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TRAIL in cancer therapy: current and future challenges.

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Abstract

Since its identification in 1995, TRAIL (TNF-Related Apoptosis Inducing Ligand) has sparked growing interest in oncology due to its reported ability to selectively trigger cancer cell death. Contrary to other members of the TNF superfamily, TRAIL administration *in vivo* is harmless. The relative absence of toxic side effects of this naturally occurring cytokine in addition to its antitumoral properties has led to its preclinical evaluation. However, despite intensive investigations, little is known with regard to the mechanisms underlying TRAIL selectivity or efficiency. Appropriate understanding of its physiological relevance, regulatory pathways and of the mechanisms controlling cancer cells escape to TRAIL-induced cell death will be required to optimally use the cytokine in clinics. The current review focuses on recent advances in the understanding of TRAIL signal transduction and discusses the current and future challenges of TRAIL-based cancer therapy development.

1. Introduction

During the past 20 years empirically designed chemotherapy regimens have diminished the risks of death in patients suffering from cancer. Ongoing attempts to improve chemotherapy efficacy are now entering new era with rationally designed studies based on specific understanding of the mechanisms of action, interactions and pharmacology. Recent breakthroughs promise even more successful outcomes, particularly with the advent of more selective therapeutic approaches. Among the latter, the TRAIL system should show encouraging levels of efficacy. TRAIL has now been recognized, as one of the few tumour selective agents able to eradicate cancer cells selectively by activating a signalling pathway that is used by the innate immune system, opening an entirely novel dimension to cancer research and therapy.

2. TRAIL: a natural anti-tumoral cytokine?

TRAIL, also known as Apo2L [1,2], is a type 2 membrane protein belonging to the TNF superfamily. The human TRAIL ligand interacts with 2 agonistic receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5/KILLER) [3,4,5], and 3 antagonistic decoy receptors

(TRAIL-R3/DcR1/TRID, TRAIL-R4/DcR2/TRUNDD and OPG) [6,7,8]. TRAIL is a remarkable member of the TNF ligand family, due to its unique ability to bind to 5 receptors. The reasons for this remain obscure. However TRAIL's binding abilities suggest that its physiological functions as well as the molecular mechanisms involved in the regulation of its signalling pathways could be more complex than anticipated.

The primary role of TRAIL appears to be the triggering of apoptosis. Upon TRAIL binding, DR4 and/or DR5 aggregate, enabling the recruitment of the adaptor protein FADD through homotypic interactions between their respective DD (Death Domain). In turn, FADD recruits the initiator caspases-8 and -10 through interaction of their respective DED (Death Effector Domain). Initiator caspases are activated within this molecular platform, known as DISC (Death Inducing Signalling Complex) and released to the cytosol where they trigger the proteolytic cascade leading to apoptosis (Figure 1). In addition to the membrane-bound DISC, TRAIL binding to its cognate agonistic receptors was recently shown to trigger the formation of a secondary complex allowing the activation of signalling pathways such as JNK, p38 or NF-κB [9]. Interestingly, the sequential signalling pathways engaged by TRAIL and its agonistic receptors are in sharp contrast to TNFR1. TNFR1 engages primarily a membrane-bound complex that triggers cell survival in most cases, followed by a secondary complex for the trigger of apoptosis. However, activation of the apoptotic machinery by this secondary complex only occurs when the survival pathway, activated by complex I, is impaired [10]. Like TNFR1, TRAIL non-apoptotic complex II is thought to arise from complex I or TRAIL DISC. These sequentially occurring signalling platforms provide excellent molecular explanations for the pleiotropic properties of TRAIL.

TRAIL has been shown to be expressed in diverse tissues, such as liver, lung, placenta, kidney, spleen, immune-privileged sites and immune cells, at the protein or mRNA level [11]. TRAIL is expressed by immune cells, such as human PBL (Peripheral Blood Lymphocytes) following anti-CD3 and IFNγ stimulation [12] or monocytes and neutrophils upon IFNγ treatment [13,14]. In some $CD4^+$ T cell clones, the constitutive expression of TRAIL was shown to contribute to perforin-and granzyme B-independent cytotoxicity [15]. TRAIL was also proposed to play a role in the cytotoxic activity of dendritic cells [16,17,18,19,20], including umbilical cord blood dendritic cells [21].

Constitutive TRAIL expression has also been found in freshly isolated neutrophils [22]. In some circumstances, TRAIL is released into the circulation upon viral infections [23,24,25], and in some autoimmune [26], inflammatory [27] or malignant [23,25,28] diseases[29].

TRAIL expression pattern could be more restricted than initially expected. Accordingly, its physiological functions have mainly been shown to occur in the immune system. The first demonstrations that TRAIL played a role in immune anti-tumour response were based on studies using neutralizing anti-TRAIL antibodies and experiments obtained from TRAIL and TRAIL-receptor gene knockout mice. TRAIL deficient mice do not present developmental deficiencies, but display an increased susceptibility to experimental and spontaneous tumour formation due to impaired NK cells anti-tumour activity [30,31,32,33,34]. In line with these findings, IFNγ-induced TRAIL expression in mouse liver NK cells, was shown to be required to inhibit liver metastasis formation *in vivo* [30,35,36,37]. Yet, the exact function of TRAIL in modulating the anti-tumour response remains poorly defined. For instance, while on the one hand TRAIL deficient mice display reduced tumour immune surveillance, TRAIL-receptor knock out mice on the other hand exhibit enhanced innate immune response [38]. Thus the impact of recombinant TRAIL administration towards immune homeostasis still deserves careful analysis.

TRAIL appears to increase the growing list of immune cell weapons, joining Granzyme B, Fas or TNF. Like them however, TRAIL remains dispensable to elicit an efficient immune response. The redundancy in cytotoxic molecules secreted by immune cells certainly allows for a better defence against a wide panel of cancer cells but also probably accounts for our difficulty to clearly define the physiological functions of TRAIL.

3. Resistance of cancer cells

TRAIL was initially reported to kill more easily tumour than normal cells, which suggested that the cytokine could be of great interest in cancer treatment. TRAIL cancer cell selectivity was further demonstrated recently using stepwise tumorigenic cellular systems [39,40]. In both cases, while normal cells or immortalized cells remained

unresponsive to TRAIL, cellular transformation-induced either by Ras or c-Myc ectopic expression restored cell sensitivity to TRAIL-induced cell death. However, numerous tumour cells also exhibit a relative resistance to TRAIL-induced apoptosis [41,42,43]. Resistance to TRAIL can be explained by the different mechanisms described below.

Upstream regulators

The first level of regulation of TRAIL-sensitivity is related to the level of expression at the cell surface of TRAIL cognate receptors. A deficit in the expression of agonistic receptors [44,45,46,47], or an unusual DR4/DR5 ratio [48,49] have been shown to account for the observed resistance in some cancer cells. Cell surface expression of these TRAIL agonistic receptors is the first requirement for the triggering of the apoptotic machinery by TRAIL. However, mutations within critical domains (such as the death domain or the ligand-binding domain) of either DR4 [50,51], or DR5 [52,53] can also hamper TRAIL-induced cell death, leading to a “decoy receptors”-like phenotype.

TRAIL antagonistic receptors DcR1 and DcR2 were initially coined decoy receptors since they lack functional death domain and cannot recruit DISC components. Originally these receptors, which confer a specific resistance to TRAIL-induced cell death, were proposed to be expressed in normal tissues and down-regulated in tumour cells [54]. Accordingly, DcR1 and DcR2 expression was found to be impaired in various tumour types, such as neuroblastomas, primary breast or lung cancers, due to promoter hypermethylation [55,56]. However, DcR are also expressed in some primary tumours such as gastrointestinal [57], prostate [58], lung [59] and acute myeloid leukemia cancer cells [60] (Table I). In addition, the correlation between DcR expression and TRAIL-resistance remains highly controversial [61,62,63,64,65]. This discrepancy could be partly explained by the fact that the expression of these receptors is not always explored at the tumour cell surface but at the mRNA or protein level in whole cell extracts [51,66,67] (Table I). Alternatively, this lack of correlation can also be related to the presence of other inhibitors of the TRAIL-apoptotic pathway, in the absence of DcR expression.

It has been suggested that DcR may compete with agonistic receptors for TRAIL binding [6,7,68]. The affinity of decoy receptors to TRAIL was initially reported to be lower than that of agonistic DR5 [69], which was not confirmed in other experimental

settings [70]. If decoy receptors are not able to recruit FADD, but bind TRAIL at the membrane level with an affinity similar to that of agonistic receptors, they may act as "dominant negative" receptors. Then, the DR/DcR ratio at the cell membrane could be a determinant point as regards TRAIL-sensitivity. Ectopic over-expression of DcR1 or DcR2, in TRAIL sensitive cells, impairs TRAIL-induced apoptosis provided that DcR are expressed at the cell surface [6,7,8,71,72,73]. Accordingly, removal of DcR1 expression, by use of PI-PLC, a molecule that sheds GPI-anchored proteins from the membranes [74,75], or inhibition of TRAIL binding to DcR1 using blocking anti-DcR1 antibody (Personal communication), restores TRAIL sensitivity in DcR1-expressing cells. Similar results were obtained using an anti-DcR2 blocking antibody [48] or siRNAs to down-regulate DcR2 expression in cells that endogenously express DcR2 at their surface [58,76,77].

While both receptors share the same inhibitory function, they are structurally different. DcR1 is a GPI anchored membrane protein devoid of intracellular domain, while DcR2 is a transmembrane receptor containing a truncated death domain. We have recently shown that whereas DcR1 sequesters TRAIL within lipid rafts, thus titrating TRAIL competitively and preventing DISC formation, DcR2 allows DISC formation but impairs caspase-8 activation [72]. Interestingly, DcR1 is unable to interact with any of the agonistic receptors, while DcR2 interacts with DR5 in a TRAIL-dependent manner. It has been recently proposed that DcR2 could interact spontaneously with DR5 though the PLAD (PreLigand Associated Domain) [78]. In our hands, although weak interaction could readily be found at the steady state, a stronger interaction was obtained upon TRAIL stimulation, including in cells expressing endogenous DcR2 [72,79]. How DcR2 impairs caspase-8 activation is still unclear. Caspase-8 activation within TRAIL or Fas DISC has been shown to require close proximity, therefore it is probable that DcR2 recruitment within the DR5 DISC impinge caspase-8 activation by steric hindrance. The absence of a functional death domain within DcR2 intracellular region explains its inability to recruit initiator caspases. Yet, this trans-membrane receptor could nevertheless account for the activation of survival pathways such as NF-κB [8], or allow the recruitment of a yet to be determined inhibitory protein that would prevent caspase-8 activation within the DISC.

Downstream regulators

Besides the presence of DcR, TRAIL-induced cell death can be inhibited by a plethora of less specific intracellular mediators, at the level of the DISC or downstream. At the DISC level, a deficiency in caspase-8 and caspase-10 expression, mutations affecting their function [80], gene promoter methylation [41,81,82], or CARP-dependent mediated degradation [83] have been shown to prevent TRAIL-induced cell death. Elevated expression of FLIP (FLICE-inhibitory protein) also results in TRAIL resistance [84,85].

Downstream of the TRAIL DISC, tumour resistance can be mediated by overexpression or mutations of Bcl-2 [86] or IAP (Inhibitor of Apoptosis Proteins) family members [87,88].

While the main function of TRAIL is the induction of cell death, accumulating evidences also suggest that this ligand is able to signal non-apoptotic pathways, such as Akt, NF-κB and MAPK, involved in cell survival and proliferation [89,90,91]. Akt kinase was proposed to play a protective role against TRAIL toxicity in many tumour cells [92,93,94]. Yet some Akt inhibitors such as amiloride [95], complestatin [96], quercetin [97], sulforaphane [97], arsenic [98] or EGFR inhibitor [99] enhance TRAIL-mediated apoptosis. On the other hand however, more specific inhibitors of Akt (*e.g.* LY294002, Wortmannin, PI3K siRNA) were shown to be potent TRAIL inhibitors [100,101,102,103].

TRAIL is thought to induce NF-κB activation through the serine/threonine kinase RIP1 [104,105]. Likewise, the NF-kB pathway is thought to inhibit TRAIL-induced cell death, but the issue remains controversial. NF-κB activation has either been shown to inhibit [106,107] or to promote [108] TRAIL-induced apoptosis [109].

Among the MAPK superfamily, p38, ERK and JNK, would favour TRAIL-induced apoptosis [110,111], whereas ERK would display either anti-apoptotic [112,113,114,115] or pro-apoptotic functions [116]. These apparent controversies could be due to our poor

understanding of the TRAIL signalling pathway, and the molecular mechanisms involved in its regulation could be more complex than anticipated.

4. Therapeutic challenges related to TRAIL:

Recombinant TRAIL administration

TRAIL has attracted great expectations in the last years for oncologists. The first hints that this cytokine may hold novel antitumour properties came from the demonstration that recombinant soluble TRAIL injection in xenografted animals induced tumour regression without systemic toxicity [28,36,117,118,119,120,121,122]. TRAIL-induced tumour regression was documented in SCID mice bearing human tumours, such as colon and breast carcinomas [118,121,123], multiple myeloma [124], multiple glioma [125], pancreatic adenocarcinoma [126] or colon carcinoma [127]. Human recombinant TRAIL is now evaluated in phase I clinical trials (Genentech and Amgen). Preliminary results indicate so far that it is well tolerated in patients, but its rapid clearance from the circulation may hamper its antitumoral properties.

However, studies on xenografted animals indicated so far that the administration of recombinant TRAIL rarely induced a complete eradication of established tumours. In addition, the resistance of fresh human tumour cells to TRAIL cytotoxic effects remains poorly known [127,128]. Besides, TRAIL has been demonstrated to induce cell proliferation in some resistant cancer cells *in vitro* [107,129], as well as to promote tumour cell proliferation and metastasis, *in vivo* [130,131]. These findings could dampen the potential interest of recombinant TRAIL preparations for cancer therapy.

Other strategies have been considered to improve the efficiency and/or specificity of the TRAIL-death signalling pathway for cancer therapy. In order to avoid TRAIL-inhibitory functions of TRAIL Decoy Receptors, several recombinant TRAIL variants binding exclusively to DR5 have been developed [132]. *In vitro*, these variants are more efficient than TRAIL itself in inducing the apoptotic machinery in ovarian cancer cell lines. More recently, a chimeric form of TRAIL, activable by matrix metalloproteinases, proteases essentially present in human tumour sites, has been proposed as an alternative molecule with the idea of targeting specifically tumour cells [133]. It remains to be determined, however, whether these TRAIL variants will exhibit sufficient half-life in

patients to retain antitumoral selectivity, whether they will be tolerated and whether these preparations will lack TRAIL proliferative properties.

TRAIL gene therapy

Several gene therapy approaches have been considered to deliver TRAIL to the tumour. TRAIL gene transfer into cancer cells can efficiently suppress established tumour growth, without major side effects [42,134,135,136,137,138], even in metastatic prone cancers cells [139]. Using a syngeneic mouse model, TRAIL retroviral-mediated gene transfer in the bone marrow was shown to induce tumour growth regression [140]. Lentiviral-mediated gene transfer can also be efficient *ex-vivo*, but the efficiency of such strategy could be lower *in vivo* [141]. The efficacy of TRAIL gene transfer could be enhanced when combined to other antitumour drugs [134,142,143]. For instance, it has been shown recently that combination of TRAIL gene therapy with actinomycin D was an efficient treatment of multiple liver metastasis in a mouse model [144].

Chemosensitization to TRAIL

In vitro, several studies showed that pretreatment of resistant cancer cells with classical chemotherapeutic drugs sensitizes them to TRAIL mediated cell death [145,146,147,148]. Chemosensitization to TRAIL-induced cell death was also observed in immunodeficient mice, resulting in the regression of xenografted colon carcinomas, osteocarcinomas or breast carcinomas [48,117,118,123,147,149].

The mechanisms underlying this chemosensitization depend on both the drug and the cell type [150]. Chemotherapeutic agents can upregulate agonistic receptor expression [48,151,152,153], facilitate the activation of the mitochondrial cell death pathway [120], or activate the caspase signalling cascade [154]. However, if chemotherapy enhances TRAIL cytotoxic effect in cancer cells, the hepatotoxicity of such combinations has to be carefully evaluated, especially as far as cisplatin is concerned [155,156,157].

Radiation sensitization to TRAIL

Ionizing radiations sensitize breast cancer, leukemic, colon carcinoma, melanoma and glioma cells to TRAIL-induced apoptosis [158,159,160,161,162]. This synergistic

effect is thought to occur through a p53-dependent mediated DR5 upregulation, induction of Bax and Bak, inhibition of Bcl-2, and caspase activation [163]. Alone, endogenous TRAIL could play a role in radiation-induced cell death, since some tissues arising from the TRAIL-R knockout mice are more resistant to apoptosis following ionizing radiation, compared to wild type littermate [164].

The increasing interest in combining TRAIL with radio- or chemotherapy, which are the main treatments currently used at the clinic to cure cancer, lies on the observation that cross-resistant tumours are most of the time efficiently killed by the combination of both drugs. This strategy would therefore be useful when current treatments fail, for instance in pancreatic or lung cancers.

Agonistic TRAIL receptor antibody use

The use of agonistic antibodies targeting DR4 or DR5 could be more effective than recombinant TRAIL to treat cancers, since these compounds target selectively the agonistic receptors [165,166] and are thus able to trigger apoptosis even in cells which harbour at their cell surface the antagonistic receptors DcR1 or DcR2 [72] (Figure 1). These antibodies have been shown to induce apoptosis in human cancer cell lines and primary cells *in vitro* [167], as well as in a variety of human tumours grown in immunodeficient mice [168,169]. Combination of these antibodies with chemotherapy [165,168,169,170] or radiotherapy [171] enhances their anti-tumoral efficiency.

In mouse orthotopic models their administration has been shown to induce primary and metastatic tumour regression through ADCC (Antibody-Dependent Cellular Cytotoxicity) and CDC (Complement-Dependent Cytotoxicity) inducing thus a long-term protection against tumour recurrence [172,173]. Administration of murine agonistic antibodies against DR4 or DR5 induces death of tumour cell *in vitro* and *in vivo*, in xenograft models [174,175].

Some of these humanized agonistic antibodies to DR4 and DR5 are undergoing phase II (HGS-ETR1 or Mapatumumab, human genome sciences-Cambridge antibody technologies) or phase I clinical trials (HGS-ETR2, also named Lexatumumab). Compared to TRAIL, these antibodies exhibit a higher half-life in patient plasma and their

administration is as safe as TRAIL [176,177]. Since DR4 and DR5 expression levels are though to be higher in cancer cells than in normal cells [65,178,179], the safe administration of these antibodies could warrant an improved tumour specificity.

Yet their efficacy remains to be demonstrated in patients. A phase II trial testing the anti-DR4 HGS-ETR1 antibody was performed in 40 patients with relapsed or refractory non-Hodgkin lymphoma and gave rise to promising results [180]. To date, 8% of the patients responded to the treatment, with one complete remission, and two partial responses, and a prolonged stabilization in 30% of patients. A phase II trial associating chemotherapy to the anti-DR4 has also been initiated and results are expected by the end of 2007.

Combination of TRAIL with other molecules

Several protein inhibitors have been shown to sensitize resistant cells to TRAIL-mediated apoptosis, such as mTOR inhibitors [181], proteasome inhibitors [182,183], HDAC inhibitors [143,184,185], Hsp90 inhibitors [186,187,188], Akt inhibitors [189], IFN [190,191], DNA methyltransferase inhibitors [41,192,193] and casein kinase 2 inhibitors [194]. Other molecules that sensitize tumour cells to TRAIL include resveratrol [195], tunicamycin [196], peroxysome proliferators-activated receptor agonists [197], betulinic acid, reactive oxygen species [198], telomerase-dependent virotherapy [199], herbal compound such as wogonin [200] or Bcl2 family inhibitory molecules and small Smac mimetics [201,202,203,204,205].

Other approaches consisting in targeting the extrinsic pathway downstream of TRAIL receptors have been proposed. Synthetic triterpenoids are antitumour compounds that have been shown to donwregulate c-FLIP and to sensitize tumour cells to TRAIL-induced cell death [206,207]. More recently, using a chemical library screen novel compounds affecting c-FLIP expression have been found [208]. These compounds, which enhance caspase-8 recruitment and activation within TRAIL DISC, could be useful combined to TRAIL in cancer therapy.

However, all these strategies, which often target a limited number of anti-apoptotic pathways in a given cell type, could be inefficient against the wide panel of TRAIL-resistant cells, especially considering the impressive variety of the molecular mechanisms allowing these cells to escape from TRAIL-induced cell death.

TRAIL and immunotherapy

Immunotherapy protocols are based on the combination of a tumour-cell apoptosis inducer with immuno-stimulators. TRAIL, as a cancer cell death inducer, may be responsible for the release of tumour antigens, up-taken by APC (Antigen Presenting Cells) and presented to CTL (Cytotoxic T Lymphocytes). Promoting APC stimulation or T-cell co-stimulation could in principle enhance the anti-tumour response, and provoke the eradication of TRAIL-resistant tumours.

Proof-of-principal for such an approach has been obtained recently, *in vivo*, using cells expressing TRAIL ectopically in syngeneic mice challenged for tumour regression in combination with cyclophosphamide, a compound shown to break immune tolerance [209]. Since tumour cells highly express DR5, the use of antibody against DR5 could induce a greater T cell immunity, by recruiting the Fc-receptor innate immune cells [172]. More recently, trimAb therapy combining antibodies against DR5, CD40 and CD137 has been shown to induce the rejection of established tumours in 80% of mice, and a complete cure in 60% of mice with spontaneous and distant metastases, after surgical resection of the primary orthotopic tumours [210]. This strategy allowed the rejection of tumours resistant to anti-DR5 antibody, stimulating the different steps of the immune response to give rise to an efficient tumour-specific induction of CTL, and a long-term protection against tumour recurrence.

5. Expert opinion and concluding remarks

Recombinant TRAIL or TRAIL derivatives are remarkable antitumour compounds that trigger cell death in a wide variety of cancer cells without major side effect *in vivo*. Yet, the ability of cancer cells to escape from TRAIL-induced cytotoxic activity is an important issue that needs to be considered in order to design novel therapeutic approaches aiming at targeting this deadly pathway. Combining TRAIL with current or recently developed anticancer drugs should overcome this resistance and provide greater

therapeutic benefit than the use of these compounds alone. Given the complexity of the TRAIL system, compared to other TNF related death domain containing receptors, extensive investigations are still required to understand TRAIL regulatory pathways, since to date no simple predictive markers are available to determine the optimal combination that should be used to treat patients. Whether the use of TRAIL as an immunostimulatory cytokine in specific protocols would overcome TRAIL resistance and favour the complete eradication of tumours has also to be demonstrated. Challenging these strategies against a wider range of primary tumour cells both in syngeneic animal mouse models and in clinical trials should help to figure out whether TRAIL will hold its promises for cancer therapy.

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** Good example of the use of the TRAIL system in immunotherapy