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Developing TRAIL/TRAIL-death receptor-based cancer therapies

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Abstract

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the TNF superfamily that can initiate the apoptosis pathway by binding to its associated death receptors DR4 and DR5. The activation of the TRAIL pathway in inducing tumor-selective apoptosis leads to the development of TRAIL-based cancer therapies, which include recombinant forms of TRAIL, TRAIL receptor agonists and other therapeutic agents. Importantly, TRAIL, DR4 and DR5 can all be induced by synthetic and natural agents that activate the TRAIL apoptosis pathway in cancer cells. Thus, understanding the regulation of the TRAIL apoptosis pathway can aid in the development of TRAIL-based therapies for the treatment of human cancer.

Keywords

TRAIL; apoptosis; resistance; cancer therapy

1 Introduction

Inducing apoptosis in tumor cells is a key anti-cancer treatment strategy [1]. There are two major signaling pathways that lead to apoptosis, namely the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway [2]. The intrinsic apoptosis pathway is controlled by the Bcl-2 family members, which can be initiated by the activation of the tumor suppressor p53 in response to DNA damage by chemotherapy and radiotherapy [2]. However, conventional chemotherapy often fails to activate the intrinsic apoptosis pathway due to the loss of p53-mediated apoptosis [3]. On the other hand, the extrinsic apoptosis pathway is initiated by death receptor activation by ligands such as TNF-Related Apoptosis-Inducing Ligand (TRAIL) [2,4]. TRAIL binds to the death receptors DR4 and DR5 and triggers the apoptotic cascade by recruiting Fas-associated protein with death domain (FADD) via death domain interactions and thereafter, by FADD binding to the death effector

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domain present on pro-caspases-8 and -10 to form a death-inducing signaling complex (DISC). TRAIL can thus lead to direct activation of the caspase cascade resulting in apoptotic cell death. However, the intrinsic and extrinsic apoptotic pathways can crosstalk through caspase-8-mediated cleavage of Bid, triggering the intrinsic apoptotic pathway.

The early observation that tumor cells exhibit exquisite sensitivity to TRAIL over normal cells highlighted its potential as a novel cancer agent [5]. Consequently, recombinant human TRAIL (RhTRAIL) proteins or agonistic antibodies against DR4 and DR5, also called PARAs (pro-apoptotic receptor agonists), have been developed and shown to be effective in inducing apoptosis in various tumor cell lines [6,7]. In addition, a number of studies have indicated that rhTRAIL and PARAs enhance tumor sensitivity to chemotherapy, targeted therapy and radiotherapy [8–10]. However, development of resistance to TRAIL-induced apoptosis can greatly diminish the clinical potential of TRAIL-based agents. Thus, identifying the mechanisms of TRAIL resistance and restoring the sensitivity of tumor cells to TRAIL-based therapies could help improve their therapeutic efficacies. In this review, we discuss the potential for targeting TRAIL signaling in human cancers and the diverse molecular mechanisms by which tumor cells develop TRAIL resistance. In addition, emphasis is placed on synthetic and natural agents that stimulate the expression of TRAIL and its death receptors to induce cancer cell death.

2 TRAIL signaling

TRAIL is a 281-amino acid type II transmembrane protein that belongs to the TNF superfamily [11]. TRAIL is expressed in a variety of human fetal and adult tissues including small intestine, colon, spleen, thymus, prostate and placenta, and in immune cells such as natural killer (NK) cells, B cells, monocytes and dendritic cells [12–16]. The extracellular domain of TRAIL can be shed from the cell surface and are active as self-assembling non-covalent trimers. Both the soluble and membrane-bounded TRAIL can bind to its five distinct receptors DR4, DR5 DcR1, DcR2, and osteoprotegrin (OPG) [17]. DR4 and DR5 are type I membrane proteins with 2–4 similar cysteine-rich domains in the extracellular portion and a ~70 amino acid “death domain” in the cytoplasmic portion. The death receptors induce apoptosis upon TRAIL binding. DcR1 and DcR2 are two membrane decoy receptors while OPG is a soluble decoy receptor. Those three decoy receptors compete with the death receptors for TRAIL binding and thus block apoptotic signals.

Activation of death receptors by TRAIL leads to the recruitment of caspase-8 and FADD to form the DISC [4]. This can result in the activation of downstream effector caspases-3, -6, and -7 and subsequently induce apoptosis. It has been shown that many other proteins can be recruited into the DISC, including Cul3, a member of the cullin family of E3 ligases and PP2AC, a catalytic subunit of protein phosphatase 2A [18–20] (Figure 1). In some cells, the death receptor-initiated signal is not sufficient to trigger the caspase cascade. Here, the death receptor-induced caspase-8 activation cleaves the pro-apoptotic BH3-only Bcl-2 family member, Bid, thereby generating active truncated Bid (tBid), which interacts with Bax and Bak at the mitochondrial membrane to promote the release of apoptotic factors [21]. These apoptotic factors bind to apoptotic peptidase activating factor 1 (Apaf-1) and pro-caspase-9 to form a functional apoptosome, which initiates the caspase cascade to induce apoptosis.

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TRAIL can also induce lysosomal translocation of Bim and Bax through recruitment of the multifunctional sorting protein phosphofurin acidic cluster sorting protein-2 (PACS-2) to DR5-positive endosomes [22]. PACS-2 forms a complex with Bim and Bax on lysosomal membranes and releases cathepsin B to induce apoptosis. The metabolic status of the cell significantly affects TRAIL-induced cell death. For instance, 2-deoxyglucose, an inhibitor of glycolysis enhances TRAIL-induced cell death [23]. Paradoxically, inhibition of glycolysis by means of glucose deprivation can inhibit apoptosis [23]. This varied responses to glycolytic inhibition is determined by the balance between the activation of AKT and AMPK (AMP-activated protein kinase) pathways. The consequence of the balance impacts protein translation and the levels of anti- and pro-apoptotic Bcl-2 family member proteins. This indicates that cellular metabolic status can regulate the mitochondrial apoptotic pathway and thereby sensitivity to antitumor agents such as TRAIL. Treatment with methylglyoxal, a side product of glycolysis, or inhibition of glyoxalase I (GLO1) can also sensitize cancer cells to TRAIL [24]. TRAIL signaling is also positively regulated by mitogen-activated protein kinase kinase (MEK)/extracellular-signal-regulated kinase (ERK) signaling as MEK inhibition decreases sensitivity of cancer cells to TRAIL treatment [25]. Mechanistically, MEK inhibition negatively regulates DR4 expression and cellular response to TRAIL-induced apoptosis [25]. Increasing evidence indicates that endoplasmic reticulum (ER) stress can stimulate the activation of TRAIL receptors [26,27]. In macrophages, ER stress is a potent inducer of TRAIL signaling, and specific inhibition of Jun N-terminal kinase (JNK) and transcription factor AP-1 can inhibit the expression of TRAIL [28]. Mechanistically, ER stress induces the expression of activating transcription factor 4 (ATF4), which in turn regulates ATF3 and CCAAT/enhancer-binding protein homologous protein (CHOP) expression. ATF3 physically interacts with CHOP forming a complex to regulate DR5 expression. Loss of ATF4, ATF3, or CHOP reduced the DR5 levels and decreased apoptosis [29]. Alternately, TRAIL can induce ER stress via caspase-8-mediated cleavage of B cell receptor-associated protein 31 (BAP31) [30]. Increased production of reactive oxygen species (ROS) can regulate TRAIL signaling by ROS-ERK-CHOP-mediated up-regulation of DR4 and DR5 expression [31]. ROS can also induce Bax phosphorylation at threonine-167, sensitizing cells to TRAIL-mediated apoptosis [32]. TRAIL signaling has been implicated in activating the NF-κB pathway via the TRAIL receptor death domain (DD), FADD, and caspase-8 [33]. Loss-of-function mutation in FADD halts the recruitment of caspase-8 and thus prevents NF-κB activation [33].

3 Physiological roles for TRAIL signaling

TRAIL signaling is known to regulate metabolism and differentiation and is also involved in some diseases. For example, in adipocytes TRAIL treatment results in a reduction of insulin-stimulated glucose uptake as well as de novo lipogenesis [34]. This is mediated by caspase-8/caspase-3 activation and cleavage of PPARgamma, which in turn down-regulates the expression of lipogenic genes, such as Glut-4 and FASN [34]. TRAIL also plays a role in spermatogenesis [35]. Specifically, *Trail* knockout (*Trail*$^{-/-}$) mice exhibit significantly lower testis to body weight ratios and spermatid head counts, while displaying increased levels of basal germ cell apoptosis [35]. In addition, TRAIL is implicated in osteoclast differentiation through a TNF receptor-associated factor 6 (TRAF-6)-dependent signaling pathway [36].

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TRAIL signaling is also involved in the pathogenesis of pulmonary arterial hypertension (PAH) [37]. TRAIL promotes microvascular hyperpermeability through caspase-3 cleavage of the endothelial adherens junctions, which is dependent on the phosphatidylinositol 3-kinase (PI3K) pathway [38]. Furthermore, data from multiple rodent models indicate that genetic deletion or antibody blockade of TRAIL can hinder the development of PAH [37]. In allergic airway inflammation, TRAIL regulates airway remodeling by up-regulating the E3 ubiquitin ligase Midline-1 (MID-1), which decreases the dephosphorylation of proinflammatory signaling molecules by protein phosphatase 2A [39]. *Trail*$^{-/-}$ mice lack airway remodeling, including peribronchial fibrosis, smooth muscle hypertrophy, and mucus hypersecretion [40]. Moreover, TRAIL signaling may be a new target for the treatment of some diseases, including liver fibrosis and influenza [41,42]. In addition, TRAIL signaling contributes to antiviral immunity by inducing apoptosis and promoting immune homeostasis during infection [43]. In a rat model of harmful focal ischemia, immunoneutralization of TRAIL significantly decreased tissue damage and exhibited functional recovery, underscoring a potential for the treatment of stroke [44]. Studies in the murine inner ear revealed a role for increased expression of TRAIL in triggering hair cell and neuronal degeneration, which can be suppressed with antibodies against DR5 [45].

4 Mechanisms of TRAIL resistance in cancer

TRAIL has been recognized as a promising target for cancer therapy because it can induce apoptosis in tumor cells but not normal cells. Although TRAIL shows high anti-tumor activity, resistance to TRAIL-induced apoptosis in tumor cells has been considered a clinical obstacle to its application. It is known that tumor cells with high nuclear localization of DR5 are resistant to TRAIL, whereas tumor cells without nuclear DR5 are highly sensitive to TRAIL [46]. The mutation of functional nuclear localization signals or knockdown of importin β1 can block the nuclear localization of DR5 and result in increased DR5 expression on the cell surface, and therefore, TRAIL sensitivity [46]. Low sensitivity to TRAIL also correlated with expression of anti-apoptotic members of the Bcl-2 family. For example, overexpression of Bcl-2 can inhibit TRAIL-induced apoptosis [47,48], and Bcl-xL inhibition significantly sensitized cells to TRAIL-induced apoptosis [49]. In addition, TRAIL resistance has been associated with lipid rafts, where the EGFR pathway is activated while TRAIL fails to induce effective death-inducing signaling complex formation [50]. Inhibition of epidermal growth factor receptor (EGFR) along with knockdown of casitas B-lineage lymphoma-b (Cbl-b) enhances TRAIL-induced apoptosis in these cells [50]. TRAIL-induced apoptosis is also altered by the multidrug transporter P-glycoprotein (Pgp) and the latter regulates endogenous TRAIL expression [51,52]. Blocking Pgp transport activity increases cell sensitivity to TRAIL [51,52]. It is also known that survivin and myeloid cell leukemia sequence 1 (Mcl-1) confer TRAIL resistance, and that inhibition of survivin and Mcl-1 sensitizes resistant tumor cells to TRAIL [53].

In breast cancer, cell lines of mesenchymal origin are susceptible to TRAIL while epithelial-like cell lines are TRAIL-resistant [54]. TRAIL sensitivity of breast cancer stem cells was inversely correlated with the cellular FLICE-like inhibitory protein (cFLIP), while overexpression of cFLIP in the cytosol relieved these cells from cytotoxicity [55]. The ERK1/2 pathway regulates cFLIP levels and thus impacts TRAIL sensitivity [56]. Caspase-8

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is also involved in TRAIL sensitivity. Pro-caspase-8 mutations inhibit activation of the TRAIL pathway and confer resistance to death receptor activators [57]. Smad7, a negative regulator for the transforming growth factor-β (TGF-β) signaling pathway, binds to the caspase-8 promoter and enhances the recruitment of the interferon regulatory factor 1 (IRF1) transcription factor to the interferon-stimulated response element (ISRE) on the caspase-8 promoter [58]. Thus, Smad7 expression can restore the caspase cascade in apoptosis-resistant cells, rendering them susceptible to TRAIL-induced cell death. NF-κB signaling also plays a role in resistance against death receptor-induced apoptosis where TRAIL-resistant cells display a significant increase in TRAIL-inducible NF-κB activity, while TRAIL-sensitive cells display only a moderate level of NF-κB activity [59]. Activation of the NF-κB pathway upon TRAIL treatment is dependent on caspase-8-mediated cleavage of RIP1 [60]. Cleavage of RIP1 impairs IκB kinase (IKK) recruitment and thus NF-κB activation. In TRAIL-resistant cells, cFLIP restricts caspase-8 activity and RIP1 cleavage, which generates a cleaved fragment that can activate NF-κB but not apoptosis [60]. *In vivo*, the interaction of TRAIL, DR5 and NF-κB induces lung metastasis of melanoma in mice [61]. In cells with a defective mitochondrial apoptotic pathway, TRAIL induced phenotypic changes such as membrane blebbing and a transient loss of substrate adhesion properties while stimulating the migration potential of these cells [62]. Suppression of the apoptosis inhibitor cFLIP results in partial sensitization of TRAIL-resistant cancer cells to the pro-apoptotic effects of TRAIL, and the levels of cFLIP positively correlated with the survival of cancer patients [63,64].

The cytosolic translocation of the nuclear protein, HMGB1 (high mobility group box 1), plays a key role in TRAIL-mediated cancer cell death through autophagy [65]. TRAIL triggers PARP1 (poly [ADP-ribose] polymerase 1) activation and ADP-ribosylation of HMGB1 in cancer cells. PARP1 inhibition blocks HMGB1 cytoplasmic translocation and formation of the HMGB1-BECN1 complex, resulting in decreased autophagy, increased apoptosis, and increased sensitivity to TRAIL both *in vitro* and *in vivo* [65].

Promoter hypermethylation and/or inactivation of TRAIL decoy receptors are observed in a majority of cervical cancer patients. Such cervical cancer cell lines were able to effectively induce apoptosis upon treatment with TRAIL [66]. MicroRNAs (miRNAs) also play a role in the development of TRAIL resistance in different types of cancer. For example, miR-494 induces TRAIL resistance in non-small-cell lung cancer (NSCLC) by down-regulating the apoptosis regulator BIM [67]. In contrast, miR-212 inhibits the anti-apoptotic protein PED/PEA-15 and thereby overcomes TRAIL resistance [68].

5 Targeting the core machinery of the TRAIL pathway

Identification of TRAIL as an inducer of apoptosis that is selective towards cancer cells has been met with great enthusiasm, which has led to the development of TRAIL signaling agonists as anti-cancer agents, including TRAIL ligand and antibodies against DR4 and DR5 [69]. There are a number of TRAIL or TRAIL receptor-based clinical trials for cancer patients (Table 1). One such agent, recombinant human TRAIL (rhTRAIL), dulanermin, functions as a ligand to death receptors DR4 and DR5 [70]. In a clinical report, a patient with refractory chondrosarcoma who developed progressive metastatic chondrosarcoma to

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the lung showed a partial response to dulanermin treatment that was potentially mediated by DR4 present in the patient tumor cells [71]. However, resistance was observed after 62 months, which may have arisen due to the up-regulation of the pro-survival proteins, including NF-κB and Bcl-2 [71].

While death receptor activation can be mediated through soluble human recombinant TRAIL, its short half-life as well as sequestration by decoy receptors limits its functionality. Generation of DR4 or DR5 agonist antibodies as therapeutic agents attempts to overcome the limitations of rhTRAIL [72]. Studies indicate that some monoclonal antibodies to DR4 or DR5 have been successful in mounting an anti-tumor response. One such example is LaDR5, which binds to DR5 and induces apoptosis in tumors [73]. Another DR5 agonist antibody, lexatumumab, induces apoptosis in a number of cancer cells [74]. Tigatuzumab (TIG), another anti-DR5 agonist antibody, resulted in apoptosis induction in basal-like breast cancer cells both *in vitro* and *in vivo* [75]. In a phase II trial in triple-negative breast cancer (TNBC) patients, use of TIG in combination with albumin-bound paclitaxel (nab-PAC) resulted in more patients with complete remission as well as prolonged progression free survival [76]. The efficacy of TRAIL receptor agonists also depends on antibody multimer formation that leads to receptor clustering on cancer cells. The agonist APG350 addresses this issue by incorporating six death receptor-binding sites per drug molecule and shows anti-tumor activity both *in vitro* and *in vivo* [77]. Secretory TRAIL-armed adenoviral (Ad.TRAIL) treatment has also exhibited enhanced apoptotic efficacy. In colorectal cancer xenograft models, the treatment with Ad.TRAIL blocked tumor growth and increased survival [78]. Ad.TRAIL in combination with mitomycin C and hyperthermia was shown to induce the JNK-Bak pathway, leading to apoptosis [79]. Strategies have also been developed for targeted delivery of TRAIL-based drugs. For example, TR3 is a TRAIL-based platform incorporating a genetically fused trimer that can be further modified to include tumor directed targeting moieties [80]. Meso-TR3 incorporates Mesothelin, which is known to interact with MUC16, a biomarker associated with several cancer types [81]. Meso-TR3 displayed binding selectivity and killing efficacy both *in vitro* and in a xenograft mouse model of MUC16-positive ovarian cancer [81]. In addition, other delivery systems, including nanoparticles and DNA vaccination were developed to target TRAIL-mediated tumor cell death [82,83]. For instance, Decarbazin (DTIC)-loaded polylactic acid (PLA) nanoparticles (DTIC-NPs), when conjugated to a highly specific targeting functional TRAIL-receptor 2 (DR5) monoclonal antibody, were able to specifically target DR5-overexpressing malignant melanoma cells and resulted in high cytotoxicity and increased apoptosis [84]. However, the current available data from these clinical trials are disappointed. The reasons of these disappointed results can be due to several aspects including resistance and patient selection. For example, in breast cancer, only TNBC cells but not other subtypes of breast cancer cells are susceptible to TRAIL. Therefore, it is conceivable that TRAIL-based therapy in the general breast cancer population is not expected to have a therapeutic benefit because TNBC only consists of 15–20 of all breast cancers.

6 Activation of the TRAIL pathway by anti-cancer agents

A major problem in clinical trials that use TRAIL-based therapeutics is that cancer cells are either intrinsically resistant or acquire resistance to TRAIL. Therefore, agents that can

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overcome TRAIL resistance have great therapeutic potential. Strategies have developed to increase the expression of TRAIL or its death receptors as novel cancer therapeutics.

6.1 Up-regulation of death receptors for activation of the TRAIL apoptosis pathway

Since DR5 was first shown to be induced by clinically used chemotherapeutic agents including doxorubicin and etoposide [85], a considerable interest has been generated to increase the expression of TRAIL death receptors as novel approaches for development of TRAIL-based cancer therapeutics. The idea behind this is that induced DR4 and DR5 can easily bind to TRAIL to induce apoptosis. Compounds that have abilities to increase death receptor expression can be categorized into three groups (Table 2): 1) clinically used anti-cancer drugs, 2) the agents that are currently being developed as anti-cancer agents, and 3) natural compounds that have anti-cancer activity.

6.1.1—Clinically used anti-cancer drugs include cisplatin, doxorubicin, etoposide, 5-FU, mitomycin c and mitoxantrone [86–92]. For example, cisplatin sensitized TRAIL-induced apoptosis by up-regulating DR5, leading to activation of caspases and apoptosis [93]. As a better alternative to cisplatin, Platinum(IV) complex LA-12 was tested to show higher sensitivity to TRAIL [94]. This was associated with Bax/Bak activation, decreased mitochondrial membrane potential, caspase-9 activation, and an increase in the expression of pro-apoptotic members of the Bcl-2 family of proteins. LA-12 was also a potent inducer of Noxa and BimL proteins. Treatment with Dulanermin (TRAIL) in combination with carboplatin and pemetrexed displayed increased sensitivity of malignant pleural mesothelioma cells compared to treatment with single agents [95]. The increased sensitivity to TRAIL was dependent on the increased expression of DR4 and DR5 in a p53-dependent manner mediated by carboplatin and pemetrexed [95]. Furthermore, it has been shown that the histone deacetylase (HDAC) inhibitors suberoylanilide hydroxamic acid and trichostatin A also enhanced TRAIL sensitivity in cancer cells through the up-regulation of DR4 and DR5 [96,97].

6.1.2—The second group of compounds is those agents that are being developed as cancer therapeutics with ability to increase DR4 and DR5 expression. For example, Nutlin-3, a small molecule inhibitor of MDM2, can increase DR5 expression and sensitize cancer cells to TRAIL-induced cell death [98]. This induces TRAIL-mediated apoptosis in cancer cells expressing wild-type p53. The ether phospholipid edelfosine, an asynthetic anti-tumor alkyllysophospholipid, can up-regulate DR5 to enhance rhTRAIL-induced apoptosis [99]. It has been shown that DR5 expression can be regulated by the Notch1 signaling pathway through Sp1-dependent activation of DR5 transcription [100]. Therefore, modulation of this pathway impacts TRAIL-induced apoptosis. Indeed, GW280264X, an inhibitor for a metalloproteinase needed for activation of the Notch1 pathway by cleavage, was able to increase DR5 expression and subsequently sensitize glioblastoma cells to TRAIL-induced apoptosis [100]. Suppression of heat shock protein 70 (HSP70) has also been shown to induce TRAIL-mediated apoptosis by increasing DR4 and DR5 expression [101]. Similar to HSP70 inhibition, the HSP90 inhibitor NVP-AUY922 was shown to overcome TRAIL resistance through dephosphorylating JAK2 and STAT3 and decreasing Mcl-1, which triggers the release of cytochrome c [102]. Another agent, Capsazepin, a capsaicin

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antagonist, was shown to sensitize colon cancer cells to TRAIL by inducing DR4 and DR5 via the ROS/JNK/CHOP pathway [103]. The SIRT1 inhibitor Amurensin G also induced DR5 expression, resulting in enhanced TRAIL sensitivity in TRAIL-resistant human leukemic K562 cells [104]. The small molecule ATP synthase inhibitor Oligomycin A (OMA) triggers the ER stress signaling pathway [105]. OMA induces the inositol-requiring enzyme 1 (IRE1) signaling pathway, resulting in the splicing of X-binding protein 1 (XBP1) and increasing expression of CHOP, where CHOP can bind to the DR5 promoter, thus enhancing TRAIL-mediated apoptosis [105]. In addition, the sphingosine kinase 2 inhibitor ABC294640 has been shown to induce DR4 and DR5 expression to enhance apoptosis by TRAIL in lung cancer cells [106].

6.1.3—The third group of compounds is some natural products that can activate the TRAIL pathway. There are many natural compounds that have been shown to activate the TRAIL pathway, particularly those that can induce DR5 expression. For example, ginsenoside compound K, an active ingredient of ginseng, sensitizes human colon cancer cells to TRAIL-induced apoptosis by up-regulation of DR5 through both autophagy-dependent and -independent mechanisms [107]. Magnolol and polyphenol mixture (PM), a natural product derived from Magnolia officinalis, inhibits class I HDACs, leading to epigenetic activation of DR5 and thus significant enhancement of TRAIL-mediated apoptosis in non-small lung cancer (NSCLC) cells [108]. Chikusetsusaponin IVa butyl ester (CS-IVa-Be), a triterpenoid saponin extracted from Acanthopanas gracilistylus W.W.Smith that acts as an IL6R antagonist, can sensitize the breast cancer MDA-MB-231 cells to TRAIL-induced apoptosis via up-regulation of DR5 [109]. Zyflamend®, a polyherbal preparation, can sensitize tumor cells to TRAIL through ROS-CHOP-mediated up-regulation of TRAIL death receptors [110]. Medicarpin, a naturally occurring phytoalexin l, can activate the ROS-JNK-CHOP pathway and induce DR5 expression, thus sensitizing myeloid leukemia cells to TRAIL-induced apoptosis [111]. Quercetin, a natural flavonoid, sensitizes lung cancer cells to TRAIL by increasing DR5 expression and inhibiting survivin expression [112]. In addition, the diterpene triepoxide, triptolide, sensitizes acute myeloid leukemia cells to TRAIL-induced apoptosis by increasing p53-dependent DR5 expression [113]. It has also shown that Wogonin and the structurally related natural flavones apigenin can overcome TRAIL resistance by down-regulation of c-FLIP and up-regulation of DR5 [114].

6.2 Up-regulation of TRAIL for inducing cancer cell death

In addition to induce death receptors as approaches to promote apoptosis in cancer cells, strategies have also developed to induce TRAIL expression as an approach for cancer therapies. TRAIL can be regulated by both transcriptional and post-translational mechanisms [115]. It has been shown that TRAIL is induced by retinoids and HDACis in leukemia cells, and that induction of TRAIL is the underlying mechanism by which retinoids or HDACIs cause apoptosis [116,117]. In breast cancer cells, TRAIL is induced by several anti-cancer agents including TNFα, the DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine, and the HDAC inhibitor MS275 [118–120]. In addition, TRAIL can be positively regulated by p53 [121]. Induction of TRAIL by the different agents sensitizes cancer cells to clinically used chemotherapeutic agents. Therefore, it becomes clear that identifying small molecule compounds that are capable of increasing TRAIL expression can

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be a strategy for development of novel cancer therapy. In this regard, screening the NIH small molecule compound library led to the identification of the TRAIL-inducible small molecule ONC201 (TIC10) [122]. ONC201 is a member of the imipridone small molecule family [123]. Mechanistically, ONC201 induces apoptosis by inactivating AKT and ERK-mediated Foxo3a phosphorylation, resulting in Foxo3a translocation into the nucleus, where Fox3a activates TRAIL transcription by directly binding to the TRAIL promoter [122,124]. ONC201 has also been shown to induce the unfolded protein response (UPR) and integrated stress response (ISR) pathways [125–127]. This leads to increased transcription factor ATF4 levels, which promotes apoptosis. Further elucidation of this mechanism showed that ONC201 induces TRAIL via an ISR pathway involved the transcription factor ATF4, the transactivator CHOP, and DR5, where ATF4 or CHOP knockdown diminished ONC201-induced DR5 expression and apoptosis in cancer cells [125]. A recent study indicated that ONC201 is a selective inhibitor for the dopamine D2-like receptors [128]. These studies collectively suggest that ONC201 can inhibit cancer cell growth through multiple mechanisms.

Through extensive pre-clinical studies, ONC201 was approved by the FDA for phase I clinical trials for the treatments of several cancers in 2014. In 2016, the phase I dose-escalation study was completed and the safety profile of ONC201 was established [129]. Based on the safety profile, ONC201 is now in phase II clinical trials for patients with different malignancies including glioblastoma, lymphoma, multiple myeloma, and endometrial cancer. Importantly, a recent study showed that ONC201 is very effective against glioblastoma with a H3.3K27M mutation as two patients with this mutation exhibited significant clinical response to ONC201 [130]. Based on these encouraging preclinical and phase I studies, 12 phase II clinical trials have been approved by the FDA for evaluating ONC201's anti-cancer activity in patients with various tumors (Table 3).

7 Conclusions

Accumulating evidence indicates that TRAIL and TRAIL receptor agonists offer new approaches for targeted therapy, as exampled by ONC201. Acquired resistance has limited the effectiveness of TRAIL-based therapy. More work needs to be done to evaluate the mechanisms of TRAIL resistance, which will open up new therapeutic approaches that restore TRAIL sensitivity. Novel treatment has been proposed to restore TRAIL-induced apoptosis through TRAIL and DR5 up-regulation. Significant progress has been made and more efficient natural and synthetic agents will be exploited in combination with TRAIL. However, several challenges remain in the TRAIL field. For example, TRAIL can selectively induce apoptosis of transformed or tumor cells but the mechanisms of TRAIL insensitivity in normal cells are still not fully understood. Therefore, understanding the mechanism of TRAIL resistance is still a primary focus in the field. Furthermore, it is known that TRAIL can induce tumor metastasis and activate survival pathways [131–134], but the detailed function of the TRAIL pathway in tumor metastasis and resistance is not fully understood. Thus, it is conceivable that understanding these issues will help develop TRAIL-based therapy as a novel anti-cancer agent for the treatment of human cancer.

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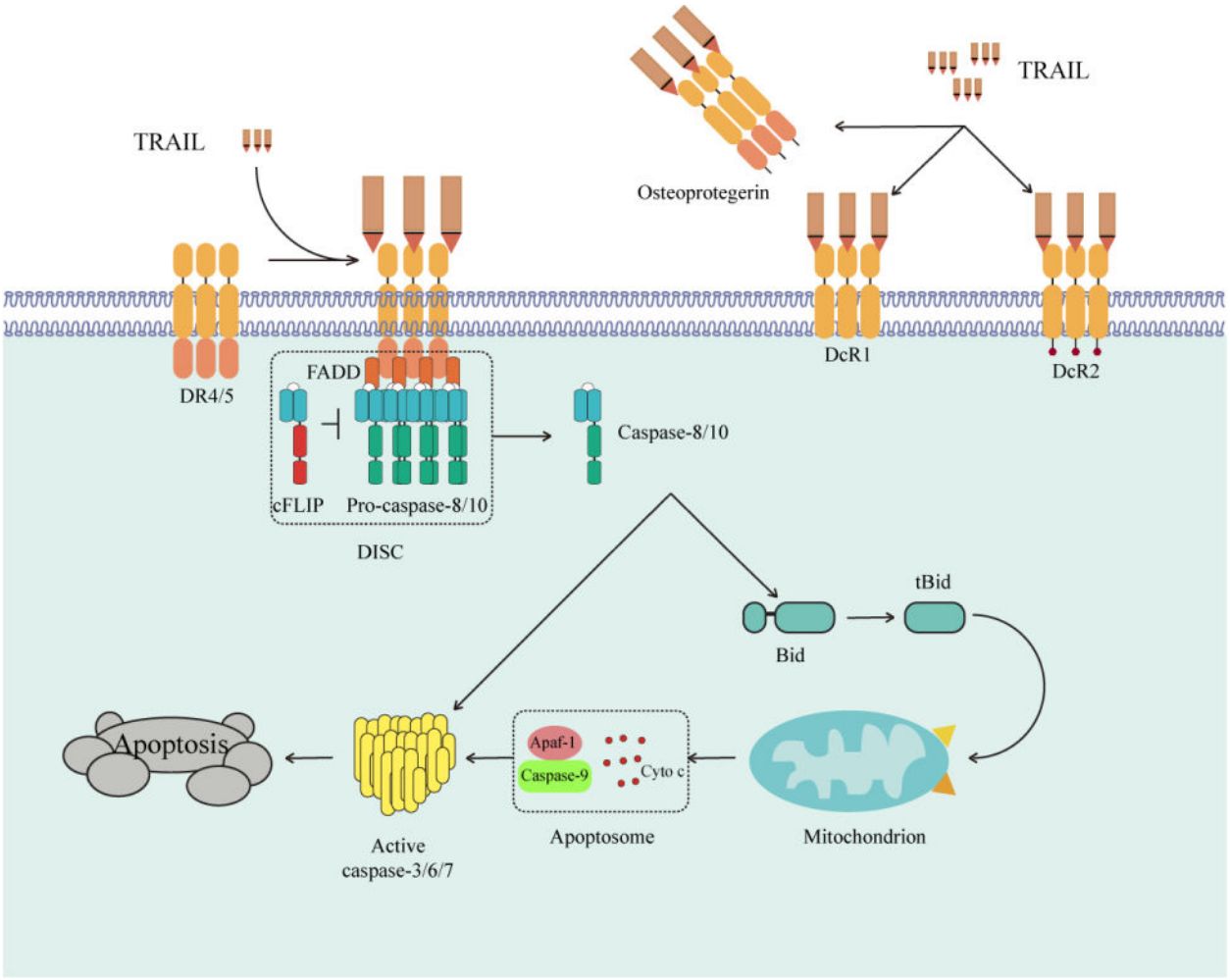

Figure 1.

The TRAIL apoptosis pathway. In response to TRAIL stimulation, FADD, caspase-8/10 and c-FLIP are recruited to death receptors DR4 and DR5 to form the death-inducing signaling complex (DISC), which triggers apoptosis. DcR1, DcR2 and osteoprotegerin are three decoy receptors. DcR1 lacks intracellular domain while DcR2 contains truncated death domain. Osteoprotegerin is a soluble decoy receptor.

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Table 1

Completed clinical trials of agents that target the TRAIL core apoptotic pathway

Therapeutic agents	In combination with	Trial type and tumor	Enrollment	Primary endpoint	Therapy effect	Reference
CPT	Thalidomide+ Dexamethasone	Phase 2; myeloma	71	ORR	Benefit	ChiCTR-TRC-11001625 [135]
CPT	Thalidomide	Phase 2; myeloma	43	Safety	2 CR, 7 PR	ChiCTR-ONC-1200206 [136]
Dulanermin	Rituximab	Phase 1b/2; lymphoma	72	Safety	No benefit	NCT00400764 [137]
Dulanermin	mFOLFOX6+ Bevacizumab	Phase 1b; colorectal cancer	23	Safety	13 PR, 7 SD	NCT00873756 [138]
Dulanermin		Phase 1a; cancer	72	Biomarkers	NR	[139]
Dulanermin	Paclitaxel Carboplatin Bevacizumab	Phase 2; NSCLC	213	ORR	1 CR, 13 PR	NCT00508625 [140]
Dulanermin	Paclitaxel Carboplatin Bevacizumab	Phase 1b; NSCLC	24	Safety	NR	NCT00508625 [141]
Dulanermin		Phase 1; cancer	71	Safety	NR	[142]
Dulanermin	Camptosar/Erbitux Folfiri Bevacizumab	Phase 1b; coloretal cancer	42	Safety	NR	NCT00671372
Tigatuzumab		Phase 1; coloretal cancer	19	Distribution	1 PR, 8 SD	NCT01220999 [143]
Tigatuzumab	Sorafenib	Phase 2; liver cancer	163	Efficacy	No benefit	NCT01033240 [144]
Tigatuzumab	Paclitaxel	Phase 2; TNBC	64	ORR	3 CR, 8 PR, 11SD	NCT01307891 [76]
Tigatuzumab	Gemcitabine	Phase 2; pancreatic cancer	62	Efficacy	Benefit	[145]
Tigatuzumab	Carboplatin/paclitaxel	Phase 2; NSCLC	97	Efficacy	No benefit	NCT00991796 [146]
Tigatuzumab		Phase 1; cancer	17	MTD	7 SD	[147]
Mapatumumab	Sorafenib	Phase 2; liver cancer	101	Efficacy	No benefit	NCT01258608 [148]
Mapatumumab	Paclitaxel Carboplatin	Phase 2; NSCLC	109	Efficacy	No benefit	NCT00583830 [149]
Mapatumumab		Phase 1b/2; NHL	40	Efficacy	2 CR, 1 PR	NCT00094848 [150]
Mapatumumab		Phase 2; colorectal cancer	38	Efficacy	12 SD	[151]
Mapatumumab	Gemcitabine Cisplatin	Phase 1; solid tumor	49	Safety	12 PR, 25 SD	NCT01088347 [152]
Mapatumumab		Phase 1; solid tumor	41	MTD	12 SD	[153]

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Therapeutic agents	In combination with	Trial type and tumor	Enrollment	Primary endpoint	Therapy effect	Reference
Mapatumumab	Paclitaxel Carboplatin	Phase 1; solid tumor	27	Safety	5 PR, 12 SD	[154]
Mapatumumab		Phase 2; NSCLC	32	Efficacy	9 SD	NCT00092924 [155]
Mapatumumab		Phase 1; solid tumor	49	Safety	19 SD	[156]
Mapatumumab	Bortezomib	Phase 2; Myeloma	105	Safety	NR	NCT00315757
Mapatumumab	Sorafenib	Phase 1b; Liver cancer	23	Safety	NR	NCT00712855
Mapatumumab	Cisplatin+ Radiotherapy	Phase 1b/2; Cervical cancer	9	Safety	NR	NCT01088347
Conatumumab	Paclitaxel Carboplatin	Phase 2; NSCLC	172	PFS	No benefit	NCT00534027 [157]
Conatumumab/Ganitumab	FOLFIRI	Phase 2; colorectal cancer	155	PFS	Benefit	NCT00813605 [158]
Conatumumab	mFOLFOX6+ Bevacizumab	Phase 1b/2; colorectal cancer	202	PFS	No benefit	NCT00625651 [159]
Conatumumab/Ganitumab	Gemcitabine	Phase 2; pancreatic cancer	125	OS	Benefit	NCT00630552 [160]
Conatumumab	Doxorubicin	Phase 1b/2; soft tissue sarcoma	134	PFS	No benefit	NCT00626704 [161]
Conatumumab		Phase 1; solid tumor	18	DLT	2 SD	[162]
Conatumumab		Phase 1; solid tumor	37	Safety	1 PR, 15 SD	[163]
Conatumumab	Panitumumab	Phase 1b/2; Colorectal cancer	53	Safety	NR	NCT00630786
Conatumumab	Birinapant	Phase 1b; Ovarian cancer	27	Safety	NR	NCT01940172
TAS266		Phase 1; solid tumor	4	Safety	NR	[164]
ONC201		Phase 2; glioblastoma	17	Efficacy	Benefit	[130]
ONC201		Phase 1; solid tumor	28	Safety	Benefit	[129]

Abbreviations: CPT, Circularly permuted TRAIL; NR, not reported; MTD, maximum tolerated dose; ORR, objective response rate; DLT, dose limiting toxicity; TNBC, triple-negative breast cancer; NHL, Non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; CR, complete response; PR, partial response; SD, stable disease.

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Table 2

The agents that increase the expression of TRAIL and its receptors DR4 and DR5 lead to the activation of the TRAIL apoptosis pathway.

Therapeutic agents	Cancer type	Mechanism(s)	Reference
Chemotherapeutics			
Doxorubicin	Ovarian terato-carcinoma	Inducing DR5	[85]
Cisplatin	Glioblastoma	Inducing DR5	[93]
Platinum(IV) LA-12	Colon cancer	Activation of mitochondrial pathway	[94]
Carboplatin, pemetrexed and TRAIL(CPT)	Pleural mesothelioma	Inducing DR4 and DR5	[95]
Trichostatin A(TSA)	Gastric cancer	Inducing DR5	[96,97]
Natural products			
Ginsenoside compound K (CK)	Colon cancer	Inducing DR5	[107]
Magnolol and polyphenol mixture	NSCLC	Inducing DR5	[108]
Chikusetsusaponin IVa butyl ester (CS-IVa-Be)	Breast cancer	Inducing DR5	[109]
Zyflamend	Pancreatic cancer	Inducing ROS, CHOP and DR5	[110]
Medicarpin(Med)	Myeloid leukemia cancer	Inducing ROS, CHOP and DR5	[111]
Quercetin	Lung cancer	Induction of DR5 and inhibition of survivin	[112]
Triptolide	Leukemia	Decreasing XIAP	[113]
Wogonin	Solid tumors	Inducing DR5, decreasing c-FLIP	[114]
Other agents			
Nutlin-3	Colon cancer	Inducing DR5	[98]
Edelfosine	Gastric cancer	Inducing DR5	[99]
GW280264X	Glioblastoma	Inducing DR5	[100]
NVP-AUY922	Colorectal cancer	Suppressing the JAK2-STAT3-Mcl-1 pathway	[102]
Capsazepin	Colon cancer	Inducing DR4 and DR5	[103]
Amurensin G	Leukemia	Inducing DR5	[104]
Oligomycin A	Cervical	Inducing DR5	[105]
ABC294640	Lung cancer	Inducing DR4 and DR5	[106]
ONC201	Solid tumors	Inducing TRAIL and DR5 and ER stress	[122,125,126]

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Table 3

Ongoing clinical trials of TRAIL-based therapies and ONC201

Therapeutic agents	In combination with	Trial type and tumor	Reference
ABBV-621		Solid tumor/Hematologic malignancies	NCT03082209
DS8273		Solid tumor	NCT02076451
ONC201		Glioma	NCT03134131
ONC201		Glioblastoma	NCT02525692
ONC201		Glioma	NCT03295396
ONC201		NHL	NCT02420795
ONC201		Leukemias	NCT02392572
ONC201		Myeloma	NCT02863991
ONC201		Solid tumor/Myeloma	NCT02609230
ONC201		Solid tumor	NCT02324621
ONC201		Solid tumor	NCT02250781
ONC201		Neuroendocrine tumor	NCT03034200
ONC201		Breast cancer/Endometrial carcinoma	NCT03394027
ONC201		Endometrial cancer	NCT03099499

Abbreviations: CPT, Circularly permuted TRAIL; NR, not reported; MTD, maximum tolerated dose; ORR, objective response rate; DLT, dose limiting toxicity; TNBC, triple-negative breast cancer; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; CR, complete response; PR, partial response; SD, stable disease.