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The TRAIL to cancer therapy: Hindrances and potential solutions

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ABSTRACT

Apoptosis is an ordered and orchestrated cellular process that occurs in physiological and pathological conditions. Resistance to apoptosis is a hallmark of virtually all malignancies. Despite being a cause of pathological conditions, apoptosis could be a promising target in cancer treatment. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), also known as Apo-2 ligand (Apo2L), is a member of TNF cytokine superfamily. It is a potent anti-cancer agent owing to its specific targeting towards cancerous cells, while sparing normal cells, to induce apoptosis. However, resistance occurs either intrinsically or after multiple treatments which may explain why cancer therapy fails. This review summarizes the apoptotic mechanisms *via* extrinsic and intrinsic apoptotic pathways, as well as the apoptotic resistance mechanisms. It also reviews the current clinically tested recombinant human TRAIL (rhTRAIL) and TRAIL receptor agonists (TRAs) against TRAIL-Receptors, TRAIL-R1 and TRAIL-R2, in which the outcomes of the clinical trials have not been satisfactory. Finally, this review discusses the current strategies in overcoming resistance to TRAIL-induced apoptosis in pre-clinical and clinical settings.

1. Introduction

Despite remarkable advances in the understanding the biology of cancer and the development of novel diagnostic and therapeutic strategies, cancer still remains as one of the major causes of death (De Miguel et al., 2016). To date, besides the surgical resection of the tumour, the central pillars of cancer therapy are the conventional radiotherapy and chemotherapy (De Miguel et al., 2016). The goal of cancer therapy is to promote the death of cancer cells without causing too much damage to the normal cells (Gerl and Vaux, 2005). However, these cancer therapies lack of cancer specificity, which might damage the normal and healthy cells, results in severe side effects with dose-limiting toxicities (De Miguel et al., 2016). Targeted cancer therapy with the use of either monoclonal antibodies (mAbs), small molecule inhibitors or immunotoxins is emerging as a promising therapeutic strategy due its specificity towards cancer cells (Baudino, 2015). However, it is limited by the development of resistance (Aldeghaither et al., 2019).

The limitations of the current cancer therapy have provided scientists with the impetus to research for alternatives. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), also known as Apo-2 ligand (Apo2L), is a member of TNF cytokine superfamily. TRAIL has the ability to induce apoptosis *via* cross-linking with TRAIL-Receptors, TRAIL-R1 (DR4) and TRAIL-R2 (DR5), expressed by a wide variety of cancer cells, sparing the vital normal cells (Walczak et al., 1997). The discovery of this unique property among TNF superfamily members has laid the foundation for the testing of the clinical potentials of TRAIL-R-targeting therapies in cancer clinics (De Miguel et al., 2016). However, the validity of TRAIL-based cancer therapies still awaits to be established, as most cancer cells are TRAIL-resistant (Huang et al., 2016) or develop resistance after multiple treatments.

The specific cancer-targeting capability of TRAIL has attracted great attention worldwide as a potential candidate for cancer therapy. However, in light of the current limitations of TRAIL-induced apoptosis, strategies to overcome the resistance towards TRAIL-induced apoptosis have been developed progressively.

This review summarizes the mechanisms of TRAIL-induced apoptosis *via* extrinsic and intrinsic apoptotic pathways. It also reviews the mechanisms of cancer cell resistance towards TRAIL-induced apoptosis. Lastly, it discusses the current therapeutic strategies of recombinant human TRAIL (rhTRAIL) and TRAIL receptor agonists (TRAs) against

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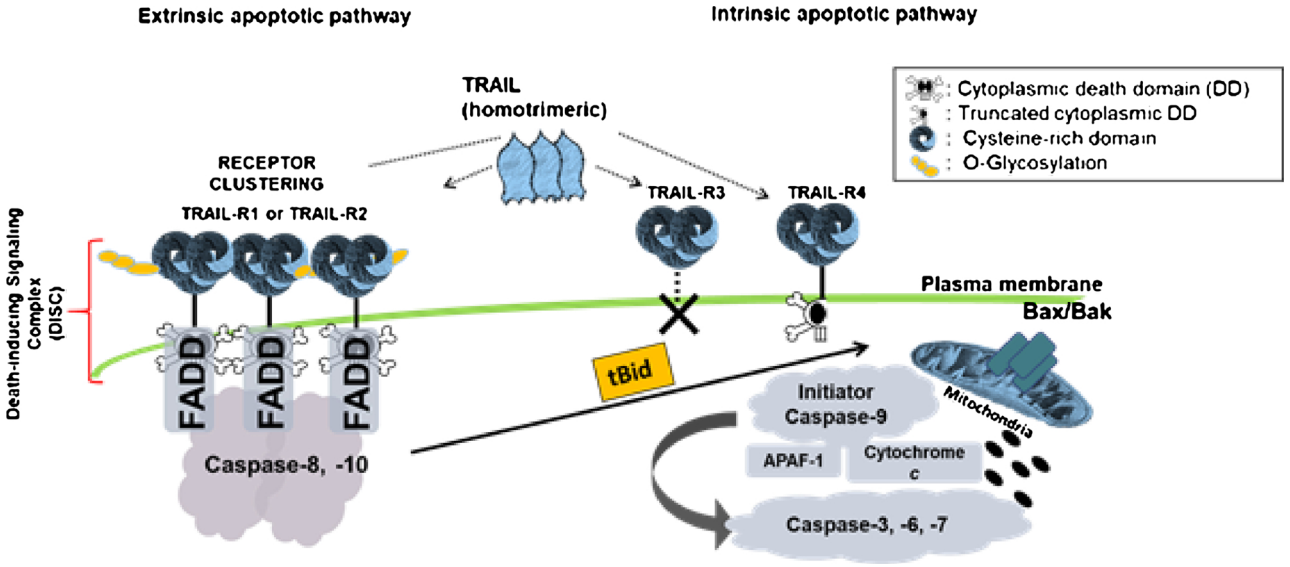

Fig. 1. TRAIL-induced apoptosis *via* the extrinsic and intrinsic pathways. In the extrinsic pathway, the ligation of TRAIL onto death receptors, TRAIL-R1 (DR4) and TRAIL-R2 (DR5), results in the activation of caspase-8. This induces the activation of effector caspase, caspase-3 and execution of extrinsic apoptotic pathway. Moreover, caspase-8 activates the BID proteins to produce tBID. tBID interacts with Bax and Bak, leading to their oligomerization in the mitochondrial membrane and causing the loss of mitochondrial membrane potential. This in turn results in the release of cytochrome *c*. Cytochrome *c* associates with APAF-1 and caspase-9 to induce the activation of caspases-3, -6, and -7, which subsequently leads to execution of the intrinsic apoptotic pathway.

TRAIL-R4 and TRAIL-R5, as well as unraveling the novel strategies to overcome TRAIL resistance in both pre-clinical and clinical settings.

2. TRAIL and its receptors

TRAIL is a Type II transmembrane protein which belongs to the TNF family proteins (Daniels et al., 2005). TRAIL is a 20 kDa protein encoded by a gene consisting of five exons and three introns located on chromosome 3 (Snell et al., 1997; Herr et al., 1999; Jeremias et al., 1998). TRAIL is a unique protein of which its gene was cloned back in 1995 and added to the family of TNF due to its C-terminal extracellular domain homology to other members of the TNF family (Wiley et al., 1995; Marsters, 1996).

TRAIL interacts with five receptors, namely TRAIL-R1 (DR4), TRAIL-R5 (DR5) (Walczak et al., 1997; Pan et al., 1997; Sheridan et al., 1997), TRAIL-R3 (DcR1/TRID/LIT), TRAIL-R4 (DcR2/TRUNND) and osteoprotegerin (OPG) (Degli-Esposti et al., 1997; Emery et al., 1998). Both DR4 and DR5 contain a conserved death domain (DD) motif and signal apoptosis (Wang and El-Deiry, 2003). The other receptors act as "decoys" as the overexpression of these proteins inhibits TRAIL-induced apoptosis (Wang and El-Deiry, 2003). While DcR1 lacks a cytosolic region, DcR2 has a truncated, non-functional cytoplasmic DD. The physiological relevance of OPG as a receptor for TRAIL remains unclear (Wang and El-Deiry, 2003).

Though TRAIL is expressed on a wide range of tissues (Daniels et al., 2005), it is found to be mainly expressed on the cells of our immune system which play critical roles in inducing apoptosis of virally and oncogenically transformed cells (Hayakawa et al., 2004; Jansen et al., 1998). Due to the fact that DR4 and DR5 are often highly expressed in different malignancies, the use of TRAIL or other agonists for DR4/DR5 for cancer therapy appears as an appealing concept (De Miguel et al., 2016).

Besides DR4 and DR5, TRAIL also interacts with DcR1 and DcR2, but these block the apoptosis signal from being transmitted due to the lack and truncation of the cytoplasmic DD, respectively (Mérino et al., 2006). These decoy receptors which are widely expressed in normal cells have a protective effect against TRAIL-induced apoptosis (Daniels et al., 2005), supporting the notion of TRAIL inducing apoptosis in the transformed cells, leaving the normal cells unharmed. Although the expression of these DcRs does not correlate with TRAIL sensitivity or confer resistance of normal cells towards TRAIL-induced apoptosis, DcRs do play a vital role in reducing TRAIL apoptosis-inducing efficacy towards malignant cells, especially the DcRs expressed in the tumor stromal tissue (O'Leary et al., 2016). In addition, TRAIL binds to OPG with low affinity. This regulates the osteoclastogenesis besides having the decoy functions by defending the survival of cells such as leukaemia Jurkat cells and prostate cancer cells (Emery et al., 1998; Holen et al., 2002), implying a negative correlation between the levels of OPG and TRAIL-induced apoptosis (Holen et al., 2002).

2.1. TRAIL-induced apoptosis signalling

TRAIL is a homotrimeric protein which induces apoptosis by interacting with its receptors (Ivanov et al., 2003; LeBlanc and Ashkenazi, 2003; Ozören and El-Deiry, 2003) *via* two well-elucidated apoptotic pathways: the extrinsic pathway and the intrinsic pathway (Falschlehner et al., 2007). The choice of apoptotic pathway depends on the cell types (Wang and El-Deiry, 2003; Lemke et al., 2014). For instance, Type I cells particularly undergo extrinsic apoptotic pathway while Type II cells require an amplification of apoptotic signal *via* the execution of the intrinsic apoptotic pathway (Wang and El-Deiry, 2003; Thorburn, 2007; Wang, 2008).

2.1.1. Extrinsic apoptotic pathway

The extrinsic apoptotic pathway is triggered by TRAIL *via* its receptors, DR4 or DR5. Ligation of TRAIL results in trimerization of the respective death receptors, DR4 and DR5. These multiple protein complexes are assembled into death-inducing signalling complex (DISC) *via* the recruitment of Fas-associated protein with death domain (FADD) (Wang and El-Deiry, 2003; Thorburn, 2007; Ashkenazi, 2002). This adaptor protein translocates to DISC where its DD interacts directly with the DD of the death receptors (Trivedi and Mishra, 2015). Thereafter, this assembly of protein complex starts to recruit initiator caspases, for instance, pro-caspase-8 and/or pro-caspase-10. These initiator caspases are auto-activated *via* proteolysis followed by the transmission of apoptotic signal to effector caspases such as caspase-3. The activated caspase-3 thereby cleaves several cellular proteins and forms signalling cascade that results in the biochemical and morphological hallmarks of apoptosis (Fig. 1) (Daniels et al., 2005; Ashkenazi, 2002; Johnstone et al., 2008).

2.1.2. Intrinsic apoptotic pathway

Apart from the extrinsic pathway, in most cancer cell lines, scientists have uncovered that TRAIL-induced apoptosis signal requires intensification from the activation of the intrinsic apoptotic pathway *via* the B-cell lymphoma 2 (Bcl-2) regulated mitochondrial pathway (Gonzalvez and Ashkenazi, 2010; Holland, 2013). Bcl-2 homology domain 3 interacting-domain death agonist (BID) is the substrate for activated initiator caspase, caspase-8 (Li et al., 1998) which results in the cleavage of BID into activated truncated BID (tBID). Subsequently, tBID interacts with pro-apoptotic Bcl-2 family members Bak and Bax, causing their oligomerization in the mitochondrial membrane, leading to the loss of mitochondrial membrane potential. This directs the release of cytochrome *c* and mitochondrial proteins second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI (SMAC/DIABLO) that are involved in the pro-apoptotic process (De Miguel et al., 2016; Lemke et al., 2014; Wang, 2008; Johnstone et al., 2002). Cytochrome *c* associates with apoptotic protease activating factor 1 (APAF-1) and pro-caspase-9, forming apoptosome, leading to the activation of caspase-9. Consequently, the apoptosis signal culminates in the apoptotic effector apparatus of executioner caspases-3, -6, and -7, resulting in cellular apoptotic demise (Fig. 1) (Almasan and Ashkenazi, 2003; Ashkenazi, 2008; Kelley and Ashkenazi, 2004; Schulze-Osthoff et al., 1998).

3. Dysregulation of TRAIL-induced apoptosis contributes to carcinogenesis

Apoptosis is an orchestrated cellular process that occurs in physiological and pathological conditions (Ngai and Wong, 2018; Wong, 2011). This process is essential in maintaining the physiological balance between cell death and cell growth (Koff et al., 2015). Dysregulation of apoptosis leads to carcinogenesis. The dysregulation of TRAIL-induced apoptosis renders the cancerous cells developing resistance towards TRAIL-induced apoptosis. The mechanisms involved in dysregulating TRAIL-induced apoptosis include: (1) disrupted balance of pro-apoptotic and anti-apoptotic proteins, (2) reduced caspase function, (3) impaired death receptor signalling, (4) downregulation of glycosylation and others (Ngai and Wong, 2018; Wong, 2011) (Fig. 2).

3.1. Disrupted balance of pro-apoptotic and anti-apoptotic proteins

3.1.1. Bcl2 family proteins and TRAIL resistance

As aforementioned, the role of TRAIL in regulating the intrinsic apoptotic pathway is well documented. The intrinsic apoptotic pathway is routinely governed by a subset of Bcl-2 protein family which shares four Bcl homology domains (BH1-4) except BH-3 only proteins (Lemke et al., 2014; Thomas et al., 2013; Zhang and Fang, 2005). These include (i) anti-apoptotic proteins: Bcl-2, Bcl-xL, Mcl-1, Bcl-w, A1, Bcl-B; (ii) pro-apoptotic proteins: Bax, Bak, Bok; (iii) BH-3 only proteins: Bid, Bim, Puma, Noxa, Bik (Thomas et al., 2013; Czabotar et al., 2014). Structural studies denoted the importance of these protein domain interactions to exert pro- and anti-apoptotic effects. For instance, pro-apoptotic proteins neutralize the anti-apoptotic activities to break the hindrance in apoptosis induction during cytotoxic stress. Similarly, enhanced activation of Bax and Bak directs further caspase activation and augments the apoptosis process (Czabotar et al., 2014; Delbridge and Strasser, 2015). During cytotoxic stress, caspase-8 activation causes the cleavage of BID, forming tBID. tBID directs the oligomerization of Bax and Bak and subsequently causes mitochondrial outer membrane permeabilization (MOMP), the hallmark of the intrinsic apoptotic pathway. This is followed by the release of intermembrane space proteins such as cytochrome *c*, which triggers the caspase cascade activation leading to cell death (Thomas et al., 2013; Delbridge and Strasser, 2015; Kalkavan and Green, 2017; Kelly and Strasser, 2011). Nevertheless, the presence of anti-apoptotic proteins represses apoptosis by opposing the Bax and Bak activities to maintain the mitochondrial membrane integrity (Thomas et al., 2013; Yip and Reed, 2008). Despite the importance of Bcl-2 in regulating apoptosis, the TRAIL-regulated intrinsic apoptotic pathway is strictly cell type-dependent; in Type I cells, the apoptotic signalling is unaffected by Bcl-2 expression. In Type II cells, the insufficient DISC assembly and caspase-8 activation direct the intrinsic apoptotic pathway through the activation of Bax and Bak. This process is stringently controlled by Bcl-2 expression (Zhang and Fang, 2005; Fulda et al., 2002; Sprick and Walczak, 2004).

Dysregulation of Bcl-2 family proteins is one of the main culprits in a broad range of cancer development. For example, gene amplification of Bcl-2, Bcl-xL and Mcl-1 has been documented in lung and breast cancers. Frame shift mutation led to Bax and Bak dysfunction in colon cancer and acute myeloid leukaemia patients (Delbridge and Strasser, 2015; Joensuu et al., 1994; Glaser et al., 2012). The significance of Bcl-2 in regulating apoptosis is further evidenced by gene knockout studies in which the deletion of Bcl-2 reverted the difficulties in apoptosis induction (Chawla-Sarkar et al., 2004; Huang and Sinicrope, 2008). The blockage of TRAIL-induced apoptosis is abolished by compound administration that sequestered and downregulated the Bcl-2 anti-apoptotic protein level (Huang et al., 2009; Kisim et al., 2012; Hetschko et al., 2008). Bypassing Bcl-2 mediated resistance in apoptosis, small molecule mimetics of pro-apoptotic BH-3 only proteins (BH-3 mimetics) have been designed as a novel strategy of cancer therapy, for example, ABT-737, ABT-199 (Venetoclax) and ABT-263 (Lessene et al., 2008; Roberts and Huang, 2017). Nevertheless, ABT-737 and ABT-263 only bind to a subset of Bcl-2 like anti-apoptotic proteins. Overexpression of Mcl-1 or A1/BFL-1, both of which are not inhibited by these compounds, has the potential to confer resistance to this therapy (Merino et al., 2012). Nonetheless, these BH-3 mimetics could be best employed in combination with drugs which activate BH-3 only proteins, such as Bim or Puma, that potently neutralise Mcl-1 and/or A1 (Delbridge and Strasser, 2015). Moreover, these BH-3 mimetics may best be used in combinational therapy with drugs that target cancer cells, such as inhibitors of oncogenic kinases, rather than using them with cytotoxic drugs that cause DNA damage in both normal and malignant cells (Cragg et al., 2009). Since Bcl-2 and TRAIL-induced apoptosis are correlated, this implies that the combination therapy of BH-3 mimetics and TRAIL can potentially achieve an enhanced therapeutic effect in targeting cancerous cells.

3.1.2. cFLIP and TRAIL resistance

Cellular-FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (cFLIP) is a member of apoptosis inhibitory protein family which shares the homology with caspase-8, but lacks the protease activity for apoptosis induction (Safa, 2012; Bagnoli et al., 2010; Shirley and Micheau, 2013). In the early stage, scientists found that cFLIPs were imperative in regulating T cell proliferation and cardiac development in *in vivo* studies (Zhang et al., 2008; Yeh et al., 2000). However, in the later stage, cFLIP has been a focus in the negative regulation of apoptotic signalling. cFLIP is recruited to DISC by its own binding to the FADD binding site *via* its death motifs. These series of events impeded the activation of pro-caspase-8 and the downstream apoptotic signalling (Zhang and Fang, 2005; Bagnoli et al., 2010; Shirley and Micheau, 2013). There are 3 isoforms of cFLIP protein which have been shown to negatively regulate the apoptotic pathways: the 56 kDa long form cFLIP ($cFLIP_L$) (Zhang et al., 2004), the 26 kDa short form cFLIP ($cFLIP_S$)(Kaminskyy et al., 2013) and the 24 kDa Raji isoform cFLIP ($cFLIP_R$) (Golks et al., 2005). Albeit few reports revealed the pro-apoptotic role in $cFLIP_L$ during high caspase-8 expression (Schleich et al., 2012; Yu et al., 2009), $cFLIP_L$ upregulation signified the inhibition of apoptotic pathways especially in TRAIL-induced apoptosis (Zhang et al., 2004; Zang et al., 2014). Excessive cFLIP expression is highly correlated with poor clinical outcome of cancer patients, which is mainly attributed to TRAIL resistance and chemoresistance. The link between TRAIL resistance and overexpression of cFLIP has been well demonstrated in *in vitro* studies, notably ovarian carcinoma (Li et al., 2011), breast carcinoma (Zang et al., 2014; Piggott et al., 2011; Day et al., 2008) and non-small cell lung carcinoma (Riley et al., 2013). Various strategies such as RNA interference (RNAi) and administration

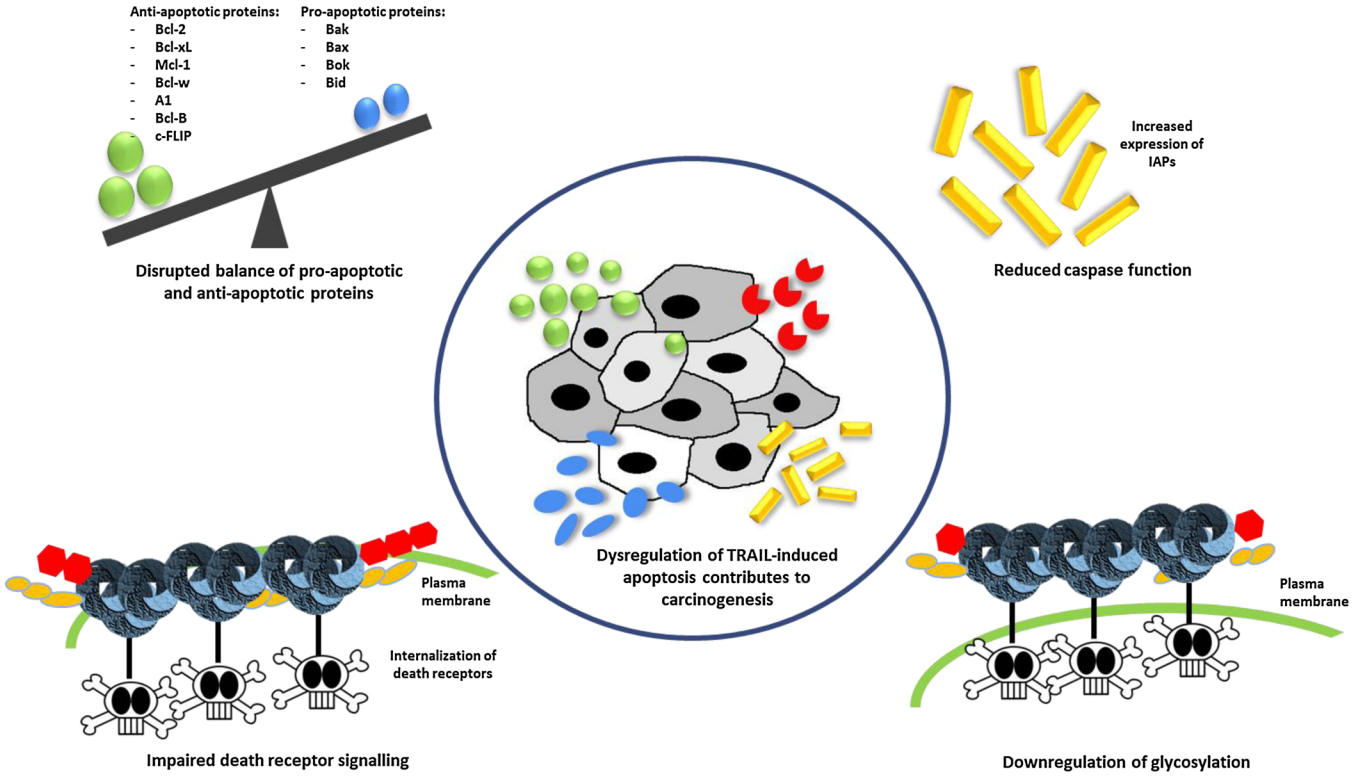

Fig. 2. Dysregulation of TRAIL-induced apoptosis in carcinogenesis. The mechanisms which inhibit apoptosis execution are: (1) disrupted balance between pro-apoptotic and anti-apoptotic proteins, resulting in dysregulated apoptosis in the affected cells which could be due to over-expression of anti-apoptotic proteins (such as Bcl-2, Bcl-xL, cIAPs, XIAP and c-FLIP) or under-expression of pro-apoptotic proteins (such as Bak, Bax, Bok, Bid); (2) reduced caspase function which leads to decreased apoptosis; and (3) impaired death receptor signalling which can be caused by down-regulation of receptor surface expression and downregulation of glycosylation that lead to evasion of the extrinsic apoptotic pathway (Ngai and Wong, 2018).

of sensitizers downregulated the cFLIP expression and rendered the cancerous cells becoming sensitive towards TRAIL-mediated apoptosis have been demonstrated (Piggott et al., 2011; Lagadec et al., 2008; Kauh et al., 2010; Wang et al., 2007; Ortiz-Ferrón et al., 2008). These findings provided the notion that cFLIP is one of the main factors in rendering cancerous cells resistant towards TRAIL-induced apoptosis.

3.2. Reduced caspase function

3.2.1. IAPs and TRAIL resistance

Inhibitor of apoptosis (IAP) proteins are prominent in influencing the downstream signalling of both the extrinsic and intrinsic apoptotic pathways through inhibition of caspase activities. Highly expressed IAP proteins are often associated with reduced survival, poor prognosis and chemoresistance development among cancer patients (Engesæter et al., 2011; Hussain et al., 2017; Zhang et al., 2011). These mammalian IAP proteins, including X-linked IAP (XIAP), cellular IAP protein 1 (cIAP1), cellular IAP protein 2 (cIAP2) and survivin, inhibit the caspase activities in their distinctive manners (Lemke et al., 2014; Rathore et al., 2017). Generally, the inhibition of caspase activities is mostly influenced by the presence of one to three baculovirus IAP protein repeat (BIR) domains. These domains frequently attach to the active pocket of caspases-3, -7 and -9, thus avoiding its activation and diminishing the apoptotic events (Gyrd-Hansen and Meier, 2010; Silke and Meier, 2013). Furthermore, the presence of really interesting new gene (RING) domain in IAP proteins exerts anti-apoptotic function *via* E3 ligase activities. This causes mono-ubiquitination, poly-ubiquitination followed by proteasomal degradation of caspases; thereby halting the apoptotic events (Lemke et al., 2014; Rathore et al., 2017; Deshaies and Joazeiro, 2009).

The role of IAP proteins in regulating TRAIL-induced apoptosis has mostly elucidated through RNAi and antisense oligonucleotide knock-down studies. These studies demonstrated that downregulation or complete elimination of IAP proteins such as XIAP and survivin has successfully elevated the caspase activities and augmented TRAIL-induced apoptosis in cancerous cells (Chawla-Sarkar et al., 2004; Lopes et al., 2007; Allensworth et al., 2012; Cao et al., 2004). Besides, administration of sensitizers has reverted the TRAIL sensitivity in cancerous cells along with decreased expression of IAP proteins (Engesæter et al., 2011; Kim et al., 2004; Park et al., 2014; Guicciardi et al., 2011). These interventions suggest the significance of blocking IAP proteins to achieve the maximum effect of TRAIL-based therapy for cancers.

In the intrinsic apoptotic cascades, SMAC/DIABLO is released to promote apoptosis *via* the direct inhibition of IAP proteins (Zhang and Fang, 2005; Finlay et al., 2014; Martinez-Ruiz et al., 2008). This inhibition is followed by the spontaneous activation of NFκβ, production of TNFα and augmentation of cell death (Gyrd-Hansen and Meier, 2010). With respect to this, SMAC mimetics were discovered to antagonise IAP proteins' activities, thus reversing the resistance to TRAIL-induced apoptosis. The research illustrated that SMAC mimetics caused downregulation and rapid degradation of IAP proteins *via* E3 ligase activity, thus augmenting TRAIL-induced apoptosis (Zhang and Fang, 2005; Bockbrader et al., 2005; Lu et al., 2011; Feltham et al., 2011). In short, IAP proteins are critical regulators of TRAIL-induced apoptosis *via* their inhibition on caspase activities. Hence, IAP proteins may serve as attractive therapeutic targets to reverse TRAIL resistance in cancer treatment.

3.3. Impaired death receptor signalling

3.3.1. Internalization of death receptors

Death receptors and their associated ligands are key players in the extrinsic pathway of apoptosis (Wong, 2011). Several abnormalities in the death signalling pathways that lead to the evasion of the extrinsic pathway have been identified, one of which is the down-regulation of the surface expression of death receptors (Wong, 2011). The lack of

death receptor surface expression limits the sensitivity of cancerous cells towards TRAIL-induced apoptosis (Rahman et al., 2009a; Di et al., 2013), even though some have reported that the mRNA and protein expression levels of DR4 and DR5 do not correlate with TRAIL resistance in breast cancer cells (Rahman et al., 2009b; Zhang and Zhang, 2008; Chen et al., 2012). For instance, a TRAIL-sensitive breast cancer MDA-MD-231 cell line with highly expressed DR4 and DR5 may utilize down-regulation of cell surface DR4 and/or DR5 as a mechanism to escape TRAIL-induced apoptosis (Rahman et al., 2009b; Zhang and Zhang, 2008). This is confirmed by the immunohistochemistry results obtained from the tumors of breast cancer patients which indicated the mislocalization of surface death receptors to the cytoplasm and the nuclei of cells (Chen et al., 2012). The loss of surface death receptor expression is attributed to its internalization *via* the clathrin-mediated endocytosis (CME). As the master regulator of CME, dynamin1 (Dyn1) has an important role in regulating the surface expression of death receptors. The dephosphorylation of Dyn1 activates the CME machinery which then causes the endocytosis of death receptors, thereby diminishing the apoptotic effects (Reis et al., 2017; Austin et al., 2006). To circumvent this phenomenon, blocking the Dyn1-regulated CME and restoration of surface death receptors are the potential strategies to overcome TRAIL resistance in cancers.

3.4. Downregulation of glycosylation confers TRAIL resistance in cancers

Post-translational modification of death receptors is another factor in determining TRAIL sensitivity in cancer cells. For instance, glycosylation of the death receptors increased TRAIL-induced apoptosis in cancerous cells (Twomey et al., 2015; Wagner et al., 2007; Dufour et al., 2017). Being an evolutionarily conserved mechanism, glycosylation involves the attachment of glycans to specific protein sites, most commonly at asparagine (N-linked) and/or serine/threonine (O-linked) (Trivedi and Mishra, 2015; Twomey et al., 2015). Catalysed by the N-acetyl galactosamine transferase 14 (GALNT14) and further processed by the fucosyltransferase (FUT), O-glycosylation on DR5 augments TRAIL sensitivity in cancerous cells. O-glycosylation is hypothesized to maintain the membrane stability in preventing endocytosis of death receptors. Moreover, this process is significant in facilitating the clustering of death receptors upon ligand binding, thus recruiting DISC and mediating the activation of caspase cascades (Twomey et al., 2015; Wagner et al., 2007). Whole-genome profiling of TRAIL-sensitive and TRAIL-resistant cancerous cells revealed the higher mRNA expression of GALNT14 in TRAIL-sensitive cells as compared to TRAIL-resistant cells. This is further proven by the knockdown and pharmacological inhibition studies of O-glycosylation enzymes in which the deleted/downregulated GALNT14 would reduce the sensitivity of cancer cells towards TRAIL-induced apoptosis (Wagner et al., 2007). N-glycosylation at DR4 contributes similar function in which it regulates the distribution and arrangement of DR4 at the cell surface before TRAIL-binding. Thus, this process further promotes TRAIL-induced apoptosis *via* death receptor aggregation and DISC recruitment (Dufour et al., 2017). Since neoplastic transformation involves drastic changes in glycosylation, therefore glycosylation could act as a potentially important regulator in overcoming TRAIL resistance in cancerous cells and in mediating TRAIL-induced tumor killing.

On the other hand, fucosylation involves the attachment of an L-fucose residue to an oligosaccharide or protein and is one of the most important glycosylations in cancers (Moriwaki and Miyoshi, 2010). A common feature of death receptor signalling is the formation of DISC and secondary independent signalling platform in the cytoplasm (termed as complex II), which amplifies the caspase activation in the cytosol, generating activated caspase-8 (Lavrik et al., 2008). A deficiency of fucosylation could affect the signalling between DISC and complex II formation (Moriwaki et al., 2011). Downregulation of fucosylation which is attributed to the mutation of GDP-mannose-4,6-dehydratase (GMDS), a notable enzyme responsible for fucosylation, confers resistance towards TRAIL-induced apoptosis. Research demonstrated that GMDS deficiency induced the acquisition of TRAIL resistance in human colon cancer cells and caused them to escape from the natural killer cell-mediated tumor surveillance (Moriwaki et al., 2011, 2009; Miyoshi et al., 2012). Another report revealed that the epigenetic regulation of fucosylation is responsible in modulating TRAIL-induced apoptosis *via* the upregulation of fucosylation-related enzymes upon treatment with zebularine (Zeb), a DNA methytransferase inhibitor (DNMTi) (Moriwaki et al., 2010). While an increase in fucosylation occurs during the early stage of carcinogenesis, defucosylation through genetic mutation in certain types of advanced cancer would lead to the escape of tumor surveillance and the acquisition of more malignant characteristics (Moriwaki and Miyoshi, 2010). Therefore, fucosylation level of the tumor tissue could serve as a biomarker in predicting the efficacy of TRAIL-targeted therapy (Moriwaki and Miyoshi, 2010). In short, targeting the glycosylation level is a potential strategy in reversing TRAIL resistance in cancerous cells and it could serve as biomarker in predicting the sensitivity of cancer cells towards TRAIL therapy.

3.5. Other mechanisms

3.5.1. Six1 and TRAIL resistance

Six1 is a homeobox gene transcription factor which mainly regulates proliferation, survival, migration and apoptosis inhibition during the developmental process (Coletta et al., 2008). It is profoundly expressed during embryogenesis while its expression is gradually decreased in adult differentiated tissues (Behbakht et al., 2007; Thangaraju et al., 2012). Nevertheless, dysregulation of *Six1* is implicated in carcinogenesis and metastasis of cancer cells. Aberrant *Six1* overexpression was reported in ovarian cancer (Behbakht et al., 2007), breast cancer (Coletta et al., 2008; Reichenberger et al., 2005) and hepatocellular carcinoma (Ng et al., 2006). In concordance with this, *Six1* is a potent negative regulator of TRAIL-induced apoptosis in cancerous cells. Research findings illustrated that upregulation of *Six1* repressed ovarian carcinoma cells from TRAIL-induced apoptosis. On the contrary, siRNA knockdown studies demonstrated the importance of *Six1* in rendering the ovarian carcinoma cells sensitive towards TRAIL (Behbakht et al., 2007). To circumvent this issue, recent studies demonstrated that various microRNAs were able to downregulate *Six1* proteins. This strategy has enhanced TRAIL-induced apoptosis, reduced metastasis and slowed down the tumor progression in cancerous cells (Zhu et al., 2017; Imam et al., 2010; Yang et al., 2017). Moreover, a study suggested that inhibiting *Six1* has reversed chemoresistance in breast carcinoma (Li et al., 2013). *Six1* overexpression is highly correlated with poor survival rate among ovarian and breast cancer patients (Coletta et al., 2008; Behbakht et al., 2007; Reichenberger et al., 2005). Therefore, *Six1* could potentially be a biomarker to evaluate the sensitivity of TRAIL therapy for cancer patients.

3.5.2. Intersection of cell death pathways

Other mechanisms of TRAIL resistance include aberrant protein synthesis, protein misfolding, ubiquitin-regulated death receptor expression, metabolic pathways, epigenetic dysregulation and metastasis (Trivedi and Mishra, 2015). Some of these mechanisms overlapped with the mechanisms described previously. For example, ubiquitination is a crucial regulator of DISC activity through recruitment of E3 ligase Cullin3 to DISC. This recruitment leads to poly-ubiquitination of caspase-8 which results in DISC recruitment of the ubiquitin-binding protein p62, leading to stabilization of the activated caspase-8 and thus facilitating DISC activation (Lemke et al., 2014; Trivedi and Mishra, 2015). The overexpression of cIAP1 (caspase inhibitor) results in its auto-ubiquitination and degradation, allowing cells to commit to the execution of apoptosis (Trivedi and Mishra, 2015; Yang and Li, 2000), in which the relation between IAP and TRAIL resistance has been elucidated in the section of the reduced caspase function above.

However, detailed resistance mechanisms are not well elucidated and it is not known whether different types of cancer undergo TRAIL resistance through similar or specific mechanisms.

4. TRAIL clinical trials to date

As soon as TRAIL's potential as a selective anti-cancer agent was observed in pre-clinical studies on its functionalized variants, a great deal of effort has been placed on human clinical trials of TRAIL and TRAs (Stuckey and Shah, 2013). The first of such effort was done with the soluble rhTRAIL or dulanermin on 71 patients with metastatic solid tumors in a Phase I dose-escalation study. rhTRAIL was demonstrated to be safe and well tolerated at doses up to 30 mg/kg with no observable antibody formation and rhTRAIL-related hepatoxicity (Herbst et al., 2010a). Another Phase III clinical trial of rhTRAIL for injection was conducted on stage IV non-small-cell lung cancer (NSCLC) in 2016. The study was estimated to be completed in June 2018, however, no results have been posted to date (NCT03083743 at http://www.clinicaltrials.gov).

Beside acting as a single therapeutic agent, dulanermin has also been tested in combination with various chemotherapeutic drugs like paclitaxel, carboplatin, bevacizumab, vinorelbine, cisplatin and FOLFOX (folinic acid, fluorouracil and oxaliplatin) regimen in clinical trials for advanced NSCLC and locally advanced, recurrent, or metastatic colorectal cancers (Table 1). In a Phase 1b study for advanced NSCLC treated with a combination of rhTRAIL with paclitaxel, carboplatin and bevacizumab (PCB), the treatment regimen was well tolerated with no increase in toxicity; the overall response rate was 58% and the median progression-free survival (PFS) time was 7.2 months (Soria et al., 2010). In another Phase III study for advanced NSCLC treated with the combination of dulanermin plus vinorelbine and cisplatin, the treatment regimen significantly improved PFS and objective response rate (ORR) (Ouyang et al., 2017). However, in a Phase II study on the advanced NSCLC treated with dulanermin plus paclitaxel, carboplatin (PC) and bevacizumab (PCB), adverse events were common and the treatment regimen did not improve the patients' clinical outcomes (Soria et al., 2011). These contradicting results warrant further research in obtaining consistent objective response and positive patients' clinical outcomes.

The current limitations of either using TRAIL as a single therapeutic agent or in combination with chemotherapeutic agents have instigated the development and advancement of several TRAs in Phase I clinical trials. These TRAs are either used as single therapeutic agents or in combination with other sensitizers such as chemotherapeutic drugs, immunotherapeutic agents, mABs, therapeutic proteasome inhibitors and tyrosine kinase inhibitors (Table 2). One of the earliest TRAs was mapatumumab, which is a human agonistic mAB targeted against DR4. Both the Phase I clinical trials on advanced cancers gave promising outcomes of excellent safety and tolerability profiles as well as prolonged plasma mapatumumab terminal half-life. Nonetheless, no objective responses were obtained except for the achievement of stable disease in approximately 30% of the study patients (Hotte et al., 2008; Tolcher et al., 2007). On the other hand, TRAs against DR5 have also progressed to Phase I clinical trials. Conatumumab (Herbst et al., 2010b; Doi et al., 2011), lexatumumab (Plummer et al., 2007; Wakelee et al., 2010) and drozitumab (apomap) (Camidge et al., 2010) have been reported as safe in multiple Phase I clinical trials on advanced cancers. However, similar to TRAs against DR4, they generally displayed no objective responses in patients. On the basis of TRAs displaying generally safe and tolerable profiles even at high doses of 10–30 mg/kg, some of these TRAs have moved on to Phase II clinical trials either as single agents or combined with the other potential TRAIL sensitizers (Table 2).

When combined with chemotherapy or other potential TRAIL sensitizers, TRAs showed improved efficacy in terms of pathological response. For instance, mapatumumab combined with gemcitabine and cisplatin gave a partial response in 12 out of 49 patients (Mom et al., 2009). While in the combination with paclitaxel and carboplatin, 5 out of 27 patients responded partially (Leong et al., 2009) in Phase I clinical studies. Nonetheless, randomized controlled Phase II trials of mapatumumab combined with bortezomib and chemotherapy on patients with multiple myeloma (Belch et al., 2010) and lung cancer (von Pawel et al., 2014), respectively, did not yield significant anti-cancer activities in terms of response rate, PFS or overall survival (OS). Recently, an ongoing randomized Phase II trial of mapatumumab combined with sorafenib on patients sufferring advanced hepatocellular carcinoma has shown no significant improvement in time to (radiologic) progression or other efficacy end points, directing towards an inferior clinical feasibility of mapatumumab (Ciuleanu et al., 2016). Similar trend of poor response rate and insignificant anti-tumor activity was observed in Phase I and Phase II trials of TRAs against DR5 like conatumumab, lexatumumab, tigatuzumab, drozitumab and LBY-135 in combination with chemotherapy (Table 2). Some of the ongoing clinical trials on TRAs combined with other anti-cancer entities targeted against proliferation, angiogenesis and immune checkpoint inhibitors are summarized in Table 2.

In short, TRAIL and its receptor agonists have proven their clinical success so far, with the consistency of safe and tolerable profiles even at high-dose administration to cancer patients. By supplementing the standard chemotherapy, TRAIL performed better in terms of response rate. Nevertheless, due to the fact that TRAIL in combination with standard chemotherapy did not produce a favorable clinical outcome in randomized controlled trials, novel potential TRAIL-sensitizers and TRAIL functionalization will still be an important research area before TRAIL can ace in the clinical settings.

5. Potentiation of TRAIL therapy

5.1. Delivering TRAIL via gene therapy

Lessons learned from the various TRAIL resistance mechanisms and varied clinical responses have instigated the pursuit of further means of potentiating effective TRAIL therapy. As good as the different functionalizations of TRAIL and TRAs have achieved to improve tumor sensitivity towards TRAIL, the inherent lack of stability, rapid inactivation and renal clearance of TRAIL *in vivo* (Kim et al., 2011; Lim et al., 2011) have constrained its therapeutic potential by limiting its therapeutic window to only high concentrations maintained by repeated injections. Therefore, this has hastened the further research into more regulated and specific delivery of TRAIL's apoptosis-inducing effect to the tumor site.

An appealing approach is to deliver TRAIL cDNA to the tumor site using non-replicative adenoviral (Ad) vector to achieve specific intratumoral TRAIL expression. Ad vectors are advantageous with respect to its recognition system on host cells *via* Coxsackie virus and adenovirus receptor (CAR) and the secondary integrin receptors which are widely expressed across benign human tissues (Lee et al., 2017). The first delivery of TRAIL *via* this mean was documented almost two decades ago when Griffith and his colleagues have demonstrated that Ad5-TRAIL could successfully deliver the TRAIL gene into human prostate cancer cells and that the cell surface TRAIL expression has been sustained for up to 7 days (Griffith et al., 2000; Griffith and Broghammer, 2001). Ad5-TRAIL has also been brought to Phase I clinical trial in men with primary prostate cancer. Evidences of DNA fragmentation, inflammatory cells and plasma caspase-3 activity were the indicative of apoptosis event, thereby confirming the efficacy of TRAIL delivery *via* Ad5-TRAIL in Gelfoam (Griffith et al., 2009).

Nonetheless, CAR expression is highly varied across malignant cells (Reeh et al., 2013; Giaginis et al., 2008), hindering the goal of efficient and consistent transfer of TRAIL gene across different tumors. Various modifications to the Ad vector have been made to accommodate for this cellular resistance against Ad vector-mediated gene delivery. Scientists have tapped on the cancer-selective recognition receptor of other Ad serotypes to engineer Ad vectors suited for various cancer cells based on the expression level of these recognition receptors. A typical case was the addition of the integrin-binding motif, Arg-Gly-Asp (RGD), to Ad vector carrying TRAIL (Ad/TRAIL-F/RGD) which significantly enhanced the selective TRAIL expression and apoptosis induction in pancreatic cells both *in vitro* and *in vivo* (Jacob et al., 2004). Moreover, the use of Ad35 rather than Ad5 also changed the vector tropism towards CD46 recognition, and enhanced the killing of glioblastoma (Belanich et al., 1996), which is known for its downregulation of CAR (Huang et al., 2005). More recently, Ad-mediated gene therapy has attained another level of advancement whereby TRAIL is expressed on the Ad capsid component *via* the leucine zipper-like

Table 1
Representative clinical trials conducted on soluble recombinant human Apo2L/TRAIL (rhTRAIL), as a single therapeutic agent or in combination with the potential sensitizers such as chemotherapeutic drugs and monoclonal antibodies.

Cancer type	Intervention	Dosage	Outcome	Phase (Status)	Reference
Soluble recombinant human TRAIL (rhTRAIL)/Dulanermin					
Advanced cancer	Soluble recombinant human Apo2L/TRAIL (rhTRAIL)	0.5-30 mg/kg/d intravenously (IV) on days 1 to 5 of each 21-day cycle	rhTRAIL was safe and well tolerated; dose escalation up to serum concentrations on par with preclinical anti-tumor efficacy	I (Ongoing as of 2010)	(Herbst et al., 2010a)
Stage IV non-small-cell lung cancer (NSCLC)	Recombinant human Apo-2 ligand (Injection)	150 μg/kg/d IV, on days 1 to 7 of each 21-day cycle	(Ongoing)	III (Active, not recruiting)	+NCT03083743
In combination with the potential sensitizer(s)					
Advanced NSCLC (with no prior treatment)	Combination of rhTRAIL with paclitaxel, carboplatin and bevacizumab (PCB)	Paclitaxel, carboplatin (IV), and bevacizumab (IV) on day 1 followed by 4 or 8 mg/kg/d dulanermin (IV) for 5 days or 20 mg/kg/d dulanermin (IV) for 2 days of each 21-day cycle	Well tolerated with no increase in toxicity; overall response rate was 58%; the median progression-free survival (PFS) time was 7.2 months	Ib (Ongoing with long term follow-up as of 2008)	(Soria et al., 2010)
Follicular and low-grade CD20+, B-cell Non-Hodgkin's Lymphoma (NHL)	Combination of dulanermin with rituximab	4 or 8 mg/kg/d dulanermin (IV) on days 1 to 5 of each 21-day cycle; 375 mg/m^2 rituximab (IV) weekly for up to 8 doses	Improved PFS with combination therapy (17.9 months) compared to dulanermin alone (6.9 months)	Ib, II (Terminated with results)	+NCT00400764
Advanced NSCLC	Combination of dulanermin with paclitaxel and carboplatin (PC) and bevacizumab (PCB)	PC (IV) with dulanermin 8 mg/kg/d for 5 days (Squamous NSCLC); PCB (IV) with dulanermin 8 mg/kg/d for 5 days or 20 mg/kg/d for 2 days (Nonsquamous NSCLC)	Grade ≥3 adverse events were common; elevated caspase-cleaved cytokeratin-18 after dulanermin treatment; did not improve patient outcomes.	II (Ongoing as of 2009)	(Soria et al., 2011)
Stage IIIb to IV NSCLC	Combination of dulanermin with vinorelbine and cisplatin	Vinorelbine (25 mg/m^2) (IV) on days 1 and 8; cisplatin (30 mg/m^2) (IV) on days 2 to 4 for up to six cycles plus dulanermin (75 μg/kg) (IV) on days 1 to 14 in every 21 days	Significantly improved PFS and objective response rate (ORR); similar adverse events AE profile across placebo and treatment	III (Completed in 2012)	(Ouyang et al., 2017)
Locally advanced, recurrent, or metastatic colorectal cancer	Dulanermin administered in combination with the FOLFOX regimen and bevacizumab	Drug: FOLFOX regimen IV repeating dose (Dose not stated) Drug: bevacizumab IV repeating dose (Dose not stated) Drug: dulanermin IV repeating dose (Dose not stated)	No results posted	1 (Completed in 2014)	+NCT00873756

Note: †NCT represents the clinical trial identifier which has been registered at https://www.clinicaltrials.gov, as accessed on 4th September 2018.
Key for abbreviations: Progression-free survival (PFS); Adverse events (AE); Objective response rate (ORR); Intravenous (IV).

Table 2
Representative clinical trials conducted on TRAIL receptor agonists (TRAs) against TRAIL-R1 (DR4) and TRAIL-R2 (DR5), either as single therapeutic agents or in combination with the other potential sensitizer(s) such as chemotherapeutic drugs, monoclonal antibodies and immunotherapeutic drugs.

Cancer type	Intervention	Dosage	Outcome	Phase	Reference
TRAIL receptor agonists against TRAIL-R1(DR4)					
Single agent					
Advanced cancers	Mapatumumab	0.01 to 20.0 mg/kg (IV)	AE events were mostly grade 1 or 2; no ORR observed; 12 patients had stable disease for 1.9 to 29.4 months.	I (Completed)	(Hotte et al., 2008)
Advanced solid malignancies	Mapatumumab	0.01 to 10 mg/kg (IV)	Mild AE events of grade 1 or 2; 19 patients had stable disease; attained plasma mapatumumab concentrations active in preclinical models	I (Completed)	(Tolcher et al., 2007)
Colorectal cancer	Mapatumumab	20 mg/kg every 14 days followed by 10 mg/kg (IV) every 14 days	12 patients achieved stable disease of a median of 2.6 months; median PFS was 1.2 months; plasma concentrations on par with Phase I-predicted values; no clinical activity	II (Completed)	(Trarbach et al., 2010)
Stage IIIb/IV recurrent NSCLC	Mapatumumab	10 mg/kg (IV) every 21 days	No objective single agent activity based on response evaluation criteria in solid tumors (RECIST) criteria; no evidence of renal or hepatic toxicity; 29% of patients achieved stable disease	II (Completed)	(Greco et al., 2008)
In combination with the potential sensitizers					
Advanced solid malignancies	Combination of mapatumumab with paclitaxel and carboplatin	3, 10, 20 mg/kg (IV) with standard doses of paclitaxel and carboplatin (IV) every 21 days	5 patients had confirmed radiologic partial response; 12 patients had stable disease	I (Completed in 2006)	(Leong et al., 2009)
Advanced solid tumours	Combination of mapatumumab with gemcitabine and cisplatin	1, 3, 10, 20, 30 mg/kg (IV) with gemcitabine (1250 mg/m^2) on days 1 and 8 and cisplatin (80 mg/m^2) on day 1 of each 21-day cycle	12 patients had partial response; 25 patients achieved stable disease; safe and well tolerated for doses up to 30 mg/kg	I (Completed in 2009)	(Mom et al., 2009)
Stage IIIb or IV advanced primary NSCLC	Combination of mapatumumab with paclitaxel and carboplatin	Paclitaxel (200 mg/m^2) (IV) + carboplatin area under curve (AUC) 6.0 mg min/mL (IV) + mapatumumab (10 mg/kg or 30 mg/kg IV) of 21-day cycle for up to 6 cycles	Balanced AE events across treatment groups; no improved response rate or PFS	II (Completed)	(von Pawel et al., 2014; Von Pawel et al., 2010)
Relapsed/refractory multiple myeloma	Combination of mapatumumab with bortezomib	Brotezomib (1.3 mg/m^2) (IV) on days 1, 4, 8, 11 + 10 or 20 mg/kg (IV) on day 1 of 21-day cycle	Balanced AE events across treatment groups; no improvement in response rate, PFS or duration of response	II (Completed)	(Belch et al., 2010)
Advanced hepatocellular carcinoma	Combination of mapatumumab with sorafenib	Sorafenib (400 mg orally, twice daily) and placebo or 30 mg/kg (IV) mapatumumab on day 1 of 21-day cycle	Comparable AE events across treatment arms; no improvement in time to (Radiologic) progression or other efficacy end points	II (Completed in 2013)	(Ciuleanu et al., 2016)
TRAIL receptor agonists against TRAIL-R2 (DR5)					
Single agent					
Advanced solid tumours	Conatumumab	0.3, 1, 3, 10 or 20 mg/kg (IV) every 14 days	1 NSCLC patient had partial response at 0.3 mg/kg; 1 colorectal carcinoma patient had stable disease and 24% reduction in tumour size by RECIST; safe and well tolerated at doses up to 20 mg/kg	I (Completed in 2008)	(Herbst et al., 2010b)
Advanced solid tumours	Conatumumab	3, 10, 20 mg/kg (IV) every 14 days	Well tolerated at doses up to 20 mg/kg once every 14 days; 9/18 patients achieved stable disease	I (Completed)	(Doi et al., 2011)
Advanced solid malignancies	Lexatumumab	0.1-20 mg/kg (IV) every 21-day cycle	Stable disease was sustained in 12/37 patients; safe and well tolerated up to 10 mg/kg every 21 days	I (Completed in 2006)	(Plummer et al., 2007)
Advanced solid tumours	Lexatumumab	0.1-10 mg/kg (IV) every 14 days	9/31 patients achieved stable disease; safe and tolerated at 10 mg/kg every 14 days	I (Completed)	(Wakelee et al., 2010)
Paediatric patients with recurrent or progressive solid tumours	Lexatumumab	3, 5, 8, 10 mg/kg (IV) once every 14 days	5/24 patients achieved stable disease for 3-24 cycles; no complete or partial response observed; some anti-tumor activity was evident	I (Completed)	(Merchant et al., 2012)
Advanced malignancies	PRO95780 (Drozitumab)	1-20 mg/kg (IV) every 14 days	3 minor responses observed in patients with colorectal and granulosa cell ovarian cancers (4 mg/kg) and chondrosarcoma (10 mg/kg); safe and well tolerated at doses up to 20 mg/kg	I (Completed)	(Camidge et al., 2010)
Advanced solid tumours	DS-8273a	2, 8, 16, 24 mg/kg (IV) once every 21 days		I (Completedin 2015)	(Forero et al., 2017)

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Table 2 (*continued*)

Cancer type	Intervention	Dosage	Outcome	Phase	Reference
			Well demonstrated and showed linear pharmacokinetics; no objective responses were observed		
Relapsed/refractory carcinomas or lymphoma	Tigatuzumab	1, 2, 4, 8 mg/kg (IV) weekly	No study-drug-related toxicities; no ant-tigatuzumab responses; 7/17 patients had stable disease (response duration from 81 to 798 days)	I (Completed)	(Forero-Torres et al., 2010)
In combination with the potential sensitizer(s)					
Advanced solid tumours; NSCLC, colorectal cancer, sarcoma, pancreatic cancer, ovarian cancer	Combination of conatumumab with ganitumab (monoclonal antibody to IGF1R)	1, 3, 15 mg/kg (IV) conatumumab with ganitumab (18 mg/kg) on day 1 every 21 days	No ORR observed; 28 (36%) patients had stable disease; well tolerated with no new toxicities	I/II (Completed in 2010)	(Tabernero et al., 2015)
Metastatic or locally advanced unresectable soft tissue sarcomas	Combination of conatumumab with doxorubicin	Phase I: Doxorubicin (75 mg/m^2) with conatumumab (15 mg/kg)* every 21-day cycle Phase II: Double blind conatumumab 15 mg/kg (conatumumab-doxotubicin)* or placebo (placebo-doxorubicin) *administration route not stated	No unexpected AE observed; no significant improvement of post-chemotherapy response from conatumumab dosing	I/II (Completed)	(Demetri et al., 2012)
Metastaic pancreatic cancer	Combination of conatumumab or ganitumab with gemcitabine	Gemcitabine (1000 mg/m^2) (IV) on days 1, 8 and 15 of each 28-day cycle with ganitumab (12 mg/kg) (IV) every 14 days or double-blind conatumumab (10 mg/kg) (IV) or double-blind placebo	59% of patients receiving the conatumumab-gemcitabine treatment showed anti-cancer activity based on the 6 months survival rate	II (Completed in 2009)	(Kindler et al., 2012)
Various cancer types	Combination of lexatumumab with gemcitabine, FOLFIRI (folinic acid, fluorouracil and irinotecan), pemetrexed or doxorubicin	5 or 10 mg/kg (IV) with (gemcitabine or FOLFIRI) (IV) every 14 days or (pemetrexed or doxorubicin) (IV) every 21 days	Well tolerated; tumor shrinkage was observed; partial response in the FOLFIRI and doxorubicin arms.	Ib (Completed)	(Sikic et al., 2007)
Locally advanced recurrent or metastatic colorectal cancer	Combination of drozitumab (IV) with first-line mFOLFOX6 (5-fluorouracil, leucovorin, and oxaliplatin) plus bevacizumab (IV)	(Dose not stated)	2 patients had partial response	Ib (Completed)	(Rocha Lima et al., 2012)
Chemotherapy-naive, unresectable or metastatic pancreatic cancer	Combination of tigatuzumab with gemcitabine	8 mg/kg loading dose followed by 3 mg/kg weekly (IV) tigatuzumab and gemcitabine (1000 mg/m^2) (IV) once weekly for 21 days followed by 1 week of rest	PFS rate at 16 weeks was 52.5%; ORR was 13.1%; 45.9% patients had stable disease; treatment was well tolerated	II (Completed in 2010)	(Forero-Torres et al., 2013)
Chemotherapy-naïve, metastatic or unresectable NSCLC	Combination of tigatuzumab with carboplatin/paclitaxel	Tigatuzumab (10 mg/kg on week 1 and 8 mg/kg thereafter) or placebo (IV) with carboplatin (AUC 6 mg/ml min) (IV) / paclitaxel (175 mg/m^2) (IV) every 21 days for 6 cycles	Median PFS was 5.4 months for tigatuzumab compared to 4.3 months for placebo; both the placebo and tigatuzumab cohorts had similar partial response rate; tigatuzumab was well tolerated but no improvement in efficacy of carboplatin/paclitaxel treatment	II (Completed)	(Reck et al., 2013)
Metastatic, triple negative breast cancer	Combination of tigatuzumab with abraxane	Abraxane (100 mg/m^2) (IV) on days 1, 8, and 15 of 28-day intervals; 10 mg/kg (IV) loading dose of tigatuzumab followed by 5 mg/kg (IV) for the first cycle and then every other week on days 1 and 15 for subsequent cycles	No serious AE observed; no improvement in PFS compared to abraxane alone	II (Completed in 2017)	$^+$NCT01307891
Advanced colorectal cancer	Combination of DS-8273a with nivolumab (anti-PD1)	Nivolumab (240 mg) (IV) once every two weeks on days 1 and 14 of each 28-day cycle; DS-8273a administration after nivolumab infusion in ascending doses up to 1200 mg (IV)	(No results posted)	I (Terminated)	$^+$NCT02991196
Unresectable stage III or stage IV melanoma	Combination of DS-8273a with nivolumab	Starting dose of 4 mg/kg (IV) (With dose escalation of 8, 16, 24 mg/kg and then 2, 4 mg/kg (IV) in subsequent cohorts) DS-8273a with nivolumab (5 mg/kg) (IV) every 21 days	(No results posted)	I (Recruiting)	$^+$NCT02983006

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Table 2 (*continued*)

Cancer type	Intervention	Dosage		Outcome	Phase	Reference
Advanced solid tumours	Combination of LBY135 with capecitabine		Arm 1: 0.3, 1, 3, 10, 15, 20, 40 mg/kg (IV) LBY135 on day 1 of a 21-day cycle Arm 2: 1, 3, 10, 15, 20, 40 mg/kg (IV) LBY135 on day 1 of a 21-day cycle in combination with oral capecitabine (1000 mg/m^2) twice daily, 2 weeks on and 1 week off	Arm 1: 21/38 patients had stable disease Arm 2: 3 dose-limiting toxicities (Each of grade 3) have been observed at 1, 20 and 40 mg/kg; 22% patients were detected with immunogenicity; LBY135 was well tolerated up to maximum dose of 40 mg/kg; no appreciable clinical activity was observed	I/II (Completed in 2008)	(Sharma et al., 2014)

Note: †NCT represents the clinical trial identifier which has been registered at https://www.clinicaltrials.gov, as accessed on 4th September 2018.
Key for abbreviations: Progression-free survival (PFS); Adverse events (AE); Objective response rate (ORR); Intravenous (IV).

dimerization domains (zippers) and this leads to tumor-specific killing and greater apoptosis induction as TRAIL replicates alongside the oncolytic vector (Wang et al., 2016a).

Ad-mediated gene therapy has undeniably contributed significantly to the field of gene-virotherapy. However, despite the claim that the Ad genome will not integrate into the host genome, its safety is still an issue of concern for its clinical applications, especially with the complications that come with it, including patients' death (Marshall, 1999; Raper et al., 2003). Hence, various formulations like fluorinated dendrimers (Wang et al., 2016b) and triazine-modified dendrimers (Wang et al., 2015) have been tested to increase the transfection efficiency for TRAIL while maintaining minimal toxicity. More recently, with the advent of nanotechnology, gene delivery has been fine-tuned to a miniature scale with more specificity and flexibility. Various nanoparticles (NPs) like liposomes, albumin NPs, inorganic nanovectors, DNA nanostructures, cell and cell membrane-based vectors have been tested for TRAIL gene delivery into various tumors. The advent of these NPs has a common aim in achieving excellent biocompatibility, functionalization flexibility and low toxicity while improving TRAIL's bioavailability (Wu et al., 2017).

5.2. An assemblage of TRAIL sensitizers

5.2.1. Epigenetic drugs

The anti-cancer potential of epigenetic drugs lies in their function as gene regulators by reversing heterochromatin, a tightly packed form of DNA which favours gene suppression, to euchromatin, a lightly packed form of DNA which favours gene expression. Therefore, tumor suppressor genes (TSGs) which have been suppressed by cancer cells can potentially be re-expressed by epigenetic drugs treatment. In the facet of TRAIL-induced apoptosis, epigenetic drugs have also been reported to be one of the many effective sensitizers of various cancer cells towards the apoptotic effect of TRAIL. One of the commonly studied epigenetic drugs aimed as TRAIL sensitizer is the histone deacetylase inhibitor (HDACi), which reverses the gene suppression effected by histone deacetylases (HDACs). HDACi has shown excellent cooperation with TRAIL in the killing of a panel of cancer cell types including breast, lung, colon, prostate, renal cell carcinoma and melanoma (Fulda and Debatin, 2005).

Some of the commonly studied HDACi drugs are suberoylanilide hydroxamic acid (SAHA), m-carboxycinnamic acid bis-hydroxamide (CBHA), MS-275 and trichostatin A (TSA). One of the earliest elucidated mechanisms behind the TRAIL-sensitizing effect of HDACi is the upregulation of DR4, DR5 and pro-apoptotic Bcl-2 members (Singh et al., 2005; VanOosten et al., 2005a). Besides, HDACi also exhibits pro-TRAIL regulatory effect on cell cycle-related genes, growth factors and their cognate receptors in breast cancer cell lines (Zhou et al., 2016). In view of the finding that some of the TRAIL-sensitizing effects of HDACi were also observed without the upregulation of TRAIL receptors (Inoue et al., 2004), it highlights the fact that there exists some TRAIL resistance mechanisms that can be targeted beyond the receptor level.

As aforementioned, the rapid internalization of TRAIL-ligated receptors is one of the resistance mechanisms pitched by cancer cells against TRAIL-induced killing (Zhang and Zhang, 2008). Intriguingly, prior to treatment with HDACi, depsipeptide enhances the sensitivity of prostate tumor cells to TRAIL-induced apoptosis by redistributing DR4 and DR5 to membrane lipid rafts (VanOosten et al., 2005b). In addition, the combined treatment of HDACi and TRAIL has also overcome the TRAIL resistance in breast cancer *via* various methods such as downregulation of cFLIP (Frew et al., 2008), suppression of c-Myc TRAIL-deactivating function by its acetylation (Nebbioso et al., 2017) and fine-tuning the regulation of genes related to the mitochondrial pathway (Morales et al., 2010), so as to engage the intrinsic pathway for better TRAIL anti-cancer efficacy.

Since chromatin architecture is not only regulated by histone deacetylation but also DNA methylation in CpG rich region of gene promoter, scientists have also shifted their research focus on another group of epigenetic drugs known as DNMTi. Both DNMTi and HDACi work against TRAIL resistance *via* different mechanisms. For instance, in

contrast to the upregulation of TRAIL receptors by HDACi, DNMTi, such as Zeb, was shown to enhance TRAIL-induced apoptosis in breast cancer cells by increasing cellular fucosylation level, thereby enhancing the TRAIL-receptor fucosylation-facilitated receptor clustering and apoptosis induction, while the TRAIL receptor level remain unchanged (Moriwaki et al., 2010).

Nonetheless, there is growing evidence which shows that DNA methylation and histone deacetylation are correlated. For example, attachment of methyl binding protein MeCP2 to methylated sites is followed by recruitment of HDACs which eventually leads to heterochromatin formation (Li, 2002; Sharma et al., 2009). Therefore, dual therapy of HDACi and DNMTi can be envisioned as a TRAIL-sensitizing combination with great potential based on the association between the two types of chromatin modifications. This notion has been supported by the cooperative restoration of caspase-8 expression in small cell lung carcinoma (SCLC) by prior treatment of HDACi, valproic acid (VPA) or CI-994 and DNMTi, decitabine, followed by TRAIL treatment (Kaminskyyy et al., 2011). It is also evident from this finding that prior treatment rather than concurrent treatment provides a platform for the re-expression of genes important for TRAIL sensitivity before the TRAIL treatment itself. Both Zeb and TSA increase TRAIL death receptor fucosylation (do Nascimento et al., 2015) and upregulate TRAIL receptors (Singh et al., 2005), respectively, targeting distinctive mechanisms of TRAIL resistance in breast cancer cells. In short, the addition of DNMTi and HDACi prior to TRAIL treatment displays enhanced sensitizing effects on cancer cells towards TRAIL-induced apoptosis as compared to the respective single TRAIL sensitizer.

5.2.2. Novel sensitizers of TRAIL

Findings from the literatures have shown that despite the efforts made by scientists in the quest of the most effective TRAIL sensitizer for all cancers, it is still futile because of the distinctive TRAIL resistance mechanisms maintained by different cancer cell types. Therefore, cancer type-specific high throughput screenings (HTS) for potential TRAIL sensitizers have been initiated. For instance, Booth and colleagues (Booth et al., 2009) have screened through the library of natural and synthetic compounds from which they have unearthed two synergistic TRAIL sensitizers, M259 and cyanocycline A, that could synergize with TRAIL in renal adenocarcinoma cells at doses lower than those needed for their DNA-damaging effect. Besides, another HTS using a library of pharmacologically active compounds (LOPAC) has discovered two novel TRAIL sensitizers, APDC (ammonium pyrrolidinedithiocarbamate) and YC-1 (3-(59-hydroxymethyl-29-furyl)-1-benzyl indazole), on top of the five known TRAIL-sensitizing compounds which target the caspase-8 axis in neuroblastoma cell line (Finlay et al., 2010).

In addition, another group has used an enzyme-linked immunosorbent assay (ELISA) and cell-based HTS approach in discovering small compounds which can act against the TRAIL resistance mechanism mediated by mitogen-activated protein kinase kinase 7 (MKK7)-protein phosphatase type 2A (PP2Ac)-TOR signaling pathway regulator like (TIPRL) complex in hepatocellular carcinoma (Yoon et al., 2017). The applicability of HTS approach has also been extended to glioblastoma cells in screening for TRAIL-sensitizing compounds in a library of 1200 Food and Drug Administration (FDA) approved drugs (Senbabaoglu et al., 2016). The lesson obtained from these HTS studies is that there is a great trove of compounds, both natural and synthetic, which have the potential to enhance the anti-cancer potential of TRAIL in hastening its way to patient's bench. In order to realize the success of TRAIL as an anti-neoplastic agent, further research into this trove for the cancer type-specific TRAIL sensitizers is definitely warranted.

6. Conclusion and future prospect

TRAIL is a precious jewel in the treasury of anti-cancer candidates. Nonetheless, as hard as it is to locate a gem in an underground treasury, it has also been an ardent process of pushing the gem of TRAIL to the clinical bench due to the issue of resistance. The resistance mechanisms which have been reviewed include the disrupted balance between the anti-apoptotic proteins, Bcl-2 family proteins, cFLIP (Zhang et al., 2004; Zang et al., 2014) and the pro-apoptotic proteins, Bax, Bak and Bok (Thomas et al., 2013; Czabotar et al., 2014), the reduced caspase function contributed mainly by the IAPs (Lopes et al., 2007; Allensworth et al., 2012), the impaired death receptor signaling caused by TRAIL-ligated death receptor internalization (Rahman et al., 2009b; Zhang and Zhang, 2008), downregulation of glycosylation (Twomey et al., 2015; Wagner et al., 2007) and other mechanisms which include *Six1* overexpression (Behbakht et al., 2007).

On the other hand, the numerous clinical trials being conducted on rhTRAIL and TRAs have demonstrated the bright potential of TRAIL being safe and tolerable at therapeutic doses, yet have also revealed a lesson that we are still at a distance from achieving favorable clinical response rate from TRAIL treatment, even by combining with the standard chemotherapy. Nonetheless, the enthusiastic hunt for TRAIL sensitizers and the promising potential which lie within the delivery of the gene, TRAIL, have produced hope in TRAIL-based anti-cancer therapy, both at the pre-clinical and clinical stages. Besides, TRAIL has also induced pro-survival non-canonical signaling such as ERK (Extracellular-signal-regulated kinase)-mediated phosphorylation (Belyanskaya et al., 2008; Braithwaite et al., 2018) which should not be neglected in the feat of TRAIL resistance studies. Therefore, with the continuous discovery of novel TRAIL sensitizers founded upon improved understanding on the biology behind TRAIL's action alongside TRAIL sensitivity biomarker elucidation, TRAIL can potentially be seen on the clinical bench of anti-neoplastic personalized medicine in the near future.

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Declaration of Competing Interest

The authors declare no conflict of interest, financial or otherwise.

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