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REVIEW

Escaping cell death via TRAIL decoy receptors: a systematic review of their roles and expressions in colorectal cancer

Kelly Xue Jing Jong[1] · Elsa Haniffah Mejia Mohamed[1] · Zaridatul Aini Ibrahim[1]

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Abstract

The development of targeted therapy such as tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-based therapy has gained increasing attention as a promising new approach in cancer therapy. TRAIL specifically targets cancer cells while sparing the normal cells, thus, limiting the known side effects of the majority anti-cancer therapies. As more extensive research and clinical trials are conducted, resistance to TRAIL molecule has become one of the significant issues associated with the failure of TRAIL in treating colorectal cancer (CRC). To date, the exact mechanism by which TRAIL resistance may have occurred remains unknown. Interestingly, recent studies have revealed the critical role of the TRAIL decoy receptor family; consisting of decoy receptor 1 (DcR1; also known as TRAIL-R3), decoy receptor 2 (DcR2; also known as TRAIL-R4), and osteoprotegerin (OPG) in driving TRAIL resistance. This review highlights the expression of the decoy receptors in CRC and its possible association with the reduction in sensitivity towards TRAIL treatment based on the currently available in vitro, in vivo, and human studies. Additionally, discrepancies between the outcomes from different research groups are discussed, and essential areas are highlighted for future investigation of the roles of decoy receptors in modulating TRAIL-induced apoptosis. Overcoming TRAIL resistance through modulating the expression(s) and elucidating the role(s) of TRAIL decoy receptors hold great promise for TRAIL-based therapies to be extensively explored in treating human cancers including CRC.

Keywords Colorectal cancer · Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) · Apoptosis · Decoy receptor · Osteoprotegerin (OPG) · Targeted therapy

Introduction

The crucial role of apoptosis in guarding neoplastic cell growth is well established as one of the natural protective mechanisms against cancer development [1]. Cells can be targeted for apoptosis by activating death receptors (DRs) expressed on their surface [2]. Upon binding to the DRs, tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) activates the extrinsic apoptotic pathway leading to cellular apoptosis [3]. To date, there are two major receptors known to interact with TRAIL to induce apoptosis, named death receptor 4, DR4 [4] (also known as TRAIL-R1) and death receptor 5, DR5 [5–7] (also known as TRAIL-R2). Alternatively, TRAIL is capable of binding to the anti-apoptotic decoy receptors; decoy receptor 1 (DcR1) [5, 7, 8], decoy receptor 2 (DcR2) [9], and osteoprotegerin (OPG) [10], where apoptosis will not be induced due to the absence of death domain in the biological structures of these three receptors (Fig. 1). Recent evidence indicates that the ultimate fate of the cells is highly dependent on the receptors that TRAIL activate [Fig. 1a(i)] and the complexes the receptors have formed [Fig. 1a(ii)].

The homocomplex of DRs formed upon binding to TRAIL leads to the successful recruitment of the death-inducing signalling complex (DISC). DISC consists of the Fas-Associated protein with Death Domain (FADD) and pro-caspase 8, which upon recruitment, will undergo autoproteolytic cleavage to become active caspase 8. Caspase 8, a crucial initiator of the apoptosis cascade [11–14] [Fig. 1b(i)], serves to activate the effector caspase 3, leading

Kelly Xue Jing Jong and Zaridatul Aini Ibrahim have contributed equally to this work.

✉ Zaridatul Aini Ibrahim
zaridatulaini@ummc.edu.my

[1] Department of Pharmacology, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia

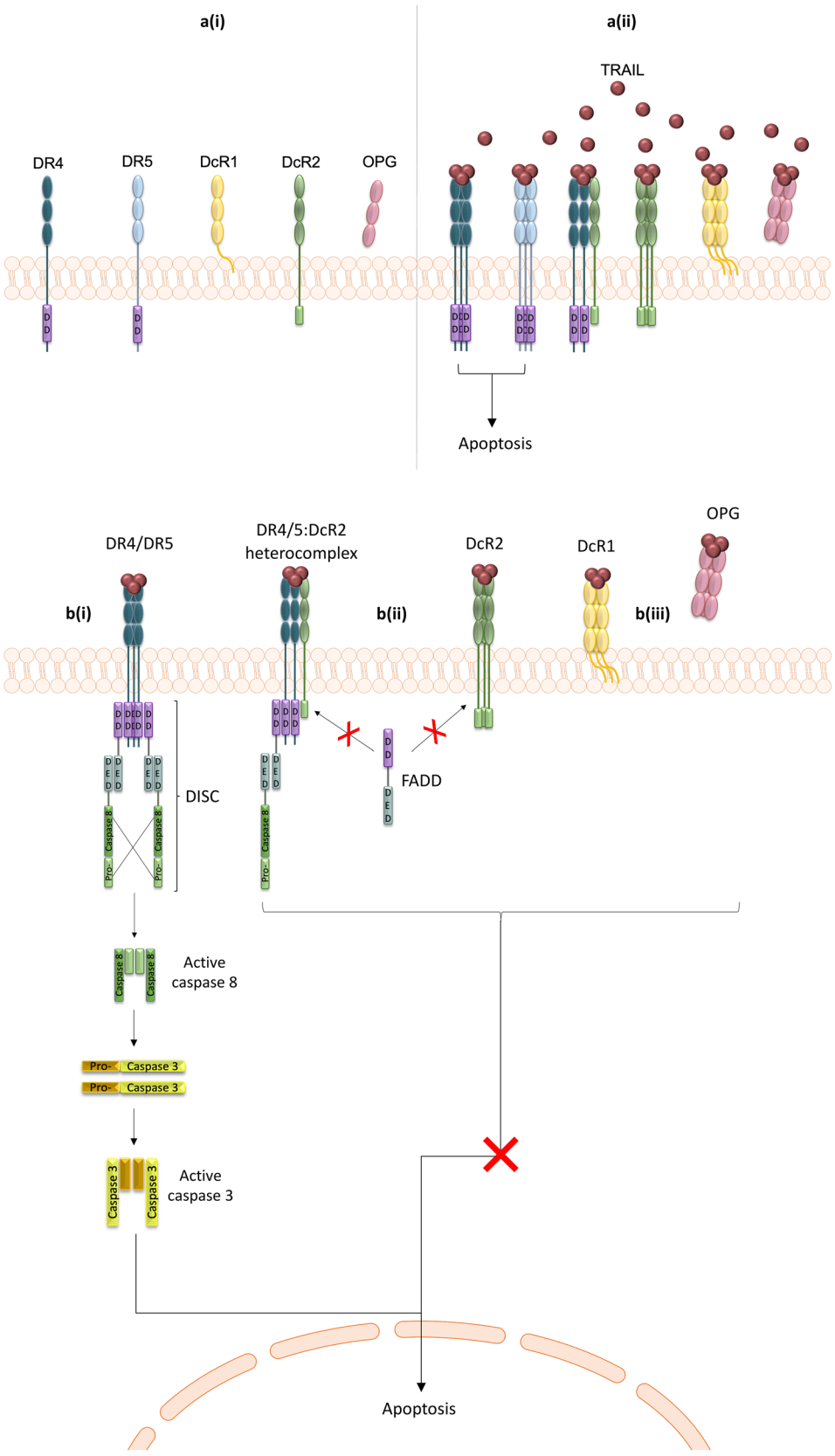

Fig. 1 The summary of functional roles of TRAIL receptors. **a(i)** The five receptors of TRAIL; **a(ii)** The formation of trimeric complex upon binding to TRAIL. **b(i)** Canonical apoptosis inducing pathway when formation of DISC is successful; **b(ii)** Formation of heterocomplex failed to recruit two active pro-caspase 8 for auto-cleavage and activation of caspase initiating apoptosis pathway; **b(iii)** Absence of intracellular domain. Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), Death-Inducing Signaling Complex (DISC), Fas-associated protein with death domain, death receptor (DR), decoy receptor (DcR), osteoprotegerin (OPG)

to the induction of apoptosis [15]. On the contrary, when a heterocomplex is formed between the DRs and DcR2 [Fig. 1b(ii)] or homocomplex formed among the decoy receptors [Fig. 1b(iii)], the apoptosis cascade will not be induced. This inhibition is due to the absence of the death domain in the decoy receptors [16, 17]. By regulating TRAIL-induced apoptosis, these differential mechanisms protect the host from excessive apoptosis induction [18]. However, cancer cells can acquire this mechanism and escape the immune surveillance of TRAIL-induced apoptosis.

Initially, TRAIL has received much attention for its potential to induce apoptotic cell death selectively in neoplastic cells [12, 19]. Several TRAIL-based therapies have been developed for the clinical applications. Recombinant human TRAIL; dulanermin [20, 21], modified recombinant human TRAIL; circulated permuted TRAIL (CPT) [22–24] and TRAIL death receptor agonists; namely mapatumumab [25, 26], tigatuzumab [27], and conatumumab [28, 29], have entered phase II clinical trials with good safety profiles. However, although promising results were obtained in preclinical studies and early phase clinical trials, these TRAIL-based therapies have yielded disappointing outcomes in randomised clinical trials [30]. It is presumed that this may have resulted from the insufficient clustering of targeted death receptors, where receptors with functional death domains did not aggregate to form active complexes to induce apoptosis [31]. Moreover, the ability of TRAIL decoy receptors to interfere with this complex formation in a domain-mediated [32] and ligand-independent manner [33] suggests that a better understanding of the decoy receptors is required to tackle the ineffectiveness of TRAIL therapy.

TRAIL resistance has become one of the significant problems in TRAIL-based therapy and has been seen in a vast proportion of human cancers [34–37], including colorectal cancer (CRC) [38]. Cumulative evidence suggests a connection between TRAIL resistance and the overexpression of TRAIL decoy receptors in CRC [39, 40]. Although the intracellular anti-apoptotic proteins appeared to be the dominant negative regulators of TRAIL-induced apoptosis, overexpression of the different decoy receptors; DcR1, DcR2, and OPG, have also been demonstrated to partake in the development of TRAIL resistance [7, 32, 40–43]. By delaying the onset of TRAIL-induced apoptosis, these decoy receptors provide a greater opportunity for cancer cells to escape immune surveillance [44], leading to the development of more aggressive cancer phenotypes and disease progression [45].

Overview of TRAIL decoy receptors

To date, it has been shown that each TRAIL decoy receptors possess a distinctive cytoplasmic molecular structure [Fig. 1a(i)], resulting in a different inhibitory mechanism of TRAIL-induced apoptosis. For instance, DcR1 (also known as TRAIL-R3) possesses a glycosyl-phosphatidylinositol (GPI)-membrane anchor but lacks an intracellular domain [44]. The absence of cytoplasmic death domain limits the inhibition of the apoptotic signal to be in the lipid rafts [32]. DcR2 (also known as TRAIL-R4), on the other hand, is a TRAIL receptor with a truncated death domain [9]. The presence of the truncated death domain allows DcR2 to exhibit additional regulatory mechanisms for TRAIL-induced apoptosis. As mentioned previously, successful signal transduction requires binding of FADD to the death domain of death receptors. The formation of inactive heterotrimeric complexes with DcR2 disrupts the binding of FADD, which eventually inhibits the activation of initiator caspase 8 and the downstream apoptotic cascade [32].

Furthermore, the engagement of death receptors and DcR2 has been demonstrated to activate the Nuclear Factor kappa B (NF-κB) pathway [8, 46]. A significant number of human cancer progressions have been correlated to the NF-κB activation through the upregulation of several anti-apoptotic proteins such as c-IAP2 [47], Bcl-2 [48], XIAP [49] and DcR1 [50]. Thus, activating the NF-κB pathway by the decoy receptor might be a substantial factor leading to TRAIL resistance and targeting decoy receptor may be helpful in overcoming this resistance [51]. Lastly, the only soluble form of the TRAIL decoy receptor named osteoprotegerin (OPG) was first identified by Emery et al. [10] as a soluble decoy receptor. Upon binding to TRAIL, OPG attenuates TRAIL-induced apoptosis with the absence of functional cytoplasmic death domains in its biological structure [Fig. 1b(iii)].

Increased expression levels of these decoy receptors were observed in various inflammatory diseases [52–55] and cancers [43, 56–58]. However, the correlation between their expression levels and their sensitivity to TRAIL-induced apoptosis in CRC remains poorly characterised. Therefore, this review provides an insight into how the expression levels of these decoy receptors contribute to making CRC more invasive and the potential outlook of how targeting them could help enhance the efficacy of TRAIL-based treatment, especially in CRC.

Methodology

Literature search strategy and eligibility criteria

Studies related to the focus of the studies were obtained through a literature search conducted in the three main databases: PubMed, Scopus, and Web of Science. Studies from inception until October 2021 were collected independently by two reviewers. MeSH terms 'TRAIL decoy receptors' AND 'colorectal neoplasms' were employed in the search strategy. Only original articles in the English language were selected for the qualitative analysis part of the study. The protocol of this systematic review was registered at PROSPERO in August 2021 (Registration ID: CRD42021260406).

A total of 890 papers were retrieved from the database search, and 191 duplicates were removed. The abstracts of the original articles were screened to exclude irrelevant articles based on eligibility criteria (Fig. 2). Complete details of the search strategy and criteria for the selection of papers are described in the PROSPERO protocol (Registration ID: CRD42021260406).

Data extraction

Data on TRAIL decoy receptors' expressions and functional roles of TRAIL decoy receptors in CRC were extracted from relevant studies. Information including study methods, model, and publication year was obtained and recorded. The key findings obtained are summarised in Table 1. All interventions were accepted for this systematic review to achieve a comprehensive and unbiased perspective on the roles of TRAIL decoy receptors in CRC.

Quality assessment strategy

Two independent reviewers critically analysed full texts of potentially relevant articles to determine their eligibility based on the inclusion and exclusion criteria. When discrepancies arose, discussion with a third reviewer was performed to resolve the issue. In the events of missing data, corresponding author of the papers will be contacted through email twice.

Data synthesis

A qualitative systematic review was performed to encapsulate the fundamental knowledge on the expression and functional roles of TRAIL decoy receptors in CRC.

Results and discussion

At the end of the screening procedure, 21 papers were selected to evaluate the differential expressions of the TRAIL decoy receptors and their potential functional roles across different study models of CRC. The key findings of each study are listed in Table 1, highlighting the approaches used to determine the expression of TRAIL decoy receptors and the research outcomes.

The expression and role of DcR1, DcR2, and OPG

The expression and distribution of these decoy receptors were investigated in biological samples collected from human subjects (serum and tumour tissues), human xenografts in animal models, and various CRC cell lines. The effect of TRAIL decoy receptors on TRAIL-induced apoptosis has been demonstrated across study models [Table 1].

The expression and role of DcR1, DcR2, and OPG in human subjects

Along with the natural variations present within the population, the expression patterns of these decoy receptors further differ in different organs. A first study by Sheikh et al. in 1999 revealed that DcR1 mRNA expression was found to be highly expressed in CRC tissue samples, whereas in normal colon, DcR1 mRNA expression appeared to be negligible [59]. Several other studies and data from the gene expression profiling analysis (GEPIA) database also indicated elevated levels of DcR1 and DcR2 mRNA in the CRC tumour in relative to its adjacent normal sites [60–62].

A study conducted by Tsikalasis et al. [63] which involved 106 tumour samples from CRC patients, demonstrated an opposite outcome with the findings discussed above. Among these 106 samples, a majority (64%) showed the downregulation of DcR1, and DcR2 mRNA expressions. However, it is worth noting that the comparison between the diseased and healthy samples was inappropriately made, as the tumour samples were compared to healthy individuals' blood samples in this study. As DcR1 [6, 7] and DcR2 [8, 9] are expressed as transmembrane proteins, comparing their expressions in tumours against blood samples might not illustrate the actual difference in the level of expression. In order to accurately investigate the expression levels and distribution of DcR1 and DcR2 in CRC, future studies are required to take into consideration the sample size and subjects included for comparisons.

Apart from looking at the transcriptional level, several studies also investigated the DcR1 and DcR2 expressions at

a translational level among the tumour tissue samples [60, 64–66]. Koornstra et al., compared the DcR1 and DcR2 protein expressions using 10 normal, 19 adenomas, and 21 carcinoma tissue samples [64]. The staining intensities were similar between all three groups of tissue samples. The comparator control tissue to the tumours in this study was, however, made using non-paired controls, which is not from the same patient. Using non-paired control-tumour samples creates difficulties in identifying cancer-specific variations. Moreover, the value of using paired control-tumour samples in predicting patients' outcomes has been demonstrated in other studies. Paired control-tumour samples accounts for the tumour microenvironments and how their interactions may affect the tumour behaviour and host immunity [67]. This experimental design should be considered for future studies to accurately demonstrate the exact expressions and roles of the decoy receptors.

The ratio between the level of death and decoy receptors has been characterised as one of the causative factors in determining the efficacy of TRAIL-induced apoptosis. Granci et al. reported that DcR1 and DcR2 were classified as highly expressed in the majority of CRC tissue samples [65]. The study also indicated a higher risk of disease progression in patients who concomitantly expressed low/medium levels of DR4 and high levels of DcR1. This suggests that the death receptors-decoy receptors axis regulates disease progression. Furthermore, utilising the altered expression levels of decoy receptors in CRC cell lines as the only parameter might not reflect the actual role(s) and function(s) of these decoy receptors.

As described above, DcR1 and DcR2 are functional transmembrane proteins due to the presence of the membrane-anchored or transmembrane region in their biological structures. DcR1 and DcR2 bind to TRAIL and prevent apoptosis induction by forming heterocomplexes with other death receptors on the cell surface. Immunohistochemistry (IHC) analysis revealed nuclear and cytoplasmic localisation of these two receptors in CRC tumour samples [60, 68]. Nevertheless, cell surface expression remained as the default parameter in obtaining an accurate comparison between the level of expression and the development of TRAIL resistance in CRC patients. Hence, future studies should not only look at the total expression of these two decoy receptors but rather focus on the cell-surface localisation as this will be the ultimate factor influencing their inhibitory function.

Osteoprotegerin levels are commonly investigated by evaluating at their expressions in patients' serum samples as they usually are expressed as a soluble protein in the human body. Lipton et al. and De Toni et al. presented consistent findings where a higher level of OPG was observed in the serum of CRC patients [69]. The level of OPG gene expression was also investigated by Tsukamoto et al.; in which the findings were comparable with the protein expressions measured by other groups [70]. Interestingly, a series of studies conducted by Kim et al. [71, 72] presented a contrasting outcome where both human samples and CRC cell lines showed a downregulation of OPG expression in CRC group compared to healthy group. The discrepancies may be explained by the type of samples used among research groups. Both Lipton et al. and De Toni et al. investigated the soluble OPG present in the serum samples of CRC patients, whereas Kim et al. and Moon et al. measured the OPG level in CRC tissues. Notably, OPG is required to be secreted extracellularly to gain TRAIL access in order to exhibit its decoy mechanism. Hence, the extracellular expression level of OPG might represent a closer manifestation of its actual role in interfering with TRAIL-induced apoptosis.

The expression of DcR1, DcR2, and OPG in the animal model

Velthuis et al. implanted rat adenocarcinoma (CC531) cells into syngeneic Wag/Rij rats and generated rat CRC cells with enhanced metastatic ability through rounds of immune selection [73]. Both total and cell surface protein expressions were investigated, and no difference in expression levels was observed in cells with different metastatic abilities [73, 74]. Sugamura et al., on the other hand, used a xenograft of severe combined immunodeficiency (SCID) mouse model with CRC cells from two independent patients who manifested different sensitivity towards TRAIL treatment [75]. There were no variations in the expression levels of DcR1 and DcR2 despite their difference in TRAIL sensitivity in this study. However, it is worth noting that the western blot analysis used to determine the protein expression was only conducted using the sample collected from one mouse of each treatment/control group. Due to a very small data set and large uncertainty of whether the results are reproducible, the findings obtained from Sugamura's study should be further validated. Future studies using mouse model of CRC with a sufficient number of replicates and sample size are warranted to appropriately examine the correlation between the expression levels of the decoy receptors and the efficacy of TRAIL therapy. Certainly, human CRC cell lines- or patient-derived xenograft mouse models should be employed as one of the experimental research strategies to closely analyse the efficacy of TRAIL treatment in the context of a human immune system and tumour microenvironment.

The expression of DcR1, DcR2, and OPG in CRC cell lines

The efficacy of TRAIL-induced apoptosis has been shown to vary across different CRC cell lines. It is still uncertain

Table 1 Expression of decoy receptors in different study models

Study model	References	Decoy receptor	Approach	Key findings
Human	Sheikh et al. [59]	DcR1	6 colon carcinomas 6 matched normal tissues (Northern blot analysis for mRNA expression)	• Lowly expressed in matched normal tissues • Higher expression in tumour than in normal tissues
	Strater et al. [60]	DcR1 and DcR2	10 adjacent normal colonic mucosae 20 colons adenomas 129 colon adenocarcinomas (RT-PCR and IHC)	• No mRNA and protein expression were detected in normal colonic mucosa • Weak expression was detected in adenoma • Majority of the tumour samples showed weak (31%) or negative (43%) expression mRNA expression—quantitative analysis was not conducted • Protein expressions were generally more pronounced in adenoma than in the normal colonic mucosa, no data shown either • Majority of the samples showed focally weak (31%) and weak (27%) expression
	Galamb et al. [61]	DcR1	10 adenomas 6 colorectal carcinomas (cDNA microarray for gene expression)	• Significantly increased in CRC than in adenoma
	Tsikalakis et al. [63]	DcR1 and DcR2	10 healthy bloods 106 Tumours (RT-PCR for relative mRNA expression)	• DcR1: 15% of the 106 samples showed upregulation and 64% of the 106 samples showed downregulation mRNA expression • DcR2: 26% showed upregulation and 37% of the 106 samples showed downregulation mRNA expression • No correlation between DcR1 mRNA level and clinicopathological characteristics were shown • Strong correlation between the elevated mRNA level and adenocarcinoma histological type
	Koornstra et al. [64]	DcR1 and DcR2	10 normal 19 adenomas 21 carcinomas (IHC staining for protein expression)	• DcR1: Positive staining in 100% of the normal, 74% of the adenomas and 90% of the carcinomas. Staining intensities were similar between positive neoplastic and normal epithelial cells DcR2: All samples showed positive staining. Staining intensities between neoplastic and epithelial cells were comparable • Correlation between TRAIL decoy receptors and histopathological characteristics and degree of apoptosis were not shown
	Granci et al. [65]	DcR1 and DcR2	53 primary CRC (pCRC) (IHC staining for protein expression)	• DcR1: More than 50% of the pCRC samples showed high expression • DcR2: More than 70% of the pCRC samples showed high expression • Higher risk of progressive disease in patients with concomitant low/medium TRAIL-R1 and high DcR1 expression • 70% of the patients with low/medium TRAIL-R1 and high DcR1 developed progressive disease Similar results for progression-free survival (PFS)
	Cui et al. [66]	DcR1	46 healthy control blood 46 CRC blood	• Downregulated in CRC patient • High expressions had favourable prognosis than of low expression
	Prabhu et al. [98]	DcR2	11 adjacent normal 11 tumours (RT-PCR for mRNA expression)	• Majority (8/11) of the tumour samples have higher gene expression relative to the adjacent normal tissue

Table 1 (continued)

Study model	References	Decoy receptor	Approach	Key findings
	Lipton et al. [69]	OPG	112 healthy individuals 16 CRC patients (ELISA for protein expression in serum)	• Significantly higher in CRC patients than in healthy individuals
	De Toni et al. [39]	OPG	40 healthy individuals 22 colonic adenomas 127 colorectal cancers (ELISA for protein expression in serum)	• Significantly elevated in UICC Stage III and IV patients • Significantly higher in patients with metastatic CRC (UICC stage IV) than in UICC Stage III
	Tsukamoto et al. [70]	OPG	77 CRC tumours 77 corresponding normal tissues (RT-PCR for gene expression and IHC for protein expression in tumour samples)	• mRNA: Significantly higher in tumours than in corresponding normal tissues • Protein: Negative staining in normal epithelium whereas strong staining at invasive tumour front and cytoplasm of cancer cells
	Kim et al. [71]	OPG	117 CRC samples 117 matched normal colonic tissue samples (RT-qPCR for gene expression and IHC for protein expression)	• Protein: staining intensity significantly decreased in CRC samples compared to normal samples • mRNA: 22 out of 30 CRC samples showed lower expression level than in matched normal colonic samples
	Moon et al. [72]	OPG	81 primary CRC (pCRC) 81 colorectal livers metastases 81 normal corresponding samples (IHC for protein expression)	• Protein: significantly reduced staining in pCRC and colorectal liver metastasis samples when compared to strong staining in normal colorectal mucosa
Animal	Sugamura et al. [75]	DcR1 and DcR2	1 TRAIL-sensitive human xenograft mice 1 TRAIL-resistant human xenograft mice (Western blot for protein expression)	• No difference in protein expressions
	Velthuis et al. [73]	DcR1 and DcR2	Rat colon carcinoma cell lines (Western blot for protein expression)	• No significant difference in protein expressions
	Velthuis et al. [74]	DcR1 and DcR2	Rat colon carcinoma cell lines (Western blot for total protein, flow cytometry for cell surface expression)	• No significant differences were found in the two different cell types
Cell lines	Hague et al. [77]	DcR1 and DcR2	4 adenomas 1 transformed adenoma 3 carcinomas (Flow cytometry for cell surface expression)	• DcR1: expressed in 2/4 adenoma cell lines; expressed in transformed adenoma; expression decreases as malignancy increases • DcR2: expressed in 1/4 adenoma cell line; expressed in transformed adenoma; expressed in 1/3 carcinoma cell line; expression decreases as malignancy increases • Cell surface receptor expression profile of adenoma and carcinoma cells cannot account for their differential sensitivity to TRAIL
	Lippa et al. [79]	DcR1 and DcR2	TRAIL-sensitive Colo205 TRAIL-resistant Colo320 (Flow cytometry for cell surface expression)	• DcR1: Greater expression on Colo205 cells over Colo320 cells • DcR2: Greater expression on Colo320 cells over Colo205 cells • TRAIL binding to both cell lines was found to be equivalent (data not shown)

Table 1 (continued)

Study model	References	Decoy receptor	Approach	Key findings
	Hofmanova et al. [76]	DcR2	Normal colon epithelial cell (FHC) Adenocarcinoma cell (HT-29) (Western blot for total protein expression)	• Higher expression in FHC than in HT-29 • The difference between the % of apoptotic cells in combination treatment and TRAIL alone is greater in FHC cells than in HT-29
	Kim et al. [71]	OPG	CCD 841 CoTr, HT-29, SW620 and HCT116 (ELISA and western blot for protein expression)	• Expression was significantly lower in CRC cell lines (SW620 and HCT116) than in normal colonic cell line
	Shao et al. [82]	OPG	NCM460, SW480, SW620, LoVo, HT-29 and HCT116 (Western blot for protein expression)	• Expression was significantly higher in all CRC cell lines than in the normal colonic cell line

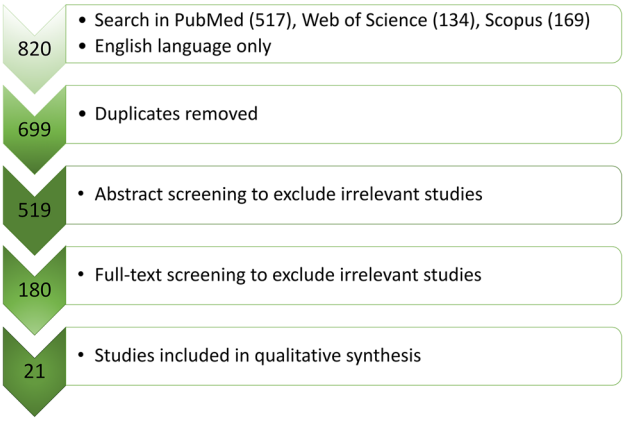

Fig. 2 Search strategies

whether the expression of TRAIL decoy receptors contributes to this heterogeneity among CRC cell lines. Nonetheless, in healthy colon epithelial cells (FHC) that are naturally resistant to TRAIL treatment, a significantly higher level of DcR2 expressions was observed in comparison to the HT-29 CRC cell line. Moreover, the expression levels of DcR1 and DcR2 decreased as the cell lines' malignancy increased [76, 77]. This further highlights that healthy cells are naturally protected from TRAIL-induced apoptosis in the presence of abundant decoy receptors. Additionally, cancer cells are supposed to be exclusively targeted by TRAIL as they develop malignancy. However, when the expression of decoy receptors is abnormally upregulated in cancer cells, protection towards TRAIL-induced apoptosis may be acquired by these cancer cells to escape immune surveillance. This is in coherence with several studies where the upregulation of DcR1 and/or DcR2 are followed by a significant impairment or delay in TRAIL-induced apoptosis [44, 78].

As mentioned previously, DcR1 and DcR2 exhibit different inhibitory mechanisms due to their distinctive biological structures. These differences were evidenced in a study by Lippa et al., where the expression patterns of DcR1 and DcR2 differed in CRC cells with contrasting TRAIL sensitivity [79]. In the TRAIL-sensitive Colo205 CRC cells, a higher level of DcR1 was observed. However, the inhibition of DcR1 towards TRAIL-induced apoptosis appeared to be limited due to the absence of an intracellular domain within its biological structure [80]. This limitation is indicated by the early protection from TRAIL-induced apoptosis, where cell viability remained unaffected at low doses of TRAIL but followed by a decrease in cell viability as higher doses of TRAIL were given. On the other hand, in the TRAIL-resistant CRC cell line Colo320, a significantly higher level of DcR2 expression was observed. Additionally, a study by Meng et al. showed the exogenous overexpression of DcR2 significantly delayed DR5- and TRAIL-induced apoptosis in CRC cells [44]. Contrastingly, Hague et al. showed that

despite an increase in DcR2 expression on the cell surface of a transformed cell line, cell viability analysis indicates that these transformed cells were more sensitive to TRAIL-induced apoptosis than their parental adenoma cells [77].

The expression of OPG in human CRC cell lines was first demonstrated by Pettersen et al., where both mRNA and protein of OPG were detected in two CRC cell lines, namely SW480 and HT-29 [81]. Furthermore, the protective role of OPG was revealed when the cell viability of these OPG-expressing CRC cells decreased upon treatment with OPG-neutralising receptor-activator of NF-κB ligand (RANKL). Following that, De Toni et al. observed a similar finding with eleven other CRC cell lines [39]. However, the expression of OPG in normal colon epithelial cells was not evaluated in these studies to determine the association between OPG level and the pathogenesis of CRC.

Kim et al. conducted the first comparison between three CRC cell lines of HT-29, SW620, and HCT116, as well as a normal colonic epithelial cell line, CCD 841 CoTr [71]. A reduction in OPG expression was observed in both the SW620 and HCT116 compared to the normal CCD 841 CoTr, in which the results obtained from western blotting were validated with ELISA and RT-qPCR for mRNA expression. However, it is worth noting that although HT-29 was mentioned in the text for comparison, the result of OPG expression in HT-29 was not illustrated, and no explanation was given for its absence. In contrast, a recent study by Shao et al. compared the expression of OPG in a different normal colonic epithelial cell line of NCM460 and five CRC cell lines of SW480, SW620, LoVo, HT-29, and HCT116 [82]. All five CRC cell lines showed significantly enhanced OPG expression compared to the normal control. The discrepancies can be explained by the difference in normal colonic epithelial cells used and the amount of total protein loaded for the detection with western blotting.

The findings discussed above do not demonstrate distinct characteristic(s) of a TRAIL-resistant or -sensitive CRC cell lines correlating with expression levels of TRAIL decoy receptors. It is not yet ascertained as to whether a cell line that naturally overexpresses decoy receptors exhibits increased protective mechanism(s) against TRAIL treatment and/or vice versa. Therefore, future research is required to determine (i) the overall expression levels of DcR1, DcR2 and OPG across human-derived CRC cell lines and (ii) the association between altered level of decoy receptor(s) and cellular protection against TRAIL-induced apoptosis leading to an increase in the malignancy of CRC cells.

The regulations of DcR1, DcR2, and OPG expression in CRC

Elucidation of signalling pathway(s) that is involved in regulating the expression of these decoy receptors is vitally important in identifying potential strategies to enhance the efficacy of TRAIL-based treatment. Researchers have tried to combine TRAIL with chemotherapeutic agents such as oxaliplatin to overcome the resistance [38, 83, 84]. This combination revealed the role of tumour suppressor protein p53 in regulating DcR1 expression. Oxaliplatin, a p53-mediated anti-cancer drug, induces overexpression of DcR1, specifically in CRC cell lines with wild-type (WT) p53 [78]. Similarly, infection with p53-expressing adenovirus and ionising radiation-induced p53 also enhances the expression of DcR2 in CRC cell lines [44, 85].

Natural compounds such as lupulone [86, 87], cardamonin [88], cycloheximide [76], ginsenoside compound K [89], and bigelovin [90] were shown to enhance TRAIL-induced apoptosis by downregulating the expressions of DcR1 and DcR2. These natural compounds enhance TRAIL-induced apoptosis by generating reactive oxygen species (ROS) in CRC cells. Reactive oxygen species are closely associated with the mutation status of p53. In cells with WT p53, ROS production will be induced upon cellular stress leading to apoptosis. In contrast, cells with mutated p53 inhibit ROS production and promote cell survival [91]. This observation may explain how p53 regulates the fate of cells via modulating the expression of TRAIL decoy receptors.

Additionally, treatment with the same regulatory agent but in a different order distinctively influenced the expression levels of TRAIL decoy receptors in CRC cells. Xiang et al. demonstrated that DcR1 and DcR2 expression were significantly upregulated (fivefold and ninefold, respectively) when cells were treated with TRAIL sequentially after exposure to the p53-inducing agent; 7-ethyl-10-hydroxycamptothecin (SN-38). On the contrary, co-administration of TRAIL and SN-38 downregulates the expression of DcR1 and DcR2 [92]. These findings can be correlated back to the decoy receptor-inducing role of p53, as discussed previously and offer a valuable perspective on how TRAIL therapy could be administered to achieve its most prominent value.

The lack of complexity in the in vitro culture of CRC cell lines remains the biggest limitation and may potentially obscure other factors contribute to the overexpression of TRAIL decoy receptors. A study conducted by O'Leary et al. unleashed an alternate potential source of TRAIL decoy receptors – the stromal cells within the tumour microenvironment. They reported that apart from just acting in a cell-autonomous manner, transcellular regulations by the neighbouring stromal cells also regulate TRAIL-induced apoptosis [93]. Therefore, employing new study models to better represent the actual tumour microenvironment would be beneficial in elucidating the pathogenesis of CRC.

Concluding remarks and future perspectives

The natural protection over healthy cells allows tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) to be an ideal candidate of anti-cancer therapy. However, considerable numbers of cancers, including CRC, demonstrates intrinsic resistance to TRAIL-induced apoptosis, and some acquire resistance after repeated exposure to TRAIL. TRAIL resistance can occur at different cancer stages along the apoptosis signalling cascade [94] and the expressions of TRAIL decoy receptors could be the first checkpoint where TRAIL-induced apoptosis can be modulated.

The role of TRAIL decoy receptors in TRAIL resistance was demonstrated by the enhanced sensitivity towards TRAIL-induced apoptosis in CRC cells where decoy receptors were neutralised by antibodies and/or expressions were silenced. All the data discussed above indicate the crucial role of TRAIL decoy receptors and its potential contribution to TRAIL resistance. While preclinical studies to understand the mechanism(s) of TRAIL-induced apoptosis and its anti-tumour mode of action remain on-going, resistance to TRAIL-induced apoptosis is still the major hurdle for TRAIL-based therapy to pass through the stall in clinical trials. Several ideas may be considered in the future to overcome this, such as investigations on the expression patterns of decoy receptors with a bigger cohort. This may lead to better correlations between TRAIL resistance and CRC, as well as delineating its associated mechanisms leading to TRAIL resistance. Tumour and serum samples from CRC patients treated with TRAIL therapy can be collected to determine the correlation between their respective TRAIL-sensitivity and their expression levels of decoy receptors.

Besides the ability of the decoy receptors to directly interfere with the activation of TRAIL-induced apoptosis by forming malfunctioning heterocomplexes with apoptosis-inducing DRs [95], these heterocomplexes also activate the anti-apoptotic NF-κB pathway [46]. Growing evidence shows NF-κB's contributions in cellular transformation, proliferation, and, more importantly, preventing pre-neoplastic and malignant cells' elimination [96]. The activation of NF-κB has also been associated with the induction of anti-apoptotic proteins [47–49] and the tumorigenesis of CRC [97]. Given that the heterocomplexes might provide an insight on how TRAIL decoy receptors play a role in not just dampening TRAIL-induced apoptosis but also in the activation of the anti-apoptotic pathway. Thus, elucidating this mechanism in CRC would help clarify the intracellular functional role of TRAIL decoy receptors.

The activation of NF-κB was shown to be responsible for the overexpression of DcR1 and, consequently the protection against TRAIL-induced apoptosis in HeLa cells [50]. However, more studies are required to elucidate this mechanism in the context of CRC to determine whether the decoy receptors and NF-κB can activate one another and facilitate the neoplastic cells from escaping immune surveillance. Additionally, investigating the factors that potentially regulate the expression of these decoy receptors in CRC would contribute to developing novel strategies to enhance TRAIL sensitivity.

Undoubtedly, as more research is carried out in this area, the exact potential and efficacy of TRAIL-based therapy may be realised as a combinatorial agent serving the standard of care while combating CRC. Studies have progressively revealed the heterogeneity of TRAIL decoy receptors in terms of their expression across different cancers, cell types, the severity of the disease, or variations in the pathway they are activating. However, the examination of available literature also exposes significant research gaps in defining the physiological factors that regulate these decoy receptors' expression/secretion in CRC. Further studies are needed to determine other crucial components involved in the regulatory pathway of TRAIL decoy receptors to gain a deeper understanding of how TRAIL therapy can be utilised to its fullest potential.

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Declarations

Conflict of interest The authors declare that no potential conflict of interest exists.

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