Role of tumor necrosis factor receptor superfamily member 19 in cancer: Diverse functions and therapeutic potential (Review)

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Abstract. Tumor necrosis factor receptor superfamily member 19 (TNFRSF19), as a principal member of the TNFRSF, is highly expressed across a variety of invasive neoplastic diseases. It facilitates the evasion of host anti-cancer immune responses by remodelling the immunosuppressive cancer microenvironment, thereby playing a key role in immune evasion; conversely, inhibiting its expression can significantly delay cancer progression. This article provides a systematic review of the functional diversity of this molecule, its encoding of two functionally distinct isoforms via differential transcription initiation, the mechanisms underlying its pro-cancer and anti-cancer effects in various cancer diseases, and its potential value in targeted intervention strategies, clinical translation and the regulation of the cancer immune microenvironment, thereby providing a theoretical foundation for further mechanistic investigations in oncology and for the development of combinatorial immunotherapeutic regimens incorporating TNFRSF19-targeted interventions.

Contents

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1. Introduction

Tumor necrosis factor receptor superfamily member 19 (TNFRSF19), as a structurally distinctive 'orphan receptor' within the TNFRSF (1), has in recent years attracted considerable attention in oncological research. The TNFRSF comprises 29 receptors which, together with the 19 members of their corresponding ligand family, the TNFSF, collectively play central roles in regulating cellular proliferation, differentiation, survival and immune homeostasis, as well as in modulating cancer immunity (2,3). As a key member of this family, TNFRSF19 exhibits complex and diverse functional characteristics in cancer biology. TNFRSF19 not only serves as a multifunctional signaling hub but also plays a key role in the development and homeostasis of various tissues, as well as in disease progression. Furthermore, it demonstrates bidirectional functions in cancer diseases, exerting both proto-oncogene and tumor suppressor gene effects; for instance, it displays pronounced oncogenic activity in malignancies such as hepatocellular carcinoma (HCC) (4), glioma (5) and nasopharyngeal carcinoma (6), whereas it exhibits inhibitory effects on cancer cell progression in cancer types such as breast cancer (7) and gastric cancer (8). To date, targeted interventional strategies directed at TNFRSF19 have achieved progress on multiple fronts and its value in guiding clinical pharmacotherapy is becoming increasingly evident. The expression level of this molecule is closely associated with the sensitivity to a variety of chemotherapeutic agents, and by mediating the transformation of the pro-inflammatory microenvironment, it may provide a foundation for the anticancer efficacy of immune checkpoint inhibitors (9); meanwhile, the mechanisms by which TNFRSF19 contributes to the development of resistance to agents such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and temozolomide (TMZ) are being progressively elucidated (10,11), and strategies for predicting chemotherapeutic sensitivity based on

its expression profile have also offered novel perspectives for personalised therapeutic approaches.

2. TNFRSF19 construction features and isotyping

TNFRSF19 is commonly referred to as TROY or TAJ (12). Due to its unique extracellular domain, which lacks sequence homology with other members of the TNFRSF, it is considered an 'orphan receptor' within this superfamily (1,13). Current research has shown that TROY is generated in rapidly circulating stem cells in the small intestine (14-16), is highly expressed during embryonic development and in specific brain regions (13,17), is moderately expressed in the heart, lungs and liver (18), is weakly expressed in neurons, and is not expressed in major lymphoid tissues such as the spleen and thymus (19).

At the molecular structural level, TNFRSF19 is classified as a typical type I transmembrane protein with a molecular weight of 46 kDa, comprising 416 amino acids (17). It primarily comprises three key functional domains. The extracellular domain (approximately amino acids 30-170) contains the cysteine-rich domain common to the TNFRSF; this domain serves as the molecular basis for recognizing and binding to its homologous trimeric ligands and is responsible for mediating specific ligand-receptor interactions (13,19,20). Although its definitive high-affinity ligand has not yet been fully identified, existing research suggests it may function as a functional receptor for TNFSF ligands, such as the lymphotoxin α1β2 complex; however, the specific regulatory mechanisms and physiological context of this interaction require further confirmation (12,13,21). This is followed by a hydrophobic transmembrane region (approximately amino acids 171-193), designated as the TROY transmembrane domain, which anchors the protein to the cell membrane via a single transmembrane helix (20). The intracellular domain (approximately amino acids 194-416) lacks a death domain and cannot directly initiate apoptosis, but contains a conserved cancer necrosis factor receptor-associated factor 2 (TRAF2) binding motif comprising 223 amino acids, a feature that essentially predetermines its ability to activate pro-survival and inflammation-related signalling pathways by recruiting TRAF family adaptor proteins (Fig. 1) (3,20,22).

The TNFRSF19 gene encodes two functionally specific isoforms, TNFRSF19.1 (423 amino acids) and TNFRSF19.2 (417 amino acids), through differential transcription initiation (Table I) (23,24). The structural differences between the two are primarily located at the C-terminus, with only TNFRSF19.2 containing a TRAF2-binding sequence. The key distinction lies in their transcriptional regulatory mechanisms: TNFRSF19.2 acts as a direct target gene of the Wnt/β-catenin/transcription factor 4 (TCF4) pathway, with its promoter containing typical TCF/lymphoid enhancer binding factor binding sites; whereas the expression of TNFRSF19.1 is indirectly regulated by β-catenin, and its promoter lacks such elements but contains features such as CCAAT enhancer binding protein (C/EBP) binding sites (24). This regulatory difference determines their functional differentiation in human mesenchymal stem cells-TNFRSF19.2 mediates Wnt signalling to promote osteogenic differentiation, whilst TNFRSF19.1 is suppressed by C/EBP to maintain adipogenic differentiation potential (23,24). Although TNFRSF19.2 is often associated with NF-κB signalling due to its TRAF-binding sequence, experiments have shown that both isoforms can activate the NF-κB reporter gene, suggesting functional overlap between the two in signal transduction (24).

3. TNFRSF19 biological functions

TNFRSF19 (TROY), a key member of the TNFRSF, is highly expressed in various invasive cancers, such as melanoma, glioma, nasopharyngeal carcinoma, lung cancer, colorectal cancer and basal cell carcinoma (25). By remodelling the cancer's immunosuppressive microenvironment, it indirectly helps mutated cells evade the host's anti-cancer immune response, thereby playing a key role in immune evasion (5,9); conversely, inhibiting its expression can significantly delay cancer progression (4).

TNFRSF19 is also a multifunctional signal control centre, playing a widespread role in development, homeostasis and disease processes. It is a direct transcriptional target of the classical Wnt/β-catenin signalling pathway, and its encoded protein, TROY, itself functions as a membrane regulator of this pathway, achieving tissue-specific Wnt signalling output by modulating signal reception levels (17). In the nervous system, this function is further extended: TNFRSF19, as a key component of the Nogo-66 receptor complex (comprising NOGO receptor 1 and leucine rich repeat and Ig domain containing 1), inhibits axon growth by activating the ras homolog family member A signalling pathway and plays a central role in the development and maintenance of the central nervous system, as well as in neuronal survival, migration and differentiation; under specific conditions, it can even substitute for the function of the low-affinity nerve growth factor receptor (22,26,27). In addition to regulating growth and survival, TNFRSF19 mediates a unique caspase-independent form of cell death, a process not accompanied by typical nuclear fragmentation or DNA fragmentation (13). The transduction of this death signal relies on its binding to members of the TRAF family (such as TRAF6), which in turn activates the downstream apoptosis signalling-regulating kinase 1, ultimately executing the cell death programme via a cascade of reactions in the JNK signalling pathway (13,28,29). This reveals another key mechanism by which it precisely regulates cell fate under specific physiological or pathological conditions.

TNFRSF19 also plays a crucial role in maintaining the development and homeostasis of various tissues; by inhibiting progenitor cell proliferation and promoting their transition towards differentiation (30), it is involved in the development of organs such as hair follicles (31) and teeth (32), as well as the differentiation of mesenchymal stem cells into osteoblasts or adipocytes (23). Its interactions with stemness markers such as leucine rich repeat containing G protein-coupled receptor (Lgr)5 further anchor its function to the maintenance of the stem cell pool (33); during tissue stress, its downregulation can drive basal cell proliferation to repair the tissue (30). A recent study also revealed its direct interactions with molecules such as UDP-GlcNAc:βGal β-1,3-N-acetylglucosaminyltransferase 5 (B3GNT5) (34), further enriching its regulatory network.

Table I. Comparison of the two subtypes of TNFRSF19.

Features	TNFRSF19.1subtype	TNFRSF19.2subtype	(Refs.)
Amino acid length	423aa	417aa	(24)
C-terminal domain	No TRAF binding sequence	Containing the consensus binding site for TRAF2 (SQLE)	(23)
Promoter type	No TATA box High GC content Containing GC box	Containing TATA box Low GC content	(23)
TCF/LEF binding site	No	Containing 6 typical sites	(23)
C/EBP binding site	Containing 3 binding sites	Containing 4 binding sites	(23)
Key transcriptional regulation	β-catenin indirect dependency; Inhibited by C/EBP	Directly activated by Wnt/β-catenin/TCF4	(23,24)
Main function (human mesenchymal stem cells)	Maintains basic expression Inhibits adipogenic differentiation	Mediates the Wnt signal Promotes osteogenic differentiation	(23)
NF-κB signal activation	Yes	Yes	(24)

TNFRSF19, tumor necrosis factor receptor superfamily member 19; TRAF2, TNF receptor-associated factor 2; TCF, T-cell factor; LEF, lymphoid enhancer factor; C/EBP, CCAAT/enhancer-binding protein; TCF4, transcription factor 4; Wnt, wingless/integrated; NF-κB, nuclear factor κB; aa, amino acid; SQLE, squalene epoxidase.

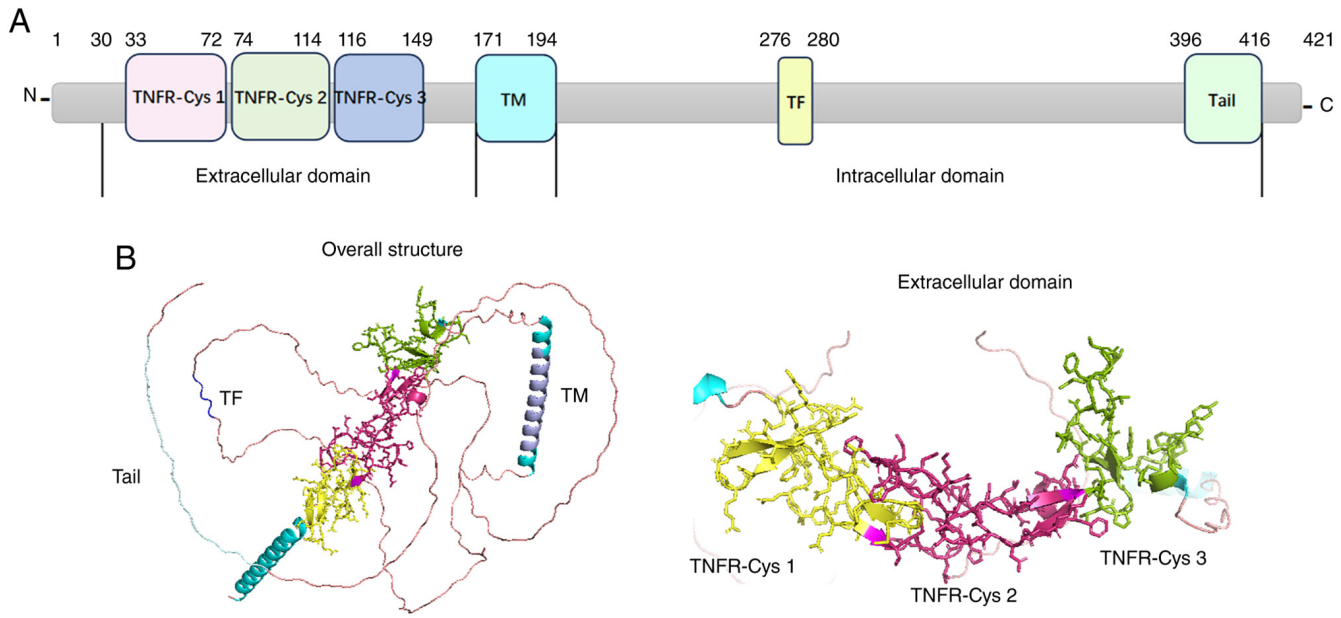

Figure 1. (A) Schematic diagram of TNFRSF19/TROY. Numeric annotations designate the starting amino acid residue of each respective domain. (B) Structure diagram of the TNFRSF19 protein. TNFRSF19, tumor necrosis factor receptor superfamily member 19; TM, transmembrane domain; TF, TNF receptor-associated factor 2-binding domain; Tail, cytoplasmic tail.

4. Research progress of TNFRSF19 in different cancers

Proto-oncogene effects

Liver cancer. Liver cancer is the sixth most common malignant cancer and the fourth leading cause of cancer death worldwide. The most common pathological type is HCC, which typically arises from persistent inflammation, hepatocyte damage and fibrotic deposits caused by metabolic stress, such as non-alcoholic fatty liver disease (9,35).

The function of TNFRSF19 exhibits significant dependence on the cellular environment. Firstly, as a direct transcriptional target of the oncogene encoding β-catenin (CTNNB1), it is significantly overexpressed in CTNNB1-mutant HCC. Overexpression of TNFRSF19 mediates cancer immune evasion by shaping an immunorepressive cancer microenvironment through the suppression of the senescence-associated secretory phenotype and the downregulation of chemokines such as IL-6 (9). In addition, Troy directly binds to the PI3K

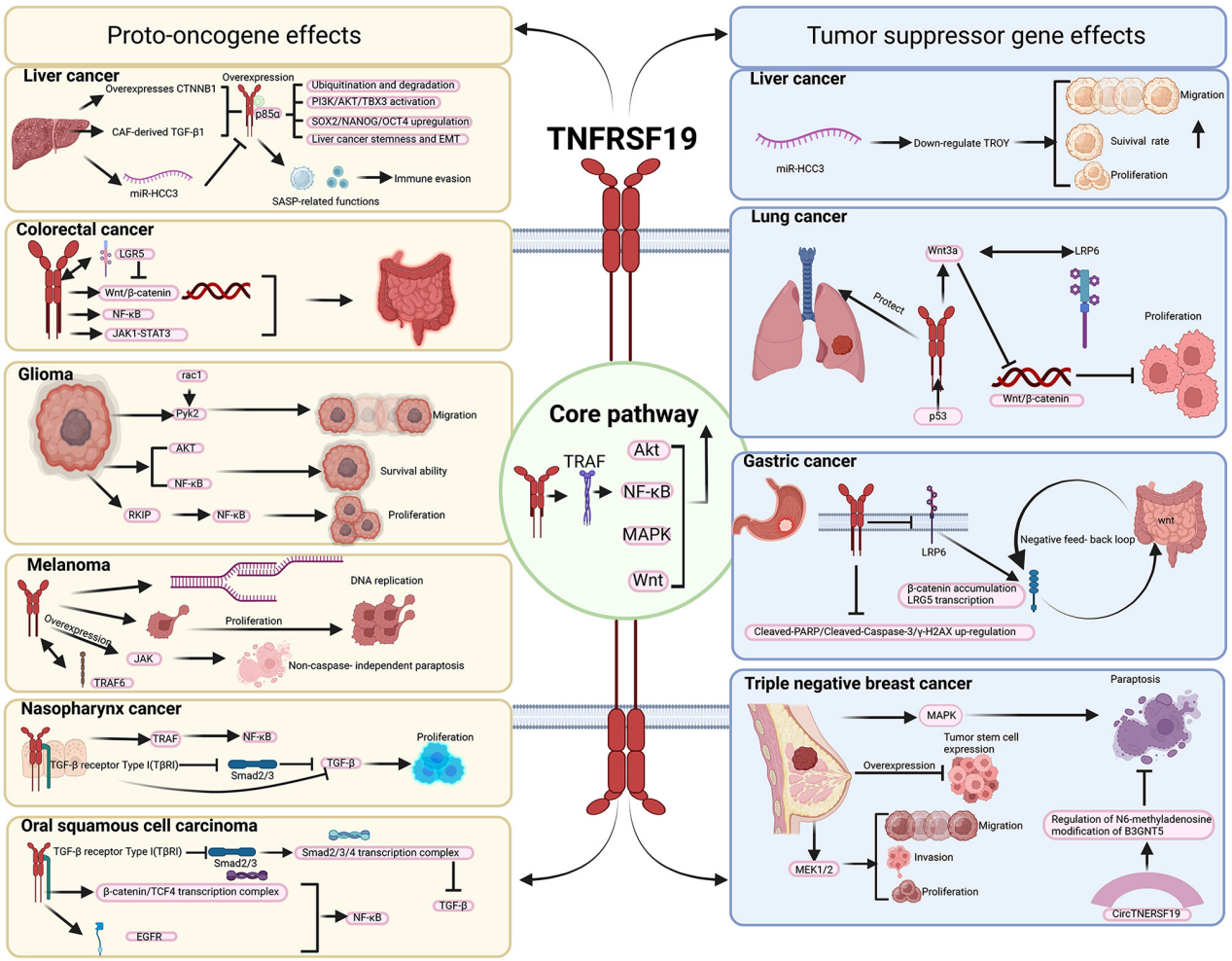

Figure 2. Diagram illustrating the mechanism of action of TNFRSF19 in different cancers. As an important membrane receptor member of the TNFRSF, TNFRSF19/TROY exhibits marked heterogeneity in its expression across different tumour types and within the tumour microenvironment, thereby exerting dual biological functions with opposing oncogenic and tumour-suppressive effects. This schematic systematically summarises the molecular regulatory mechanisms by which TNFRSF19 contributes to the progression of a range of human malignancies. The left panel illustrates the oncogenic roles of TNFRSF19 in hepatocellular carcinoma, colorectal cancer, glioblastoma, melanoma, nasopharyngeal carcinoma and oral squamous cell carcinoma, where it promotes tumour cell proliferation and invasion, while inhibiting apoptosis. By contrast, the right panel highlights the tumour-suppressive functions of TNFRSF19 in lung cancer, gastric cancer and triple-negative breast cancer, where it restrains malignant progression and suppresses tumour development. TNFRSF19, tumor necrosis factor receptor superfamily member 19. CTNNB1, catenin β1; CAF, cancer-associated fibroblast; TGF-β1, transforming growth factor β1; p85α, phosphatidylinositol 3-kinase regulatory subunit α; miR-HCC3, microRNA-HCC3; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; TBX3, T-box transcription factor 3; SOX2, SRY-box transcription factor 2; NANOG, Nanog homeobox; EMT, epithelial-mesenchymal transition; OCT4, octamer-binding transcription factor 4; LGR5, leucine-rich repeat-containing G-protein-coupled receptor 5; Wnt, wingless/integrated; NF-κB, nuclear factor κB; JAK1, Janus kinase 1; STAT3, signal transducer and activator of transcription 3; Rac1, Rac family small GTPase 1; PYK2, proline-rich tyrosine kinase 2; RKIP, Raf kinase inhibitor protein; TROY, TNF receptor superfamily member 19; p53, tumor protein p53; Wnt3a, wingless/integrated family member 3a; LRP6, low-density lipoprotein receptor-related protein 6; TRAF, TNF receptor-associated factor; MAPK, mitogen-activated protein kinase; Akt, protein kinase B; γ-H2AX, γ-H2A histone family member X; JAK, Janus kinase.

regulatory subunit P85α and induces its ubiquitination and degradation, thereby activating the PI3K/Akt/T-box transcription factor 3 (TBX3) pathway, upregulating SOX2, NANOG homeobox and OCT4, and promoting the stemness of HCC cells and epithelial-mesenchymal transition (EMT) (by downregulating E-cadherin and upregulating N-cadherin and vimentin). Furthermore, cancer-associated fibroblasts can induce Troy expression by secreting transforming growth factor (TGF)-β1, thereby further reinforcing this signaling axis (4). Troy is also negatively regulated by microRNA (miR)-HCC3; its overexpression inhibits the proliferation, migration, invasion and EMT capabilities of HCC cells, while its knockdown promotes a malignant phenotype, suggesting that it may function as a tumor suppressor under specific conditions (Fig. 2) (36).

Therapeutic strategies targeting TNFRSF19 and its associated pathways are also being actively explored. For example, in CTNNB1-mutant HCC, the Wnt/β-catenin pathway inhibitor ICG001 (PRI-724) can reverse TNFRSF19-mediated immune rejection and induce a pro-inflammatory microenvironment, thereby enhancing the efficacy of immune checkpoint inhibitors [such as anti-programmed cell death 1 (PD-1) antibodies] (9). Furthermore, given the role of TNFRSF19 in regulating the stemness of HCC, the combination of the PI3K inhibitor wortmannin with the targeted drug sorafenib has been shown to effectively impair the self-renewal capacity of TNFRSF19-positive HCC stem cells (Table II) (4), offering a new approach to combination therapy for overcoming cancer resistance and recurrence. Furthermore, targeted regulation of

Table II. Mechanisms of TNFRSF19 in distinct cancer types.

Type of cancer	Mechanism of cancer-promoting effect/anti-cancer effect	(Refs.)
Liver cancer	Proto-oncogene effects: TNFRSF19 promotes liver cancer stemness and EMT by degrading p85α to activate the PI3K/AKT/TBX3 axis, a process that is further amplified by TGF-β1-mediated positive feedback from CAFs. Tumor suppressor gene effects: It is negatively regulated by miR-HCC3; a lack of its expression actually promotes a malignant phenotype.	(4,36)
Colorectal cancer	Proto-oncogene effects: TNFRSF19 promotes tumor development by activating the Wnt/β-catenin, JAK1-STAT3 and NF-κB signaling pathways; however, as TROY, it can interact with LGR5 to inhibit R-spondin signaling, acting as a negative regulator of the Wnt pathway under specific conditions. In colorectal tumors with β-catenin dysregulation, TNFRSF19, upon activation by NF-κB (involving the TRAF-binding site and other functional domains), establishes a molecular bridge between β-catenin and NF-κB, synergistically enhancing oncogenic signaling and driving tumor initiation and progression.	(24,37,39)
Glioblastoma	Proto-oncogene effects: It promotes migration and invasion via thePYK2/Rac1 axis, activates the AKT/NF-κB signaling pathway to enhance cell survival, and, in conjunction with RKIP, lifts the inhibition of NF-κB, thereby driving proliferation and the G1/S phase transition.	(10,40-42)
Melanoma	Proto-oncogene effects: Troy is co-expressed with TRAF-6 in melanoma; although it induces paraptosis via the JNK pathway in certain cells, its high expression during embryogenesis and its re-expression in tumors both support the notion that it exerts a tumor-promoting function through the TRAF-6 signaling axis.	(48)
Nasopharyngeal carcinoma	Proto-oncogene effects: By competitively blocking the phosphorylation of Smad2/3 and the formation of the Smad2/3-transcription complex, TβRI inhibits the growth-suppressive signaling of TGF-β while simultaneously activating the NF-κB pathway, thereby driving tumor proliferation.	(6)
Oral squamous cell carcinoma	Proto-oncogene effects: TNFRSF19 competitively binds to TβRI via its intracellular domain, preventing the formation of the Smad2/3/4 transcriptional complex and thereby lifting the growth inhibition imposed by TGF-β; simultaneously, its expression is transcriptionally regulated by β-catenin/TCF4, and it activates the NF-κB pathway through both its C-terminal domain and its interaction with EGFR, synergistically driving tumor progression.	(51)
Lung cancer	Tumor suppressor gene effects: TNFRSF19 exhibits a tissue-specific dual effect in NSCLC: High expression in normal lung tissue maintains the phenotype, while downregulation in lung cancer inhibits malignant progression. Proto-oncogene effects: However, it is abnormally upregulated in gefitinib-resistant cells, driving acquired resistance, suggesting its potential as a biomarker for lung cancer risk screening, prognosis assessment and resistance intervention.	(11,56)
Gastric cancer	Tumor suppressor gene effects: As a Wnt target, TNFRSF19 is transcriptionally regulated by the Wnt pathway; by inhibiting LRP6 phosphorylation, it reduces β-catenin accumulation and downstream transcription, thereby forming a negative feedback loop that maintains gastric stem cell homeostasis. Overexpression of TNFRSF19 in gastric cancer inhibits colony formation and promotes differentiation, thereby exerting a tumor-suppressing function.	(8)
TNBC	Tumor suppressor gene effects: TNFRSF19 primarily inhibits tumor growth by inducing paraptosis via endoplasmic reticulum stress mediated by the MAPK pathway; the gene itself is lowly expressed and influences the proliferation, migration and invasion of TNBC cells through MEK1/2. Proto-oncogene effects: CircTNFRSF19, derived from its host gene, promotes proliferation and inhibits apoptosis through N6-methyladenosine modification.	(7,34)

TNFRSF19, tumor necrosis factor receptor superfamily member 19; TNBC, triple-negative breast cancer; TGF-β1, transforming growth factor-β1; CAFs, cancer-associated fibroblasts; miR-HCC3, microRNA-HCC3; Wnt, wingless/integrated; JAK1, Janus kinase 1; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor κB; TROY, TNF receptor superfamily member 19; LGR5, leucine-rich repeat-containing G-protein-coupled receptor 5; TRAF, TNF receptor-associated factor; PYK2, proline-rich tyrosine kinase 2; Rac1, Rac family small GTPase 1; AKT, protein kinase B; RKIP, Raf kinase inhibitor protein; JNK, c-Jun N-terminal kinase; TβRI, TGF-β receptor I; TGF-β, transforming growth factor-β; SMAD2, SMAD family member 2; TCF4, transcription factor 4; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; LRP6, low-density lipoprotein receptor-related protein 6; MAPK, mitogen-activated protein kinase; TNBC, triple-negative breast cancer; MEK1/2, mitogen-activated protein kinase kinase 1/2; CircTNFRF19, circular RNA TNFRF19.

upstream molecules of TNFRSF19, such as miR-HCC3, may also serve as potential intervention points for restoring its cancer-suppressive function or blocking its oncogenic activity (Table II) (36).

Colorectal cancer. Colorectal cancer is the second leading cause of cancer-associated death in the United States, about half of the population will develop a colorectal cancer before the age of 70 years (37). In inherited cases, familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer are the most well-known types. Even though medical treatments have improved, high-risk patients still have poor outcomes because their cancers can evade the immune system and often do not respond well to immune checkpoint inhibitors (37,38).

TNFRSF19 mRNA is found at high levels in cells with defects in the APC regulator of Wnt signaling pathway gene, and it is also increased in human colorectal cancer cell lines and mouse gut cancers (38,39). TNFRSF19 mainly works by turning on the Wnt/β-catenin, Janus kinase (JAK)1-STAT3 and NF-κB signalling pathways, which help cancers grow (27). TROY can interact with leucine rich repeat containing G protein-coupled receptor 5 (LGR5), and in organoid models of the gut, it can block the signals from R-spondin, which normally activates the Wnt pathway, meaning that TROY can act as a negative regulator of Wnt signals (Table II) (39). TNFRSF19 is a direct target gene of the β-catenin/TCF4 transcriptional complex; it is frequently over-expressed in colorectal cancer cell lines and primary tumors, and both subtypes (TNFRSF19.1 and TNFRSF19.2) are regulated by this pathway. TNFRSF19 can establish a molecular bridge between β-catenin and NF-κB activity by activating the NF-κB signaling pathway. Although the TRAF-binding site is partially involved in this signal transduction, other functional domains within the receptor also mediate the NF-κB-inducing effect. Therefore, abnormal upregulation of TNFRSF19 may promote the onset and progression of colorectal tumors associated with β-catenin pathway dysregulation by synergistically activating NF-κB (Fig. 2) (Table II) (24).

However, using TROY as a marker of Wnt activity or as a direct target for treatment is still difficult in drug research, and current findings suggest it may not be a suitable treatment target in human colorectal cancer, but its potential in clinical use needs more study (39).

Glioblastoma. Gliomas are the most common primary malignant cancers in the central nervous system and have a very high death rate (5), with glioblastoma multiforme (GBM) being the most aggressive type, making up 40% of primary brain cancers (40). According to the World Health Organization classification, gliomas are graded from I to IV based on features like cell atypia, mitotic activity, necrosis and new blood vessel growth. Higher grades are more invasive and have a worse clinical outcome (41).

TNFRSF19 is highly expressed in glioma tissue and cells, where its level of expression is positively linked to cancer grade and negatively linked to patient survival (5). TNFRSF19 drives cancer growth through several signalling pathways. It can interact with protein tyrosine kinase 2β (PYK2) and, through the Pyk2-Rac family small GTPase 1 (rac1) pathway, promote cancer cell migration and invasion, while also causing astrocytes to move in the cancer environment (Table II) (10,25,40). TNFRSF19 can also activate the AKT and NF-κB pathways, which helps cancer cells survive (Table II) (10,40). When TNFRSF19 binds specifically to Raf kinase inhibitory protein (RKIP), it stops RKIP from blocking NF-κB, which leads to cancer growth and causes cells to pause in the G1/S phase of the cell cycle (Fig. 2) (Table II) (41).

Using Ruxolitinib to block JAK1 or reducing JAK1 levels can weaken TNFRSF19-induced STAT3 activation, thereby reducing glioma cell migration and reversing resistance to TMZ (42). Interfering with the binding between TNFRSF19 and RKIP using a Tat-fused TROY recombinant protein (Tat-Troy) fusion protein can stop transplanted cancers from growing in the body (41), while the compound propentofylline can reduce TNFRSF19 expression and its downstream signals Pyk2, rac1 and phosphorylated JNK, thereby slowing cancer invasion caused by microglia and making glioblastoma cells more sensitive to TMZ (43,44).

Melanoma. In terms of pathological classification, melanoma is primarily divided into two categories-sun exposure-related an non-sunlight exposure-related-based on mutational characteristics, anatomical location and epidemiology, and the genetic drivers of these cancers indicate that their proliferation is primarily initiated by gain-of-function mutations in growth-promoting genes (45,46).

TNFRSF19 has been identified as a novel biomarker with a significant role in melanoma. This molecule is not expressed in normal melanocytes but is highly expressed in both primary and metastatic melanoma; furthermore, activation of its signalling pathway promotes DNA replication in melanoma cells, thereby playing a key driving role in cancer proliferation (47). Further study has shown that Troy, as a retinoic acid-regulated downstream gene, participates in the regulation of the retinoic acid signalling pathway in the S91 melanoma cell model. Troy and TRAF-6 are co-expressed in 100% of melanoma cases, suggesting that the Troy-TRAF-6 signaling axis may be involved in the regulation of this tumor (48). Although Troy overexpression in certain cells can induce non-caspase-dependent paraptosis-an effect that may be mediated by the JNK pathway rather than the NF-κB pathway-both its high expression during embryonic development and its re-expression in melanoma support its role in promoting tumor growth, consistent with its tumor-promoting function as a member of the TNFRSF family. Its ability to localize on the cell surface also provides a unique and promising intervention target for the development of targeted inhibitors, cell therapies and antibody-mediated immunotherapies (Fig. 2) (Table II) (48).

Nasopharyngeal carcinoma. Nasopharyngeal carcinoma is a head and neck malignancy characterised by significant geographical and ethnic clustering; it is particularly prevalent in South-East Asia, southern China and North Africa and its occurrence is closely associated with genetic susceptibility, Epstein-Barr virus infection and environmental factors, with the phenomenon of familial clustering suggesting that genetic factors play a key role in its development (49,50).

TNFRSF19 is frequently overexpressed in nasopharyngeal carcinoma and acts as a key driver of the disease; it interacts with the TRAF protein and activates the NF-κB pathway. The functional gain of TNFRSF19 correlates negatively with the activity of the TGF-β pathway, suggesting that the inactivation of this pathway stems primarily from the abnormal activation of TNFRSF19 rather than mutations in classical TGF-β

pathway components (Table II) (6). It acts by binding to the kinase domain of the TGF-β type I receptor (TβRI), competitively blocking the binding of R-Smads (Smad2/3) to the receptor. This inhibits the transmission of the TGF-β signalling pathway, allowing cancer cells to evade the growth-inhibitory effects mediated by this pathway and thereby promoting cancer proliferation. Overexpression, however, counteracts the growth-inhibitory effects of TGF-β, thereby allowing TGF-β to exert its tumor-suppressive effects by inhibiting the growth of normal and precancerous cells. In addition, research findings indicate that elevated TNFRSF19 expression is associated with reduced TGF-β activity and a poor prognosis in patients with nasopharyngeal carcinoma (Fig. 2) (Table II) (6).

Oral squamous cell carcinoma (OSCC). OSCC is the malignant tumor with the highest incidence rate worldwide, and even though surgery, radiotherapy and chemotherapy are widely used, the 5-year survival rate for patients is still <50%, mainly because the cancer can invade nearby tissues, spread to regional lymph nodes and metastasise to distant sites, making it challenging to treat (51,52).

TNFRSF19 can bind to TβRI in the cytoplasm. This stops Smad2/3 from interacting with the receptor, so the Smad2/3/4 transcription complex cannot form, thereby inhibiting the proliferation-negative regulatory function of the TGF-β pathway, leading to uncontrolled cell proliferation. The expression of TNFRSF19 is controlled by the β-catenin/TCF4 transcription complex, which binds to its promoter. TNFRSF19 can also activate the NF-κB pathway through its C-terminus. The EGFR can also bind to TNFRSF19 to form a complex, which then activates the NF-κB pathway, further promoting cancer growth (Fig. 2) (Table II) (51). In cisplatin (DDP)-resistant cell lines (such as SCC25-DDP), TNFRSF19 is expressed at much higher levels than in the parent plant SCC-25 cells, while ankyrin repeat domain 2 (ANKRD2) is expressed at lower levels, suggesting that abnormal upregulation of TNFRSF19 may be closely linked to chemotherapy resistance (51). Patients with OSCC who exhibit high ANKRD2 expression coupled with low TNFRSF19 expression have a significantly poorer prognosis, suggesting that these genes may serve as potential therapeutic targets.

Tumor suppressor gene effects

Lung cancer. Lung cancer is the leading cause of cancer-related death worldwide (53), with ~85% of cases being non-small cell lung cancer (NSCLC). The main pathological subtypes are adenocarcinoma and SCC, which differ significantly in terms of anatomical location, cellular origin and biomarker expression (54,55).

In recent years, the role of TNFRSF19 in the development of NSCLC and in mechanisms of drug resistance has attracted considerable attention. TNFRSF19 is highly expressed in normal adult lung tissue and is essential for maintaining the normal lung phenotype; however, its expression levels tend to be downregulated in lung cancer tissue (Table II) (56). For example, following the introduction of TNFRSF19 with low expression of this gene into A549 lung cancer cells via a lentiviral vector, the cells' malignant phenotypes-such as soft agar colony formation and invasive capacity-were significantly suppressed, suggesting that TNFRSF19 may act as a potential cancer suppressor (56). However, in NSCLC cells resistant to the molecularly targeted drug gefitinib, the mRNA and protein levels of TNFRSF19 were significantly upregulated, indicating that its abnormally high expression is closely associated with acquired resistance (Table II) (11). Given its differential expression in lung cancer tissues and its association with drug resistance, TNFRSF19 and its upstream regulatory elements, such as 13q-Enh, have been proposed as potential biomarkers for lung cancer risk screening, clinical prognosis assessment and drug resistance intervention (Table II) (56), and in the future, they may serve as new targets for overcoming resistance to targeted therapy in NSCLC.

Gastric cancer. Gastric cancer is a common and highly heterogeneous malignant cancer worldwide, and a large part of its development is driven by abnormal activation of the Wnt/β-catenin signalling pathway (57). TNFRSF19, a member of the TNFRSF, is a key regulator in this pathway and has attracted much attention in gastric cancer research in recent years (8).

TNFRSF19 is not only a marker of chief cells in the base of the gastric glands, which have stem cell potential (58), but also acts as a target gene of the Wnt signaling pathway. Its promoter contains a TCF binding site and its expression is regulated by Wnt. At the same time, Troy inhibits the phosphorylation of the Wnt co-receptor LRP6, thereby reducing β-catenin accumulation and the transcription of downstream target genes (such as LGR5), forming a negative feedback loop that regulates Wnt signaling intensity and maintains gastric stem cell homeostasis. Overexpression of Troy inhibits colony formation in gastric cancer cells (such as MKN45) and promotes differentiation, thereby driving malignant progression (Table II) (8). However, during gastric cancer progression, the expression pattern of TNFRSF19 changes, whose levels are positively linked to cancer differentiation: High in well-differentiated and intestinal-type gastric cancers, but almost absent in poorly differentiated cancers (Table II) (8), and TNFRSF19 expression also shows a negative correlation with LGR5, suggesting that downregulation of TNFRSF19 may release LGR5 from inhibition, driving malignant progression (Fig. 2) (59). Troy deficiency upregulates cleaved-poly(ADP ribose) polymerase, cleaved-caspase-3 and γ-H2AX, suggesting a decline in DNA damage repair capacity and significantly increasing the sensitivity of gastric cancer cells to chemotherapeutic agents; conversely, Troy overexpression partially reverses the chemoresistance caused by small nucleolar RNA host gene 8 (SNHG8) downregulation (60). In a study of chemotherapy resistance, the long non-coding RNA SNHG8 was indicated to act as a molecular scaffold to bind heterogeneous nuclear ribonucleoprotein A1 and regulate TNFRSF19 expression at the post-transcriptional level, which provides a potential new strategy to overcome chemotherapy resistance (60).

Triple-negative breast cancer (TNBC). TNBC is a subtype of breast cancer; due to the fact that the estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 are all negative, and there are no endocrine or targeted therapy targets, chemotherapy is the main treatment. TNBC is highly aggressive and prone to metastasis to organs and the brain, with a 5-year mortality rate of up to 40% after diagnosis (61,62).

In this subtype, TNFRSF19 shows a typical dual role. It mainly induces parapoptosis through MAPK pathway-mediated endoplasmic reticulum stress, thereby

inhibiting tumor growth (Fig. 2) (Table II) (7). At the same time, the circular RNA CircTNFRSF19, which comes from the TNFRSF19 host gene, is highly expressed in TNBC tissue and in MDA-MB-231 and BT-549 cells, which promotes cancer cell proliferation and inhibits apoptosis by regulating B3GNT5 through N6-methyladenosine modification, acting as an oncogene (Table II) (34); however, the TNFRSF19 gene itself is expressed at low levels in TNBC. Bioinformatics analysis of RNA-sequencing data from The Cancer Genome Atlas database indicates that TNFRSF19 expression in breast cancer tissues may be associated with tumor size and lymph node metastasis. It influences the proliferation, migration and invasion of TNBC cells via MEK1/2 and overexpressing the gene can significantly reduce cancer cell proliferation, migration and invasion, showing a cancer-suppressing effect (Table II) (7), an observation that is not obvious in non-TNBC cell lines, suggesting its cancer-suppressing function is subtype-specific. Furthermore, a higher mRNA interference score was associated with low TNFRSF19 expression, suggesting that low levels of TNFRSF19 in patients with breast cancer may promote the expression of tumor stem cells. Patients with TNBC and high TNFRSF19 expression may respond better to doxorubicin plus lapatinib (7), indicating that TNFRSF19 expression not only has a dual, subtype-specific role, but could also serve as a biomarker to guide chemotherapy and targeted drug choices.

5. Mechanisms of action of TNFRSF19 in cancer

The main way TNFRSF19 works in cancers is by recruiting TRAF family members to activate the NF-κB pathway (22,63), which also interacts with other key pathways, such as PI3K/AKT, MAPK and Wnt, showing either cancer-promoting or cancer-suppressing effects, depending on the cancer type (Fig. 2) (7,27). Through TRAF-mediated cascades, TNFRSF19 can continuously activate NF-κB, which can also work together with pathways such as JAK1/STAT3 to drive cancer cell proliferation, migration and treatment resistance in cancers like glioblastoma, liver cancer, colorectal cancer and melanoma. In liver cancer, TNFRSF19 acts as a marker of cancer stem cells (CSCs) and maintains stemness via the p85α/AKT/TBX3 axis, in colorectal cancer, it promotes cancer progression by activating Wnt/β-catenin, JAK1-STAT3 and NF-κB pathways (27), and in gliomas, TNFRSF19 interacts with PYK2, activating the Pyk2-Rac1 axis to enhance cancer cell migration and invasion. It also induces astrocyte migration in the cancer environment and cooperates with AKT and NF-κB activation to improve cell survival (25,40). TNFRSF19 has a negative regulatory role in cancers such as lung cancer, TNBC and certain gastric cancers, where it can induce paraptosis through endoplasmic reticulum stress mediated by the MAPK pathway, which suppresses cancer growth in TNBC (7), and in maintaining gastric mucosal homeostasis, TNFRSF19 is not only a marker of chief cells in the gastric gland base, which have stem cell potential, but also forms a negative feedback loop to precisely control Wnt signalling, and when activated as a Wnt target gene, it binds LGR5 and affects the co-receptor LRP6, limiting excessive signalling and showing a protective role against cancer formation in specific tissue environments (8). Furthermore, the function of TNFRSF19 may depend on its expression levels in cancer tissues. In tumors with high expression, such as glioblastoma and nasopharyngeal carcinoma, it promotes invasion, proliferation and carcinogenesis by activating the Rho/Rac1/NF-κB pathway or inhibiting TGF-β signaling; in tumors with low expression, such as gastric and lung cancers, it exerts a tumor-suppressing effect by inhibiting the WNT pathway or malignant transformation. Furthermore, TNFRSF19 is highly expressed in most human cancers, suggesting that its high expression is a common feature of tumors (7).

6. Therapeutic advances in TNFRSF19-targeted cancer therapy

As TNFRSF19 plays a key role in the development of numerous malignant cancers, it has attracted attention as a potential molecular target for cancer therapy. Studies have shown that TNFRSF19 is highly expressed in glioblastoma (5), HCC (4), NSCLC (11) and colorectal cancer (60). This makes it a promising target for intervention.

TNFRSF19 mainly drives cancer progression by activating three core signalling pathways: NF-κB, PI3K/AKT and Wnt/β-catenin (4,25,60). In glioblastoma, high TNFRSF19 expression increases cancer invasiveness and enhances resistance to TMZ and radiotherapy through Akt and NF-κB activation (5,25). In HCC, TGF-β1 can upregulate TNFRSF19 expression, activating the PI3K/AKT/TBX3 axis, which gives liver cancer cells stem-like properties and resistance to sorafenib (4). More research has confirmed that TNFRSF19 also promotes GBM cell invasion and drug resistance and drives colorectal cancer progression via activation of Wnt/β-catenin, JAK1-STAT3 and NF-κB pathways (60).

Targeted intervention strategies for TNFRSF19 have made multiple advancements. Some researchers have attempted to directly target TNFRSF19 itself or its interaction network. Pentoxifylline can reduce TNFRSF19 expression, inhibiting glioblastoma invasion (40); TAT-TROY fusion protein interferes with the interaction between TROY and RKIP, effectively slowing glioma growth in animal models (41), but TNFRSF19 small inhibitory (si)RNA reduces EMT and CSC markers, overcoming gefitinib resistance (11), and siRNA technology has laid the foundation for the future development of drugs targeting TNFRSF19 through its research on this protein (39). In NSCLC, TNFRSF19 is an important mediator of acquired resistance to first-generation EGFR-TKIs, especially in cancers without the T790M mutation (11). Furthermore, given that inhibiting Akt or NF-κB can reverse TMZ resistance mediated by TNFRSF19, combined intervention in the downstream signaling pathways of TNFRSF19 is expected to become a new strategy for improving chemotherapy sensitivity (10). For example, targeting downstream TNFRSF19 signalling may improve treatment sensitivity, and PI3K inhibitor Wortmannin can block TNFRSF19-induced stem-like features and works synergistically with sorafenib in liver cancer cells (4). The JAK inhibitor ruxolitinib blocks STAT3 phosphorylation and enhances the cytotoxic effect of TMZ on glioblastoma stem cells (42). These findings provide a diverse new direction for overcoming clinical drug resistance.

The guidance value of TNFRSF19 in clinical drug selection is also worthy of attention, as TNFRSF19 expression levels are clearly associated with sensitivity to various chemotherapeutic agents. Analysis based on the CellMiner database indicates that

patients with high TNFRSF19 expression exhibit significantly lower predicted IC_{50} values for doxorubicin and lapatinib, suggesting that such patients may derive greater benefit from these agents; conversely, patients with low expression show greater sensitivity to paclitaxel (5,7). This finding provides a molecular basis for the selection of personalised chemotherapy regimens based on TNFRSF19 expression profiles. Concurrently, the regulation of TNFRSF19 by miRNAs has opened up new avenues for targeted therapy; miR-HCC3 has been shown to directly target TNFRSF19 and downregulate its expression, suggesting that intervention in this regulatory axis may hold therapeutic potential (36).

Building on the aforementioned research, the potential role of TNFRSF19 in regulating the cancer immune microenvironment has attracted increasing attention in recent years. Studies have found that the shift towards a pro-inflammatory microenvironment mediated by TNFRSF19 may lay the foundation for the anti-cancer effects of immune checkpoint inhibitors (9). Given that programmed death ligand 1 (PD-L1) expression levels and cancer mutational burden are already effective biomarkers for predicting response to anti-PD-1/PD-L1 therapy, targeting TNFRSF19 may produce synergistic effects with immunotherapy (5,64). This hypothesis is supported by relevant studies, suggesting that activating co-stimulatory receptors within the TNF family, in combination with the inhibition of co-inhibitory checkpoints in the B7-CD28 family, can effectively enhance the anti-cancer response of T cells (5), thereby providing a theoretical basis for combined immunotherapy regimens incorporating TNFRSF19-targeted interventions.

7. Summary and perspectives

Based on the existing body of research on TNFRSF19, a structurally distinctive orphan receptor within the TNFRSF, substantial advances have been made in oncological investigations. This molecule exhibits complex and multifaceted functional characteristics in cancer biology; TNFRSF19 not only serves as a versatile signalling regulatory hub, extensively participating in development, homeostasis and disease progression, but also plays a pivotal role in maintaining the development and homeostasis of diverse tissues. In the context of cancer-related mechanisms, it can recruit members of the TRAF family to activate NF-κB and concomitantly engage key signalling pathways such as PI3K/AKT and MAPK, thereby driving cancer cell proliferation, migration and drug resistance in multiple malignancies, including glioblastoma, HCC and colorectal cancer, exerting a well-defined oncogenic function. It can also suppress tumorigenesis in conditions such as TNBC and the maintenance of gastric mucosal homeostasis by inducing paraptosis or establishing negative feedback loops, thereby demonstrating its tissue-specific bidirectional regulatory capacity. Furthermore, the mechanisms by which TNFRSF19 mediates resistance to therapeutic agents such as EGFR-TKIs and TMZ are becoming progressively elucidated, and the identification of its expression profile as a predictor of chemotherapeutic sensitivity provides novel avenues for personalised treatment strategies.

However, current research on TNFRSF19 remains significantly limited; the molecular basis for its bidirectional functional switching has not yet been fully elucidated and the functional differences across different cancer types or within the same cancer under varying microenvironments and their underlying mechanisms remain elusive. Furthermore, existing intervention strategies, such as siRNA, fusion proteins and small-molecule compounds, largely remain in the preclinical stage and face numerous challenges regarding delivery efficiency, targeting specificity and safety; specific antibodies or small-molecule antagonists with genuine potential for clinical translation have yet to emerge. In addition, how TNFRSF19 modulates immune cell function within the cancer immune microenvironment, as well as its practical value as a biomarker in predicting responses to immunotherapy, still requires validation through large-scale clinical cohort studies.

Looking ahead, a detailed analysis of the precise molecular mechanisms underlying the functional switching of TNFRSF19 in different cancer contexts, particularly the regulatory networks governing its interactions with signalling pathways such as Wnt, STAT3 and Pyk2-Rac1, will provide a crucial theoretical basis for precision interventions based on molecular subtyping. By leveraging structural biology and drug screening technologies to develop high-affinity antibodies or novel degraders targeting its unique extracellular domain, it is hoped that the shortcomings of current targeting strategies can be addressed. Considering the potential role of TNFRSF19 in reshaping the immune microenvironment and its synergistic effects with the PD-1/PD-L1 axis, combining TNFRSF19-targeted strategies with immune checkpoint inhibitors, or co-administering them with inhibitors of critical downstream nodes such as PI3K inhibitors (e.g. Wortmannin) and JAK inhibitors (e.g. Ruxolitinib), has already demonstrated the potential to reverse drug resistance and enhance therapeutic efficacy in preclinical models, warranting further exploration in clinical trials. Ultimately, advancing the development of companion diagnostic tools based on TNFRSF19 expression profiles and integrating them into personalised decision-making frameworks for chemotherapy, targeted therapy and immunotherapy is expected to provide a new breakthrough in improving the clinical prognosis of patients with relevant cancers.

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Authors' contributions

MX and ZL were responsible for writing the original draft and performed the literature search. JZ and YZ contributed to figure preparation and information sorting. HX and YX

were in charge of data collection and revised the manuscript. QH was involved in the conceptualization of the study and literature search. TZ conceived the study and participated in review and editing. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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