, several key “resistor” kinases were identified. These data demonstrate that use of systems biology and network modeling is revealing a vast new set of intracellular proteins that could be therapeutically targeted to increase TRAIL-induced apoptosis. Interestingly enough, TRAIL expression can be inhibited by PRAME/EZH2 complex in CML (chronic myeloid leukemia) patients, and restoration of TRAIL expression enhanced sensitivity to chemotherapeutic drugs (De Carvalho et al., 2011; De Carvalho et al., 2013).

While it is clear a variety of compounds can be used to sensitize tumor cells to TRAIL, the ability of these compounds to induce an antitumor immune response, when given alone, can be limited (Casares et al., 2005; Obeid et al., 2007; Zitvogel et al., 2008; Zitvogel et al., 2011). Consequently, cancer therapies combining TRAIL receptor agonists with cytokine therapy or other immunomodulators to elicit antitumor immunity are being explored. For example, interferons (IFNs) can directly inhibit tumor cell function, leading to their use in the treatment of many types of malignancies (Vilcek, 2006; Ferrantini et al., 2007). While the mechanism of action of most (if not all) chemotherapeutics is to kill tumor cells, IFNs induce antitumor immunity (Dunn et al., 2006; Swann et al., 2007; Fuertes et al., 2011), as well as modulate the apoptosis signaling pathway (Kayagaki et al., 1999; Varela et al., 2001). Pre-clinical studies combining TRAIL receptor agonists with IFN led to increased tumor cell death and inhibition tumor outgrowth in mice (Merchant et al., 2004). mAb against immune-stimulatory or -inhibitory receptors are another way to increase TRAIL receptor agonist efficacy (Mitsui et al., 2010). For example, the combination of anti-TRAIL-R2 mAb with T cell activating mAb against CD40 and CD137 has been especially effective in preclinical mouse tumor models (Uno et al., 2006; Takeda et al., 2007; Westwood et al., 2010).

5. Cancer therapy using TRAIL receptor agonists

The promising preclinical data showing the potent tumoricidal activity of a number of TRAIL receptor agonists paved the way for clinical testing. Recombinant human TRAIL/Apo-2L (Dulanermin) has been tested in phase I/II clinical trials in patients with range of cancer types (including solid and hematologic tumors), with most of the cancers being advanced in stage, and alone or in combination with traditional chemotherapeutics or biologics (Table I). All the clinical studies reported Dulanermin was well-tolerated by the patients, and most of the studies reported some clinical efficacy — mostly partial responses or stable disease. Unfortunately, Dulanermin did not demonstrate significant clinical efficacy when it came to complete responses, and a number of hypotheses were proposed to explain why — including short bioavailability and the potential to bind to death-inducing and — inhibiting TRAIL receptors. A variety of modified versions of TRAIL have been engineered with the intention of increasing the circulating half-life of the molecule without significantly altering function (van der Sloot et al., 2006; Tur et al., 2008; Wahl et al., 2013; Yu et al., 2014). However, these TRAIL variants have only been tested preclinically. As an alternative to Dulanermin, agonistic monoclonal antibodies (mAb) specific for DR4/TRAIL-R1 and

DR5/TRAIL-R2 have been also explored as therapeutics for activating the TRAIL apoptotic pathway in cancer cells. The benefits of mAb therapy over soluble TRAIL include a longer in vivo half-life and the inability to binding to TRAIL decoy receptors. The agonistic anti-mouse TRAIL-R-specific mAb, MD5-1, has demonstrated potent antitumor activity in mouse models of cancer (Takeda et al., 2004). Interestingly, MD5-1 was found to inhibit the growth of TRAIL-sensitive tumors as well as induce a tumor-specific immune response that could eradicate TRAIL-resistant variants. In vitro studies demonstrated the necessity for MD5-1 to be crosslinked for optimal activity (Takeda et al., 2004). In vivo crosslinking is accomplished via Fc receptor (FcR)-bearing immune cells (e.g., B cells and $CD11c^+$ dendritic cells (DC)) (Haynes et al., 2010). Crosslinking MD5-1 also results in immune cell activation and leads to recruitment of other FcR-expressing cells to the tumor microenvironment. The apoptotic tumor cells are phagocytosed by the activated FcR-expressing immune cells, which cross-present tumor antigens to T cells (Takeda et al., 2004; Haynes et al., 2010). This FcR dependence has been recapitulated with the anti-human DR4/TRAIL-R1 mAb, drozitumab (Wilson et al., 2011). As a result of these and other studies, agonistic anti-human DR4/TRAIL-R1 and DR5/TRAIL-R2-specific mAb have been tested clinically (Table II). As with the Dulanermin trials, the majority of cancer patients receiving either anti-DR4/TRAIL-R1 or -DR5/TRAIL-R2-specific mAb had advanced disease, and many of the patients were also treated with another antitumor agent (chemotherapy or biologic). The general outcome of the clinical testing with the anti-TRAIL receptor mAb was that administration of mAb was well tolerated with minimal adverse events. Unfortunately, patients with objective responses were in the minority. It remains to be determined why these reagents, which performed so well in preclinical studies, failed to achieve marked effects in humans.

It was surprising to see that Dulanermin or any of the agonistic receptor-specific mAb did not show better therapeutic activity when used in combination with chemotherapeutics or other drugs known for their ability to sensitize tumor cells to TRAIL. Perhaps one explanation may lie in the fact that many preclinical in vitro studies used established tumor cells lines, which may have evolved over the years to no longer faithfully represent the initial tumor from which it was derived. This idea is supported by data showing the majority of primary human tumor cells are resistant to TRAIL (or agonistic mAb)-induced death (Todaro et al., 2008). Another confounding factor may be that the patients enrolled in the clinical trials may had co-morbidities (such as obesity), which were not accounted for in the preclinical models, altering tumor susceptibility to TRAIL receptor agonists. A recently proposed possibility worth clinical investigation is the combination of multiple TRAIL receptor agonists, as suggested by recent preclinical studies demonstrating synergism between an agonistic anti-TRAIL-R2 mAb (conatumumab) and Dulanermin to kill primary ovarian cancer cells (Graves et al., 2014; Tuthill et al., 2014). Conatumumab binds a different epitope within TRAIL-R2 than Dulanermin, allowing concomitant binding of both reagents that enhances receptor crosslinking, enhanced DISC formation, and caspase-8 activation. Work continues in the clinical testing of TRAIL receptor agonists, but not with the same enthusiasm as there was a decade ago. The continued development of drugs with high selectivity for targeting antiapoptotic proteins within cells keeps the door open for combination therapy with TRAIL receptor agonists against cancer.

6. Immunotherapy involving TRAIL receptor agonists in non-cancer settings

It is clear the lion's share of data generated in regard to the TRAIL/TRAIL receptor system has come from studies examining the tumoricidal activity of TRAIL. As the reagents available for probing the function of TRAIL became more plentiful, it seemed logical that investigation of the physiological role of TRAIL in non-cancer settings would occur. The use of knockout mice and agonistic/antagonistic mAb to TRAIL or TRAIL receptor has expanded the physiological importance of TRAIL to a number of key clinical and pathological settings. Systemic administration of TRAIL receptor agonists during the treatment of cancer has the potential to have "off-target" complicating effects on other components of the immune system. The therapeutic benefit of engaging the TRAIL/TRAIL receptor system in non-cancer settings is only beginning to be investigated. The following sections highlight some of the pathological settings where the TRAIL/TRAIL receptor system plays key roles in either causing or preventing the disease state, demonstrating the points where therapeutic intervention may be beneficial.

6.1. Immune tolerance and autoimmunity

Introduction of antigen (Ag) before maturation of the cellular constituents of the immune system engenders Ag-specific tolerance critical to the process by which individuals avoid autoimmunity. In addition, different mechanisms are responsible to maintain self-tolerance after the full maturation of the immune system. These mechanisms are divided into central and peripheral tolerance. Data for a role of TRAIL in central tolerance have been conflicting. Human thymocytes are susceptible to TRAIL-mediated apoptosis following activation, but activation-induced deletion of thymocytes is TRAIL independent (Simon et al., 2001). In contrast to thymocytes, peripheral human T cells remain resistant to TRAIL after activation, suggesting central and peripheral human T cells regulate susceptibility to TRAIL-induced apoptosis differently. Interestingly, a subsequent study using *Trail*$^{-/-}$ mice suggested a severe defect in thymocyte apoptosis that increased susceptibility to autoimmunity (Lamhamedi-Cherradi et al., 2003b). These data using *Trail*$^{-/-}$ mice were in contrast to a subsequent report (also using *Trail*$^{-/-}$ mice) showing no requirement for TRAIL in thymocyte negative selection (Cretney et al., 2008). Differences in the types of experiments done have been suggested as a reason for the contrasting claims of TRAIL's involvement in thymocyte negative selection, and it has been suggested that TRAIL functions as a response modifier in the thymus for mitochondrial apoptosis instead of playing a direct role in thymic negative selection (Corazza et al., 2004). Importantly, these data suggest administration of TRAIL receptor agonists in the treatment of cancer would not adversely impact thymocyte development and selection.

There is increasing evidence, on the other hand, to suggest TRAIL is a key player in regulating peripheral tolerance. TNF superfamily members are well-characterized regulators of immune responses, with TNF and FasL being prime regulators of key immune system events such as auto-immunity, activation-induced cell death (AICD), immune privilege, and evasion of tumors from the immune system (Cerami & Beutler, 1988; Alderson et al., 1995; Griffith et al., 1995; L. Zheng et al., 1995; Hahne et al., 1996; Bonfoco et al., 1998; Elzey et

al., 2001). It was not a great surprise to then see data suggesting TRAIL could also play an important role in these same areas. For example, TRAIL is constitutively expressed on numerous structures within the eye, including the cornea and retina (Lee et al., 2002). Ocular tumors are rare, suggesting a potential role for TRAIL in tumor surveillance within the eye. TRAIL expression in the eye is restricted to sites of interaction between key internal ocular structures and the surrounding tissue, much like that for Fas ligand (Griffith et al., 1995; Stuart et al., 1997). TRAIL expression in the retina is also an important regulator of oxygen-induced retinopathy (Hubert et al., 2009). Examination of the placenta, another immune privileged site, found TRAIL expression in syncytiotrophoblasts and Hofbauer cells, as well as a few other placental cell types (Phillips et al., 1999). Whether TRAIL actually contributes to immune tolerance during pregnancy remains to be determined, as inbred *Trail*$^{-/-}$ mice display no overt breeding defects (Sedger et al., 2002).

The immune system is continuously exposed to self-Ag derived from dead cells throughout an organism's life. While cells can be induced to die by various insults (e.g. death receptor, toxicity, radiation, etc.), there are two main categories of cell death — apoptotic and necrotic (Wyllie et al., 1980; Cohen, 1993; Vaux & Strasser, 1996). The way the immune system responds to antigens associated with the dying/dead cells can have a major impact on immune tolerance and autoimmunity. In the context of a multicellular organism and its immune system, one can view the cell death decision molecular switches as part of a cell disposal program encompassing not only the dying cell but also the cells responsible for its recognition and removal (Pereira & Amarante-Mendes, 2011). In this regard, apoptotic cells are swiftly removed via the reticuloendothelial system or neighboring cells in the tissue, without notice by the immune response. This rapid clearance of apoptotic cells minimizes the release of inflammatory cellular components and prevents autoimmune reactions to self-proteins. The induction of tolerance by apoptotic cells has been attributed to a number of mechanisms, including the production of immunosuppressive cytokines from phagocytic cells (Fadok et al., 1998), production of inhibitors from the dead cell itself (Gao et al., 1998; W. Chen et al., 2001), and effects on the maturation of DC (Steinman et al., 2000; Albert et al., 2001), and inactivation of *D*amage-*A*ssociated *M*olecular *P*atterns (DAMPs) (Kazama et al., 2008). In addition, apoptotic cells are thought to enter the cross-presentation pathway and promote tolerance, while necrotic cells do not (Ferguson et al., 2002; Ferguson et al., 2003). In recent years, the pivotal role played by $CD4^+$ T cells in the induction of $CD8^+$ T cell responses has been highlighted (Bennett et al., 1997; Schoenberger et al., 1998; Albert et al., 2001; Janssen et al., 2005), where most $CD8^+$ T cell-mediated responses depend on concomitant $CD4^+$ T cell priming. In contrast, $CD8^+$ T cell priming in the absence of $CD4^+$ T cell help leads to their deletion, an effect that can be overcome by supplying help during the initial priming phase (Kurts et al., 1996). The priming of $CD8^+$ T cells in the absence of $CD4^+$ T cell help also alters $CD8^+$ T cell programming, which is only revealed after restimulation. Specifically, $CD8^+$ T cells activated without $CD4^+$ T cell help express TRAIL and undergo AICD upon secondary Ag stimulation (Janssen et al., 2005; Wolkers et al., 2011; Feau et al., 2012; Wolkers et al., 2012). Immune unresponsiveness associated with the generation of such TRAIL-expressing 'helpless' CD8 T cells has been reported in a number of experimental models and clinical settings (Hamilton et al., 2006; Griffith et al., 2007; Kuerten et al., 2008; Gurung et al., 2010; Unsinger et al., 2010; Griffith et al., 2011; Gurung

et al., 2011), but this concept has proven to be more tenuous in some models of infection (see below) (Badovinac et al., 2006; Sacks & Bevan, 2008). However, apoptosis does not always result in tolerance, as it seems to be the case of lymphocyte apoptosis. Lymphocytes are cytokine factories that can cause significant, nonspecific cellular damage if their contents are released to the rest of the immune system. During an infection when significant lymphocyte apoptosis occurs, immunity can be directed away from the pathogen toward self, thereby contributing to autoimmunity.

A loss of peripheral tolerance can influence a number of immunological parameters, including the susceptibility to autoimmune disease. *Trail*$^{-/-}$ and *Dr5*$^{-/-}$ mice do not spontaneously develop autoimmunity, but their use (as well as anti-TRAIL blocking mAb or soluble TRAIL receptor:Fc fusion protein) in a number of autoimmunity models has revealed that TRAIL inhibits diabetes (in NOD mice or induced by cyclophosphamide and streptozatocin), EAE, and autoimmune arthritis (Song et al., 2000; Hilliard et al., 2001; Lamhamedi-Cherradi et al., 2003a; Mi et al., 2003; Cretney et al., 2005). Moreover, therapeutic administration of recombinant TRAIL will delay the onset and reduce the severity of MOG-induced EAE (Cretney et al., 2005) or experimental autoimmune thyroiditis (S. H. Wang et al., 2005), while administration of dendritic cells engineered to express TRAIL can inhibit collagen-induced arthritis (Liu et al., 2003). It is also possible the increased TRAIL expression, as a result of some other condition, results in the increased cell death (and increased generation of self Ag) driving the initiation of autoimmunity. For example, data from several reports show increased TRAIL in the circulation of patients with autoimmune diseases, such as systemic lupus erythematosis, multiple sclerosis, ankylosing spondylitis, psoriatic arthritis, and Sjogren's syndrome (Matsumura et al., 2002; Wandinger et al., 2003; Lub-de Hooge et al., 2005; Hofbauer et al., 2006; Zai-Xing et al., 2008). Similarly, neuronal death in a T cell-induced EAE model is TRAIL mediated, and administration of soluble TRAIL-R2:Fc reduced clinical symptoms (Aktas et al., 2005). Thus, administration of a TRAIL neutralizing agent may reduce the clinical symptoms of autoimmunity, much like TNF neutralization in rheumatoid arthritis. It is also tempting to speculate that alterations in OPG expression may partially contribute to the development of autoimmune and other diseases (especially vascular pathologies) (Baud'huin et al., 2013). Together, these data suggest selective signaling or disruption of the TRAIL/TRAIL receptor pathway may prove to be a viable treatment option for a number of autoimmune diseases.

6.2. TRAIL and infection

Toll-like receptor (TLR) recognition of pathogen-associated molecular patterns triggers a cascade of signals alerting the immune system to the presence of an invading organism. Interferon (IFN) is among the multitude of cytokines produced after TLR stimulation (McNab et al., 2015), and IFN (both type I and II) is a potent inducer of TRAIL expression (Q. Wang et al., 2000). TRAIL receptor expression is also sensitive to IFN (Griffith et al., 1999; Sedger et al., 1999). Thus, the potential for the TRAIL/TRAIL receptor system in the immune response to pathogen infection has received significant attention in recent years. For example, infection with influenza A virus (IAV) generates a strong IFN response, and TRAIL is one of several effector mechanisms used by IAV-specific T cells to protect against infection (Ishikawa et al., 2005; Hamada et al., 2013). IAV-specific CD8 T cells express

TRAIL during infection, and IAV-infected lung alveolar epithelial cells upregulate DR5 expression (Brincks et al., 2008). Interestingly, *Trail*$^{-/-}$ mice are unable to clear an IAV infection as well as wild-type mice, and *Trail*$^{-/-}$ mice are more susceptible to death from immunopathology after IAV infection (Brincks et al., 2008; Brincks et al., 2011). Additional data report increased TRAIL expression after infection with Dengue virus, hepatitis virus, human immunodeficiency virus, measles virus, respiratory syncytial virus, and West Nile virus contributes to both viral clearance and immunopathology (Bem et al., 2010; Stegmann et al., 2010; van Grevenynghe et al., 2011; Barblu et al., 2012; Shrestha et al., 2012; Abdullah et al., 2013; Gandini et al., 2013; Gras et al., 2013; Werner et al., 2013; Brost et al., 2014; Limonta et al., 2014).

Viral immune evasion can occur by a variety of mechanisms, primarily through the down-regulation of proteins on infected cells that alert the immune system. It should not be surprising to see a number of viruses have evolved means to prevent cellular apoptosis by modulating TRAIL and/or TRAIL receptor expression. The adenoviral E3 complex can decrease TRAIL receptor expression in infected cells to enable persistent infection (Benedict et al., 2001; Tollefson et al., 2001; Lichtenstein et al., 2004). Cytomegalovirus (CMV) infection also leads to a significant modulation of TRAIL and/or TRAIL receptor. Human CMV infection during pregnancy can lead to serious complications, and one means by which this may occur is through placental up regulation of TRAIL via an IFN-mediated mechanism to evade responding immune cells (Andrews et al., 2007). Studies with mouse CMV (MCMV) have revealed a number of interesting aspects of how this virus modulates TRAIL/TRAIL receptor expression to elude cellular immunity. First, MCMV infection leads to decreased DR5 expression, which is mediated by m166 protein (Verma et al., 2014). Second, NK cells up regulate TRAIL following MCMV infection and play an important role in the clearance of MCMV-infected cells (Cortez et al., 2014; Schuster et al., 2014). TRAIL-expressing NK cells also mediate the deletion of $CD4^+$ T cells in the salivary glands of MCMV-infected mice, which is important in preventing autoimmune reactions within this tissue (Cortez et al., 2014).

Viruses are not the only pathogens to modulate the TRAIL/TRAIL receptor system during an infection. Bacterial pathogens stimulate a wide range of responses in the cells they infect, commonly leading to inflammation. Bacterially infected cells frequently initiate the apoptotic death mechanism to limit the spread of the infection. For some bacterial species, inhibiting inflammation and cell death is critical for allowing them to evade the immune system and establish an infection. For other species, the induction of cell death in the infected cell permits pathogen spread and (ultimately) survival. It has become evident in recent years that the TRAIL/TRAIL receptor system is a key player in both sides of that equation. For example, the pathogenesis seen during a number of bacterial infections is the result of increased TRAIL-induced death of the infected cells. A strong inflammatory response within the gastric mucosa is associated with *Helicobacter pylori* infection, which as been linked to chronic gastritis, ulcers, and carcinoma (Penta et al., 2005). *H. pylori* infection induces a Th1 CD4 T cell response, and *H. pylori*-infected gastric epithelial cells are highly sensitive to TRAIL-induced apoptosis as a result of decreasing cFLIP expression (Lin et al., 2014). Human DR4/TRAIL-R1 SNPs and murine DR5 negatively regulate the immune response against chlamydial infection (Al-Kuhlani et al., 2014). Interestingly,

TRAIL can also promote Chlamydia respiratory infection-induced pathology and inflammation, which may be the result of increased expression of type I IFNs (Qiu et al., 2008), that subsequently lead to impaired lung function (Starkey et al., 2014). These data suggest therapeutic blockade of TRAIL would improve the health of Chlamydia-infected patients. Similar findings have been reported in mouse model of listeriosis, where wild-type mice had increased *Listeria monocytogenes* loads and decreased survival compared to *Trail*$^{-/-}$ mice (S. J. Zheng et al., 2004). In contrast, therapeutic administration of TRAIL or agonistic anti-DR5/TRAIL-R2 (MD5-1) mAb can improve the survival of *Streptococcus pneumoniae*-infected mice (Steinwede et al., 2012). In this setting, neutrophil-derived TRAIL induces apoptosis in DR5/TRAIL-R2-expressing macrophages, allowing for the early killing of *S. pneumoniae*. These data suggest TRAIL receptor agonist therapy may prove beneficial for immune compromised patients infected with *S. pneumoniae*. Similarly, TRAIL expression is critical for limiting the host immune response in bacterial meningitis, and therapeutic administration of TRAIL intrathecally decreased inflammation (Hoffmann et al., 2007). We realize this is not an exhaustive listing of instances where the TRAIL/TRAIL receptor system participates (in either a good or bad way) during bacterial infection, but it does provide a sense of the types of pathogens where targeting the TRAIL could improve clinical outcomes.

6.3. TRAIL and cardiovascular health

Innate and adaptive immunity, along with inflammation, play important roles in atherogenesis. Vascular smooth muscle cells (VSMCs) and cardiomyocytes express functional TRAIL receptor, while vascular endothelial cells express low amounts of TRAIL receptor (Secchiero et al., 2003; Secchiero et al., 2004; Spierings et al., 2004). The role of TRAIL in atherogenesis has been examined in vitro and in vivo using *Trail*$^{-/-}$*ApoE*$^{-/-}$ mice, yielding variable results. Soluble and membrane-bound TRAIL can induce apoptotic death in endothelial cells (Li et al., 2003; Pritzker et al., 2004; Chen & Easton, 2008; Chen & Easton, 2010). In line with this data is the observation that coronary artery disease patients have $CD4^+$ T cells with elevated TRAIL expression (Sato et al., 2010). TRAIL-mediated tissue destruction and plaque destabilization is thought to occur in this setting. Conversely, there is also a significant amount of data supporting a protective role for TRAIL in cardiovascular disease. Circulating TRAIL levels are reduced in patients with acute coronary syndromes, coronary artery disease, diabetes, and myocardial infarction (Michowitz et al., 2005; Schoppet et al., 2006; Volpato et al., 2011; Bisgin et al., 2012). The protective nature of TRAIL is further supported in rodent models of atherosclerosis (Secchiero et al., 2006; Di Bartolo et al., 2011; Di Bartolo et al., 2013), pulmonary hypertension (Hameed et al., 2012) and diabetes (Di Bartolo et al., 2011). TRAIL-mediated anti-apoptotic effects on endothelial cells have been seen (Secchiero et al., 2004; Kavurma & Bennett, 2008; Kavurma et al., 2008). In vitro stimulation of VSMCs with physiologically relevant concentrations of TRAIL stimulates their proliferation and migration (Kavurma et al., 2008; Azahri et al., 2012). A similar effect of TRAIL on VSMCs has been reported in vivo, where vascular injury in *Trail*$^{-/-}$ mice results in reduced proliferation of VSMCs and intimal thickening (Chan et al., 2010). Interestingly, atherosclerotic plaque development is accelerated in *Trail*$^{-/-}$*ApoE*$^{-/-}$ mice (Di Bartolo et al., 2011; Di Bartolo et al., 2013; Cartland et al., 2014). The atherosclerotic plaques in the *Trail*$^{-/-}$*ApoE*$^{-/-}$ mice have reduced VSMC and collagen

content, large necrotic cores, thin fibrous caps, and significantly increased macrophage accumulation in the vulnerable regions of the plaque (Di Bartolo et al., 2011). Collectively, these data demonstrate TRAIL has the potential to exert a variety of beneficial and deleterious biological effects when it comes to the health of the cardiovascular system. It is likely the differences seen in the various in vitro and in vivo studies relate to the concentration of TRAIL used in the assays and target cells being investigated. Regardless, these data strongly suggest many of the same therapeutic approaches used in the other physiological settings described earlier to engage or block the TRAIL/TRAIL receptor system could be employed to improve cardiovascular health in patients dealing with cardiovascular anomalies.

7. Conclusions

It has been 20 years since Wiley and colleagues and Pitti and colleagues first described TRAIL (Wiley et al., 1995; Pitti et al., 1996). Over the subsequent two decades, investigation into the natural function of TRAIL in a broad range of diseases and therapeutic potential of TRAIL receptor agonists has yielded a bountiful amount of useful data. While many once viewed TRAIL as that “magic bullet” for treating cancer, it is clear this initial rosy perception has darkened with the underwhelming clinical data exploring TRAIL receptor agonists against cancer. However, hope should not be lost as exciting work continues to be published keeping TRAIL-based cancer immunotherapy a viable future goal. The identification of new drugs that sensitize tumor cells to TRAIL receptor agonists, as well as continued testing of TRAIL receptor agonists with approved drugs, is opening new doors for the treatment of tumors. Caution must be maintained, however, to limit any potential augmentation in TRAIL sensitivity in normal cells and tissues. It is also important not to overlook the knowledge gained from the preclinical and clinical testing of TRAIL receptor agonists with respect to the potential use of the same TRAIL agonists and antagonists in “non-cancer” diseases. Likewise, the concentrated efforts in using TRAIL receptor agonists have dwarfed the number of studies demonstrating the importance in inhibiting TRAIL/TRAIL receptor signaling. TNF is a good example of a protein once thought to be an ideal cancer therapy to one whose presence can be detrimental to health, and the drugs that neutralize TNF have improved the lives of millions with rheumatoid arthritis. We should not limit our studies of TRAIL to those testing its antitumor activity. Let’s hope the next 20 years of TRAIL research will build on the first 20 years, and allow us to add TRAIL receptor agonists to the growing toolbox of immunotherapeutics for cancer and beyond.

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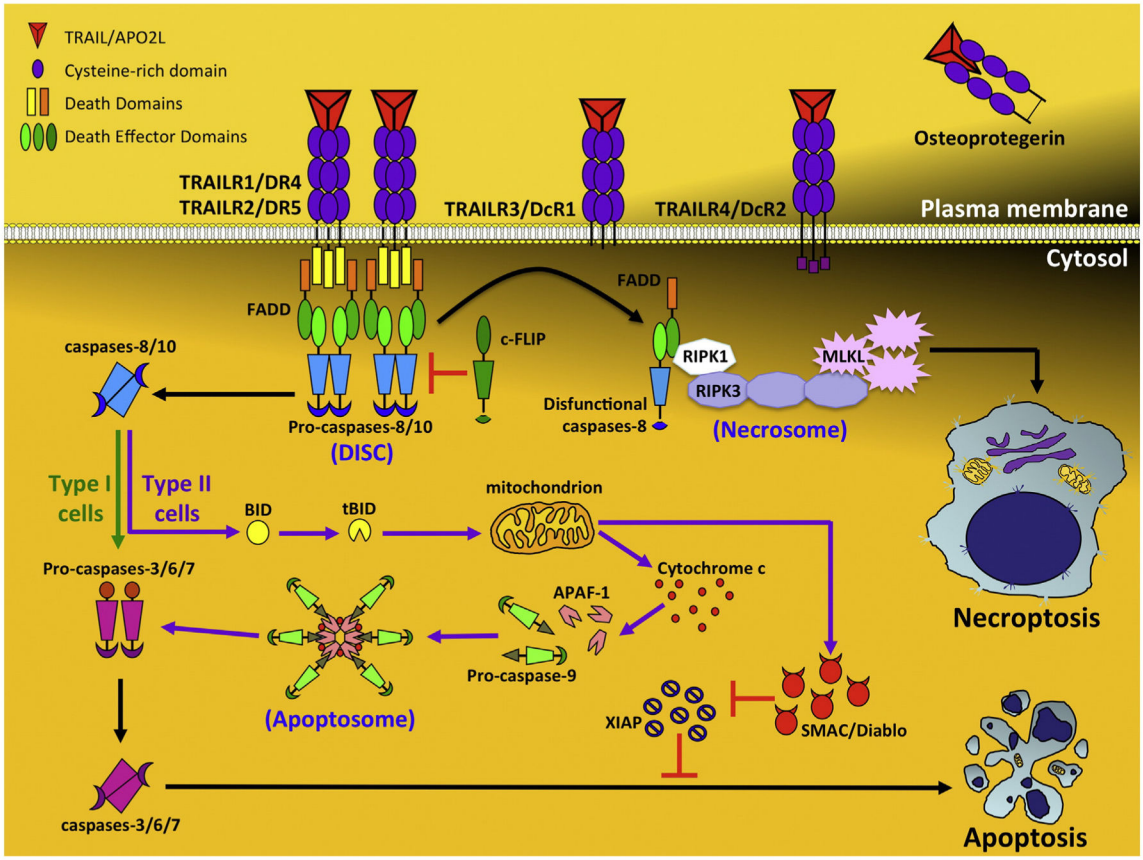

Fig. 1.

TRAIL/Apo2L, its receptors and cell death signaling pathways. TRAIL/Apo2L is a trimeric protein able to associate with five different proteins that may act as transducer of cell death and other signals (DR4/TRAIL-R1 and DR5/TRAIL-R2) or non-signaling, decoy receptors (DcR1/TRAIL-R3, DcR2/TRAIL-R4 and OPG) that act as inhibitory molecules. Binding of TRAIL/Apo2L to trimeric forms of DR4/TRAIL-R1 or DR5/TRAIL-R2 at the cell membrane leads to a high molecular weight receptor cluster formation responsible for recruitment of FADD and pro-caspase-8/10 to assemble the Death-Inducing Signaling Complex (DISC). Active caspase-8 can subsequently cleave the effector caspases-3/-6/-7 in Type I cells or process the BH3-only member BID in Type II cells. The truncated form of BID (tBID) translocates to the mitochondria and, via BAX and BAK, induces Mitochondria Outer Membrane Permeabilization (MOMP) and consequent release of apoptogenic factors to the cytosol. Cytochrome c catalyzes the assembly of the Apoptosome, a multimolecular platform comprised of APAF-1 and procaspase-9. Similarly to caspase-8, caspase-9 processes and activates the effector caspases, culminating in apoptosis. The release of SMAC/Diablo from the mitochondria to the cytosol results in inactivation of members of the Inhibitor of Apoptosis Protein (IAP) family, particularly XIAP, an endogenous inhibitor of caspases, thereby facilitating apoptosis. TRAIL-induced apoptosis can be blocked at the DISC by cFLIP, a caspase-8/10 homologous protein that lacks enzymatic activity. Under particular circumstances, such as deficiency in caspase-8, an alternative cell death-inducing

complex called necroptosome and composed by RIPK1, RIPK3 and the pseudokinase MLKL is formed, leading to necroptosis.

Table I

Clinical use of Dulanermin.

Clinical trial phase	Cancer (number of patients) treated	Combination	Reported effect	References
I	Lymphoma (7)	Rituximab	1 partial response/2 complete responses	Yee, et al., 2007
I	Colorectal (30)	Irinotecan/cetuximab or FOLFIRI	Safely combined with irinotecan-based regimens	Yee, et al., 2009
I	Advanced solid tumors or NHL (71)	None	Well-tolerated; 2 partial responses	Herbst, Eckhardt, et al., 2010
I	Advanced NSCLC(24)	Paclitaxel, carboplatin, and bevacizumab	Well-tolerated; 13 partial responses/1 complete response	Soria, et al., 2010
I	Metastatic colorectal (27)	FOLFIRI +/−bevacizumab	Well-tolerated; 6 partial responses/17 stable disease/3 progressive disease/1 no tumor assessment	Kasubhai, et al., 2012
I	Metastatic colorectal (23)	Modified FOLFOX6 and bevacizumab	Well-tolerated; 13 partial responses/7 stable disease/3 progressive disease	Wainberg, et al., 2013
II	NHL (26)	Rituximab	Well-tolerated; no improvement in objective response rates	Belada, et al., 2010
II	NSCLC (50)	Paclitaxel/carboplatin ± bevacizumab	Well-tolerated; addition of Dulanermin did not improve efficacy	Blackhall, et al., 2010; Soria, et al., 2011

Table II

Clinical use of anti-TRAIL receptor mAb.

	Clinical trial phase	Cancer (number of patients) treated	Combination	Reported effect	References
Anti-TRAIL-R1: Mapatumumab (HGS-ETR1)	I	Advanced solid tumors (49)	None	Well-toleranted; no toxicities	Tolcher, et al., 2007
	I	Advanced solid tumors (41)	None	Well-tolerated; no objective responses/12 stable disease	Hotte, et al., 2008
	I	Advanced solid tumors (49)	Gemcitabine and cisplatin	Well-tolerated; 12 partial responses/25 stable disease	Mom, et al., 2009
	I	Advanced solid tumors (27)	Paclitaxil and carboplatin	Well-tolerated; 5 partial responses/12 stable disease	Leong, et al., 2009
	I	NHL (40)	None	Well-tolerated; 1 partial response/2 complete responses	Younes, et al., 2010
	II	Advanced NSCLC (32)	None	Well-tolerated; no objective responses/9 stable disease	Greco, et al., 2008
	II	Colorectal (38)	None	Well-tolerated; no objective responses/12 stable disease	Trarbach, et al., 2010
	II	Advanced NSCLC (109)	Paclitaxil and carboplatin	Well-tolerated; no objective responses	von Pawel, et al., 2014
Anti-TRAIL-R2: Conatumumab (AMG 655)	I	Metastatic pancreatic (13)	Gemcitabine	Well-tolerated; 3 partial responses/6 stable disease	Kindler, et al., 2012
	I	Metastatic colorectal (12)	FOLFOX6 and bevacizumab	Well-tolerated; 5 partial responses/6 stable disease	Saltz, et al., 2009
	I	Advanced NSCLC (12)	Paclitaxil and carboplatin	Well-tolerated; 1 complete response/3 partial responses/3 stable disease/3 progressive disease	Paz-Ares, et al., 2013
	I	Advanced solid tumors (37)	None	Well-tolerated; 1 partial response/14 stable disease	Herbst, Kurzrock, et al., 2010
	I	Advanced solid tumors (9)	Ganitumab (AMG 479)	Well-tolerated; 3 stable disease	Chawla, et al., 2010
	I	Advanced solid tumors (18)	None	Well-tolerated; 9 stable disease	Doi, et al., 2011
	I/II	Soft tissue sarcoma (6 Phase I; 128 Phase II)	Doxorubicin	Well-tolerated; no responses	Demetri, et al., 2012
	II	Metastatic pancreatic (125)	Ganitumab (AMG 479)	Well-tolerated; no responses	Kindler, et al., 2012
	II	Advanced NSCLC (172)	Paclitaxil and carboplatin	Well-tolerated; no responses	Paz-Ares, et al., 2013

	Clinical trial phase	Cancer (number of patients) treated	Combination	Reported effect	References
	Ib/II	Metastatic colorectal (12 Phase I; 190 Phase II)	FOLFOX6 and bevacizumab	Well-tolerated; no responses	Fuchs, et al., 2013
	II	Metastatic colorectal (155)	Ganitumab (AMG 479) and FOLFIRI	Well-tolerated; no responses	Cohn, et al., 2013
Anti-TRAIL-R2: Drozitumab	I	Advanced tumors	None	Well-tolerated; no responses	Camidge, et al., 2010
	Ib	Metastatic colorectal (9)	mFOLFOX6 and bevacizumab	Well-tolerated; 2 partial responses	Rocha Lima, et al., 2012
Anti-TRAIL-R2: Lexatumumab (HGS-ETR2)	Ib	Advanced tumors (41)	Gemcitabine, pemetrexed, doxorubicin, or FOLFIRI	Well-tolerated; 3 partial responses	Sikic, et al., 2007
	I	Advanced solid tumors (37)	None	Well-tolerated; 12 stable disease	Plummer, et al., 2007
	I	Advanced solid tumors (31)	None	Well-tolerated; no responses	Wakelee, et al., 2010
	I	Pediatric solid tumors (24)	None	Well-tolerated; no responses	Merchant, et al., 2012
Anti-TRAIL-R2: LBY135	I/II	Advanced solid tumors (73)	Capecitabine	Well-tolerated; 2 partial responses	Sharma, et al., 2014
Anti-TRAIL-R2: Tigatuzumab (CS-1008)	I	Relapsed/refractory carcinoma (16) or lymphoma (1)	None	Well-tolerated; 7 stable disease	Forero-Torres, et al., 2010
	II	Metastatic pancreatic (62)	Gemcitabine	Well-tolerated; 8 partial responses	Forero-Torres, et al., 2013
	II	NSCLC (97)	Carboplatin and paclitaxel	Well-tolerated; no responses	Reck, et al., 2013
	II	Triple negative breast cancer (39)	Paclitaxel	Well-tolerated; 3 complete responses/8 partial responses/11 stable disease	Forero-Torres, et al., 2015