

# Trailing TRAIL Resistance for Targeted Cancer Therapy



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## Abstract

Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a promising anti-cancer agent due to its selective killing of cancer cells, sparing the vital normal cells. Despite its great potential in cancer treatment, its clinical application has been hampered by the cancer resistance. Various strategies have been developed to overcome resistance towards TRAIL-induced apoptosis which include the combinational therapy of TRAIL with epigenetic drugs, chemotherapy drugs and the autophagy inhibitors. To heighten the therapeutic outcome, the personalized medicine based on biomarker screening could serve as a novel strategy in tailoring the combinational therapy of TRAIL and sensitizer for targeted cancer therapy in the near future.

**Abbreviations:** TNF: Tumour Necrosis Factor; TRAIL: Tumour Necrosis Factor Related Apoptosis-Inducing Ligand; DISC: Death Inducing Signalling Complex; FADD: Fas Associated Death Domain

## Introduction

Apoptosis is an orchestrated cell death that occurs in physiological condition. The loss of balance between cell division and cell death leads to pathological condition such as cancer [1]. Despite remarkable advances in the understanding the cancer biology and the development of novel diagnostic and therapeutic strategies, cancer still remains one of the major causes of death [2]. The lack of specificity of the current cancer therapy sparked an urgency to unravel a targeted cancer therapy. Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), a member of TNF cytokine superfamily is a promising anti-cancer agent due to its selective targeting on TRAIL-R1 (DR4) and TRAIL-R2 (DR5) expressed by the cancer cells, sparing the normal cells [3].

The binding of TRAIL to TRAIL-R1 and/or TRAIL-R2 results in receptor trimerization, Fas-associated death domain (FADD) recruitment, death inducing signalling complex (DISC) assembly and caspase cascade activation, thereby inducing extrinsic apoptosis pathway in type I cells [2,4]. As a consequence of TRAIL DISC activation, the induction of intrinsic apoptosis pathway is required in type II cells for efficient TRAIL-induced apoptosis [5,6]. Despite the specificity of TRAIL towards cancer cells, the validity of TRAIL for targeted cancer therapy has yet to be established. One of the hurdles which hampers its clinical application is TRAIL resistance. The resistance of TRAIL-induced apoptosis and the strategies that have been explored to overcome TRAIL resistance in developing an improved targeted cancer therapy will be reviewed.

## Resistance

In line with TRAIL targeted cancer therapy, a recombinant form of human soluble TRAIL (Apo2L.0 or AMG-951/Dulanermin) and agonistic antibodies that specifically target TRAIL-R1 and TRAIL-R2 have been brought from bench to clinical trials [7]. TRAIL therapy has a major limitation as a large number of the cancer develops resistance towards TRAIL [8], either intrinsically resistant or acquired during the course of treatment [9-11]. The mechanisms which inhibit apoptosis execution can be divided into:

- a. Disrupted balance between pro-apoptotic and anti-apoptotic proteins, resulting in dysregulated apoptosis in the affected cells which could be due to over-expression of anti-apoptotic proteins (such as Bcl-2, Bcl-xL, cIAPs, XIAP and c-FLIP) [12] or under-expression of pro-apoptotic proteins (such as Bid) [1];
- b. Reduced caspase function which leads to decreased apoptosis [1]; and
- c. Impaired death receptor signalling which can be caused by down-regulation of receptor surface expression (mutations and epigenetic silencing) [13,14], clathrin-related endocytosis of TRAIL-death receptor, accumulation of autophagosome, co-existence of decoy receptor, post-translation modifications (down-regulation of fucosylation and O-linked glycosylation and up-regulation of N-linked glycosylation) leads to evasion of extrinsic apoptosis pathway [1,4,15-17].

The sensitization of cancer cells towards TRAIL-induced apoptosis tackling the above-mentioned mechanisms will be reviewed. The other mechanisms of TRAIL resistance include aberrant protein synthesis, protein misfolding, ubiquitin regulated death receptor expression, metabolic pathways and metastasis [8]. However, the detailed resistance mechanism is not well elucidated and it is not known whether different types of cancer undergo TRAIL resistance through similar or specific mechanisms.

### Sensitization of Cancer Cells Towards TRAIL-Induced Apoptosis

Based on its value as a targeted anti-cancer therapeutic agent, TRAIL is worth to be further investigated despite the various defensive resistance mechanisms pitched by different cancer cells to safeguard themselves from the devastating TRAIL-induced apoptosis fate. Recent advances in pre-clinical research on potential combination of TRAIL with other established drugs in sensitizing cancer cells towards TRAIL anti-cancer effects have shed light that these TRAIL resistance mechanisms can indeed be tweaked towards the favourable outcome against cancer cells.

As aforementioned, the skewed balance between pro-apoptotic and anti-apoptotic proteins can render cancer cells to be TRAIL-resistant. For instance, over expression of Bcl-2 and associated anti-apoptotic proteins Bcl-xL, Mcl-1, A1/Bf1 and Bcl-w have been commonly associated with resistance of cancer cells such as pancreatic, ovarian, lymphoma, multiple myeloma, lung adenocarcinoma, prostate adenocarcinoma against the chemotherapy-mediated cell death in the intrinsic apoptotic pathway [18]. Likewise, in the case of TRAIL-induced apoptosis axis, every stage of the extrinsic apoptotic pathway like its cognate receptors, TRAIL-R1 and TRAIL-R2, trimerization, FADD recruitment, DISC assembly, caspase activation and eventual engagement of mitochondrial intrinsic pathway can potentially be harnessed by cancer cells towards the benefit of their survival.

### Epigenetic drugs

Epigenetic dysregulation of gene expression by DNA methylation and histone deacetylation lead to carcinogenesis [19,20]. Epigenetic drugs are useful in this sense because cancer cells have, in many instances, acquired TRAIL resistance via epigenetic DNA modifications which have silenced one or a few of the aforementioned pro-apoptotic members of the extrinsic or intrinsic pathway. For instance, the silenced caspase-8 caused by the hypermethylation of the promoter in invasive neuroblastoma cell line could be re-expressed by the demethylating agent, 5'-aza-2'-deoxycytidine, and it has sensitized invasive NB cells towards TRAIL-induced cell death [21]. Another similar study on small cell lung carcinoma cell line which is highly refractory towards FasL and TRAIL-induced apoptosis due to reduced levels of caspase-8 and TRAIL-R1 mRNA has also displayed improved sensitivity towards cell death by the combined treatment of 5'-aza-2'-deoxycytidine and interferon gamma [22].

In addition, the other epigenetically modulated members of the TRAIL-induced apoptotic pathway such as TRAIL-R1, TRAIL-R2,

caspase-3 and -8 as well as the pro- and anti-apoptotic proteins have also been successfully manipulated by demethylating agents (such as decitabine, 5-aza-2'-deoxycytidine and zebularine) and histone deacetylase inhibitors (such as suberoyl anilidehydroxamic, valproic acid and Entinostat) [8,13,21,23-29] either as single agents or combination [30]. Besides, an increase in fucosylation levels has been reported in many cancer cell lines treated by zebularine, overcoming the resistance of TRAIL-induced apoptosis [26]. These finding revealing the appealing potential of epigenetic drugs as sensitizers of TRAIL-induced apoptosis in cancer cells.

### Chemotherapy Drugs

Accruing evidence suggests that TRAIL resistance mechanisms can be vastly different across various cancer types and the current elucidation of these mechanisms is only the tip of the iceberg. Before the specific targeting against resistance towards the TRAIL-induced extrinsic apoptotic pathway is illuminated, chemotherapy acts as a potential sensitizer towards TRAIL-induced apoptosis by its engagement of the mitochondrial pathway [11]. The chemotherapy drugs include paclitaxel, carboplatin, bevacizumab, doxorubicin, decitabine [8]. The sensitization mostly involves members of the intrinsic apoptotic pathway coupling it to the TRAIL-induced extrinsic apoptosis cascade like Bax [31-33] and Bak [34]. In addition, the sensitization occurs either through up regulation of DR4 or DR5, caspase-3, or through down regulation of Bcl-xL or c-FLIP has also been reported [11,35]. All these data point us towards a larger horizon in tackling TRAIL resistance via multiple unprecedented pathways with the combination of chemotherapy and TRAIL. Indeed, the combination of various chemotherapy drug and recombinant human TRAIL and TRAIL-R1 or TRAIL-R2 monoclonal antibodies is evaluated at the clinical trials [36].

### Autophagy Inhibitors

Alike apoptosis, autophagy is a catabolism of cellular constituents to maintain cellular homeostasis which is also stimulated in response to pathological conditions [37]. Despite its pro-apoptotic effect in some cases [38,39], tumour-associated autophagy has been implicated in increased of cell proliferation and chemo-resistant [40-44]. Since TRAIL is implicated in autophagy induction in different cancers [4], the inhibition of autophagy by pharmacological inhibitors such as mammalian target of rapamycin complex 1 and by silencing the Beclin-1 or ATG7 genes, has sensitized TRAIL-resistant cells to TRAIL-induced apoptosis [45,46].

### Other Sensitizers

In addition to the aforementioned sensitizers, the other sensitizers include multi-kinase inhibitor sorafenib, smac mimetics and protease inhibitor [10]. For instance, sorafenib was also shown to directly induce the rapid dissipation of mitochondrial membrane potential and reactive oxygen species production which subsequently enabled TRAIL to activate caspase-8 in renal cell carcinoma [47]. On the other hand, type II carcinoma cells which are dysfunctional in the engagement of amplification loop from the mitochondrial death signalling have recently been switched to

TRAIL-induced type I apoptosis activation through XIAP inhibition by SMAC mimetic LBW-242 and Bortezomib [48].

### Conclusion and Future Prospects

The cancer resistance to TRAIL has spurred the combinational therapy to restore apoptosis sensitivity [29]. The combinational therapy of TRAIL with either chemotherapy drugs, epigenetic modulators or autophagy inhibitors has shown to sensitize the TRAIL resistant cancer cells towards TRAIL-induced apoptosis via various molecular mechanisms. To heighten the therapeutic efficacy, the combinational therapy approach could be tailored with the screening of patients with potent biomarkers that predict the responsiveness to TRAIL therapy [12]. These biomarkers include high expression of N-acetylgalctosaminyltransferase-14 (GALNT14) (O-glycosylation initiating enzyme), the presence of at least one functional receptor and low or absent of Six1 (a homeoprotein identified as a novel mediator of TRAIL resistance) expression [9]. Besides, the search for novel biomarkers that predict the responsiveness to TRAIL therapy is warranted such as biomarkers of autophagosome [4]. The personalized medicine based on the combinational therapy of TRAIL and sensitizer tailored with the biomarker screening of patient's responsiveness towards TRAIL holds a great potential of success for TRAIL targeted cancer therapy in the near future.

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