Review Article

A literature review of the promising future of *TROP2*: a potential drug therapy target

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Background and Objective: Previous studies have demonstrated that the oncogene trophoblast cell surface antigen 2 (*TROP2*) has great application prospects as a therapeutic target. However, few literature reviews have systematically summarized and evaluated its role in cancer therapy. This study aims to summarize the molecular structure, functions, signal transduction pathways, and prognostic value of *TROP2*, and explore therapeutic agents that target *TROP2*.

Methods: A total of 1,376 published literatures from PubMed and 614 published literatures from EMBASE were retrieved by searching "TROP2" or "Trophoblast cell surface antigen 2". The search was conducted on December 12, 2020, and updated on November 20, 2022. The cBioportal and GEPIA (Gene Expression Profiling Interactive Analysis) databases were used to analyze the expression, mutation, and prognostic value of *TROP2* in different types of cancer.

Key Content and Findings: *TROP2* is overexpressed in different tumor tissues and plays roles in cell proliferation, invasion, migration, apoptosis, and treatment resistance by binding to or interacting with several molecules. As a therapeutic target, *TROP2* is particularly suitable for antibody-based therapies. Monoclonal antibodies, bispecific antibodies, antibody-drug conjugates (ADCs), virus-like particles, and antibody drugs in combination with traditional chemotherapy, immunotherapy, radioimmunotherapy, photoimmunotherapy, and nanoparticles that target *TROP2* have thus far been rapidly developed. For example, sacituzumab govitecan (IMMU-132), a *TROP2*-targeting ADC, was granted accelerated approval for the treatment of metastatic triple-negative breast cancer (TNBC). Anti-*TROP2* antibody-conjugated nanoparticles (ST-NPs) are a promising vehicle for delivering doxorubicin in targeted TNBC therapy.

Conclusions: The availability of *TROP2*-targeting ADCs makes *TROP2* an accessible and promising therapeutic target for advanced metastatic cancers. The present review describes the important role of *TROP2* in tumorigenesis and its potential applications as a promising biomarker and therapeutic target that is capable of reversing resistance.

Keywords: *TACSTD2; TROP2; TROP2* antibody; antibody-drug conjugates (ADCs); *TROP2*-targeted therapy

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Introduction

Trophoblast cell surface antigen 2 (*TROP2*), also known as tumor-associated calcium signal transducer 2 (*TACSTD2*), is a cell surface glycoprotein that acts as a transmembrane transducer of intracellular (IC) calcium signals. It is expressed in many normal tissues but is overexpressed in a variety of tumors, such as pancreatic (1), ovarian (2), prostate (3), and breast (4) cancers. *TROP2* plays an important role in tumor cell proliferation, apoptosis, and invasion, thereby impacting the prognosis and treatment of cancer patients (2). The surface *TROP2* expression is positively associated with E-cadherin expression and negatively with the mesenchymal gene signature in breast and prostate cancers, suggesting that it correlates with the epithelial phenotype (5). The ability of *TROP2* to promote migration and invasion of cancer cells was described in several types of tumors (2). The role of *TROP2* in regulating proliferation is a complex and cell type-specific phenomenon. *TROP2* stimulates proliferation and cellular growth in human cervical and bladder cancer cells, while the ability of *TROP2* to suppress cell proliferation was also reported in cholangiocarcinoma (CHOL) and MCF7 breast cancer cell lines (6,7). In addition, *TROP2* appears to have a dual function in the regulation of cancer cell survival and drug resistance. The downregulation of *TROP2* in cervical cancer cell lines increases apoptosis in ovarian carcinoma and bladder cancer cells (8,9). Contrary to these findings, cervical cancer cells overexpressing *TROP2* were more sensitive to cisplatin induced apoptosis, while cells silenced expressing *TROP2* were more resistant (10). *TROP2* signals cells via different pathways and is transcriptionally regulated by a complex network of several molecules (11). Since *TROP2* plays a critical role in the metastasis and progression of many cancers, agents that target *TROP2* have potential as therapies for advanced cancers (12). In this study, based on literature obtained from medical databases, we comprehensively reviewed relevant studies on the role of *TROP2* in tumorigenesis and the promising potential of *TROP2* as a biomarker and emerging therapeutic target for advanced cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5976/rc).

Methods

A total of 1,376 literatures from PubMed and 614 literatures from EMBASE were retrieved by searching "*TROP2*" or "Trophoblast cell surface antigen 2". The search was conducted on December 12, 2020, and updated on November 20, 2022 (*Table 1*). There were no language, publication date, or publication type restrictions. We also analyzed the expression and mutation of the *TROP2* gene using data obtained from TCGA (The Cancer Genome Atlas) through the cBioportal (13) (https://www.cbioportal.org/). Also, GEPIA (Gene Expression Profiling Interactive Analysis) (http://gepia2.cancer-pku.cn/#index) was utilized to evaluate the prognostic value of *TROP2* in different types of cancer (14).

Discussion

TROP2 expression and mutation in cancers

TROP2 was overexpressed in a variety of (but not all) malignant tumors and exhibits differential expression in certain normal tissues (15,16). Patients with bladder urothelial carcinoma (BLCA) expressed the highest level of the *TROP2* gene, followed by those with head and neck squamous cell carcinoma (HNSC) and lung squamous cell carcinoma (LUSC) (*Figure 1*). *TROP2* was upregulated in BLCA, CHOL, colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), lung adenocarcinoma (LUAD), LUSC, prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC), and downregulated in HNSC, kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), and liver hepatocellular carcinoma (LIHC). The mutation rate of *TROP2* gene was different in various tumors. Sarcoma has the highest rate of *TROP2* gene mutation, with most of the mutation types being amplified, followed by miscellaneous neuroepithelial and ovarian epithelial tumors (*Figure 2*). Moreover, congenital mutations in human *TROP2* can cause gelatinous drop-like corneal dystrophy (GDLD), which is a rare autosomal recessive genetic disease that can lead to the development of bilateral corneal amyloidosis and eventually blindness (17). Although we observed the presence of *TROP2* mutations in some tumors, subsequent studies are needed to further confirm whether *TROP2* mutations are directly or indirectly associated with cancer. Therefore, clinical studies targeting *TROP2* mutations have not been implemented. Current known reports favor the overexpression of *TROP2* in most

Table 1 Search strategies of this study

Items	Specification
Date of search	December 12, 2020 to November 20, 2022
Databases and other sources searched	PubMed, EMBASE, cBioportal and GEPIA
Search terms used	TROP2, Trophoblast cell surface antigen 2
Timeframe	From 1980 to 2022
Inclusion and exclusion criteria	Inclusion criteria: papers involved the expression, functions, interactions, prognostic values and clinical applications of TROP2
	Exclusion criteria: non-English language papers
Selection process	The selection was conducted by 3 authors independently and was discussed with other 2 authors in the case of any disagreements

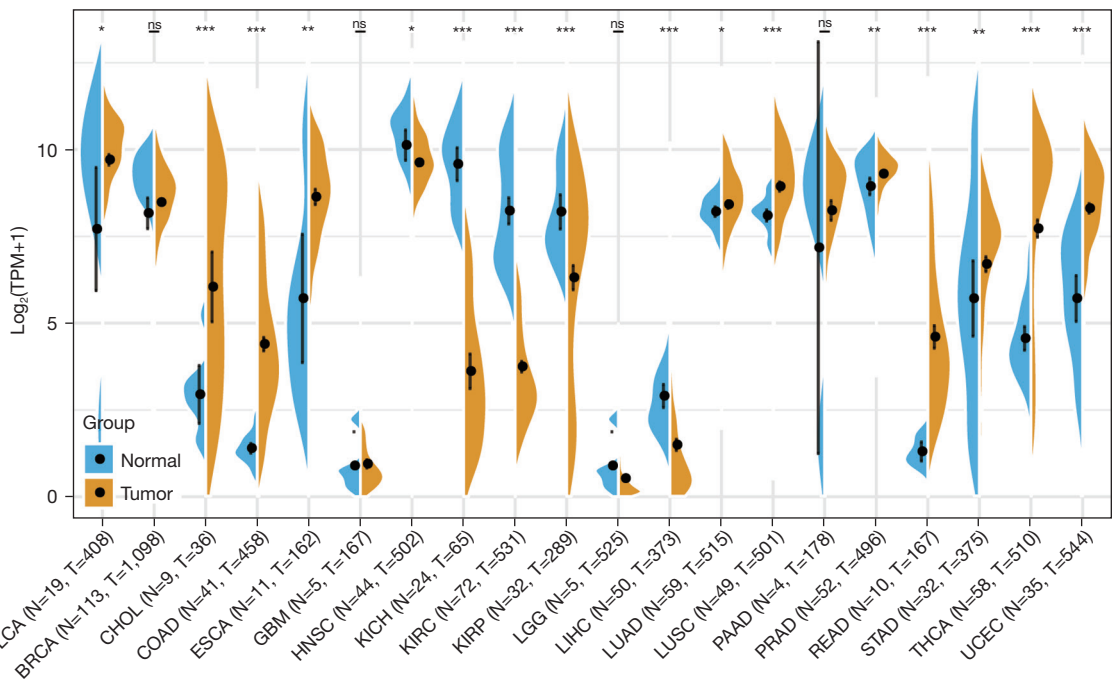

Figure 1 The expression levels of *TROP2* based on TCGA data [$\log_2$(TPM+1) scale]. ns, no significance; *, P<0.05; **, P<0.01; ***, P<0.001. TPM, transcripts per million; TCGA, The Cancer Genome Atlas.

solid tumor cancers, promoting tumorigenesis and progress of cancer (12).

TROP2 structural features

TROP2 is human trophoblast cell surface glycoprotein antigen 2 that belongs to the *TACSTD* family (18) and is also known as *TACSTD2*, epidermal glycoprotein 1 (*EGP-1*), and membrane component chromosome 1 surface marker 1 (*M1S1*) or gastric antigen 733-1 (*GA733-1*) (19-21). It is a type I transmembrane cell-surface glycoprotein originally identified in human placental trophoblasts and subsequently found to be highly expressed in most human carcinomas (22). The intronless *TROP2* gene is found on the short arm of human chromosome 1 and is located at 1p32.1. It is a type I cell membrane glycoprotein formed by N-terminal glycosylation and posttranslational modification that is composed of 323 amino acids, known as the

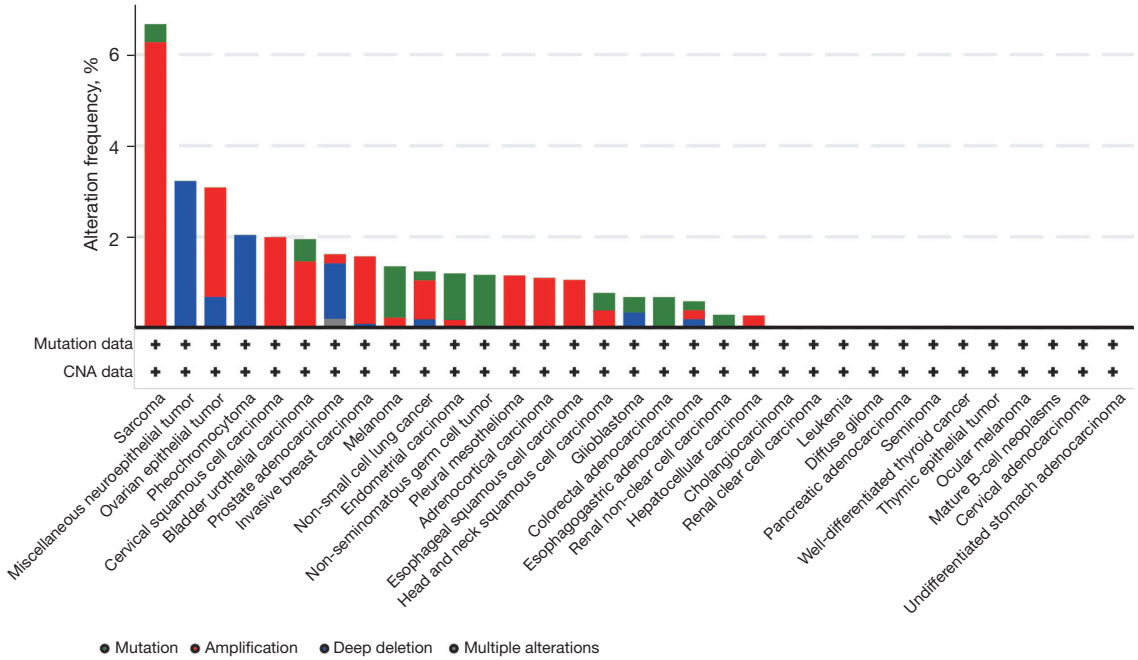

Figure 2 The *TROP2* mutation rates based on TCGA data. TCGA, The Cancer Genome Atlas.

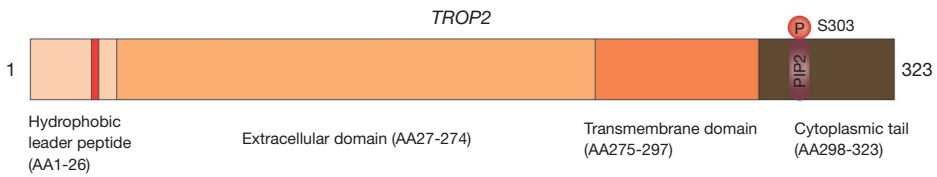

Figure 3 The structure of *TROP2*.

TROP2 protein, and is approximately 36 kD in size (23). *TROP2* is composed of a hydrophobic leader peptide (AA1–26), an extracellular domain (ECD) (AA27–274), a transmembrane domain (AA275–297), and a cytoplasmic tail (AA298–323) (21) (*Figure 3*).

TROP2 connects the N-terminal ectodomain (EC) to the IC hydrophobic polypeptide short tail through a unidirectional transmembrane helix (TM), thereby immobilizing it on the cell membrane (12). There are highly conserved phosphatidylinositol 4,5-biphosphate (PIP2) binding sequences and tyrosine and serine phosphorylation sites in the cytoplasmic tail, indicating that PIP2 has an important impact on the signal transduction of *TROP2*. The mutation of serine residue 303 inhibits the ability of *TROP2* to stimulate tumor growth. Protein kinase C (*PKC*) is responsible for its phosphorylation; the phosphorylation of *TROP2* IC induces the reorganization of the salt bridge, which causes conformational alteration of the *TROP2* functional area. These structural features may have important significance in regulating the activity of *TROP2* (12,20,24,25).

TROP2 transcriptional regulation

Compared with non-cancer cells, the reason why *TROP2* is overexpressed in many cancers is not fully understood (24). A possible explanation might be the stem cell-like characteristics of *TROP2*, which exert an inherent regulatory effect on cell growth, proliferation, regeneration, and transformation (26). *TROP2* overexpression has been shown to be necessary and sufficient to drive cancer growth (24), and therefore, will be more representative due to the proliferation of cancer cells (12). Another possible reason is the network of transcription factors that modulate

TROP2 expression. *TROP2* overexpression in cancer does not arise from structural alterations of the gene itself but rather due to deregulation at the transcriptional and post-transcriptional levels (20). This network includes tumor protein 63 (*TP63*)/tumor protein 53L (*TP53L*), Wilms tumor 1 (*WT1*), ETS-related gene (*ERG*), T-cell factor (*TCF-1*)/hepatocyte nuclear factor 1 (*HNF1A*)/lymphoid enhancer factor (*LEF1*), autoimmune regulator (*AIRE*), Glis2, forkhead box protein transcription factor (*FOXM1*), *FOXP3*, spleen focus forming virus (*SFFV*) proviral integration oncogene (*SPI1/PU.1*), and so on (24,27).

TROP2 signal transduction and function

As a new glycoprotein receptor on the cell membrane surface, *TROP2* mainly promotes tumor cell growth, proliferation, and metastasis by regulating the calcium ion signaling pathway and cyclin expression and reducing fibronectin adhesion (27). *Figure 4* illustrates the IC signaling network mediated by *TROP2* and its involvement in tumorigenesis and development.

Ca^{2+} can also further stimulate mitogen-activated protein kinase (MAPK) signal transduction, which increases the levels of phosphorylated *ERK1* and *ERK2*. ERK signal transduction leads to an increase in the transcription factor *AP-1*, which is a central regulator of tumor-associated target genes during tumorigenesis. *AP-1* induces angiogenesis by vascular endothelial growth factor (*VEGF*); cell proliferation by cyclins and CDKs; apoptosis by *Bcl-2* (B-cell lymphoma 2) or *FasL* (Fas ligand); cell invasion and metastasis by *MMPs* (matrix metalloproteinases), *Pdon* (podoplanin), *Ezrin*, and *CD44*; and EMT (epithelial to mesenchymal transition) by *Pdpn*. EMT allows more *β-catenin* to enter the nucleus and promote cell growth. Enhancement of ERK activity induces phosphorylation of *FOXO3a*, leading to ubiquitination of *MDM2* (mouse double minute 2) and proteasomal degradation. The degradation of *FOXO3a* may help to promote cancer cell survival. *TROP2* increases the expression of *Ki-67* (a cell proliferation marker) and further activates cell proliferation.

TROP2 is cleaved into the ECD and intracellular domain (ICD) by the tumor necrosis factor alpha (*TNF-α*) converting enzyme (*TACE*), followed by *γ-secretase*. The cleavage is mediated by two dominant enzymes, presenilin 1 (*PS-1*) and presenilin 2 (*PS-2*).

RACK1 (cytoplasmic protein kinase C receptor 1) is enriched on the cell membrane by *TROP2*, inhibiting the binding of fibronectin to integrin β-1. *TROP2* reduces tumor cell adhesion and promotes metastasis through the integrin β-1-RACK1-Src/FAK signal transmission axis.

TROP2 mediates cell cycle progression through the calcium ion signaling pathway

Under the action of *PKC*, the IC tail serine residue (S303) of the TROP2 protein is phosphorylated, thereby promoting PIP2 hydrolysis for inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 interacts with the IP3 receptor on the endoplasmic reticulum surface and promotes the release of calcium ions stored in the endoplasmic reticulum, activates the MAPK pathway, and promotes the cell cycle process (an increased percentage of cells enter the S phase). Moreover, m*TROP2* increases the level of phosphorylated MAPK (*ERK1/ERK2*), while enhanced ERK activity induces the phosphorylation of *FOXO3a* at residues S294, S344, and S425. This phenomenon may lead to its ubiquitination by *MDM2*, which in turn promotes the cytoplasmic localization of *FOXO3a* and proteasome degradation, thereby contributing to tumor cell survival (24,27,28). The increased concentration of IC calcium may affect cell signal activation and cell cycle progression by activating *PKC* and/or calcium/calmodulin-dependent protein kinase II (CaMKII). Consequently, the percentage of cells entering the DNA synthesis stage is increased. Moreover, *DAG* regulates the phosphorylation of *TROP2* by activating *PKC* reciprocally (29).

TROP2 regulates the cell cycle via IC hydrolysis

Under the combined action of the *TACE*, *γ-secretase*, and *PS-1/2*, *TROP2* is cleaved into two products, namely, the ECD and the ICD. ICD is released from the membrane and enters the nucleus (although some are found on the membrane). It colocalizes with *β-catenin* in the Wnt signaling cascade in the nucleus and upregulates the expressions of *cyclin D1* and a proto-oncogene (*c-myc*), thereby playing a role in the transcription of nuclear oncogenes and cell proliferation (30).

TROP2-mediated apoptosis and proliferation signals

TROP2 activates the phosphorylation of p42/p44MAPK (*ERK1/2*) and further enhances the activity of the downstream transcription factor *AP-1*, which is the central regulator of tumor-related target genes in the process of carcinogenesis (28). *AP-1* induces angiogenesis through *VEGF*, apoptosis through the pro-apoptotic *Bcl-2* or *FasL*, acceleration of the cell cycle through *cyclinD1/cyclinE* and CDK, and cell invasion through *MMPs*, *Pdpn*, *Ezrin*,

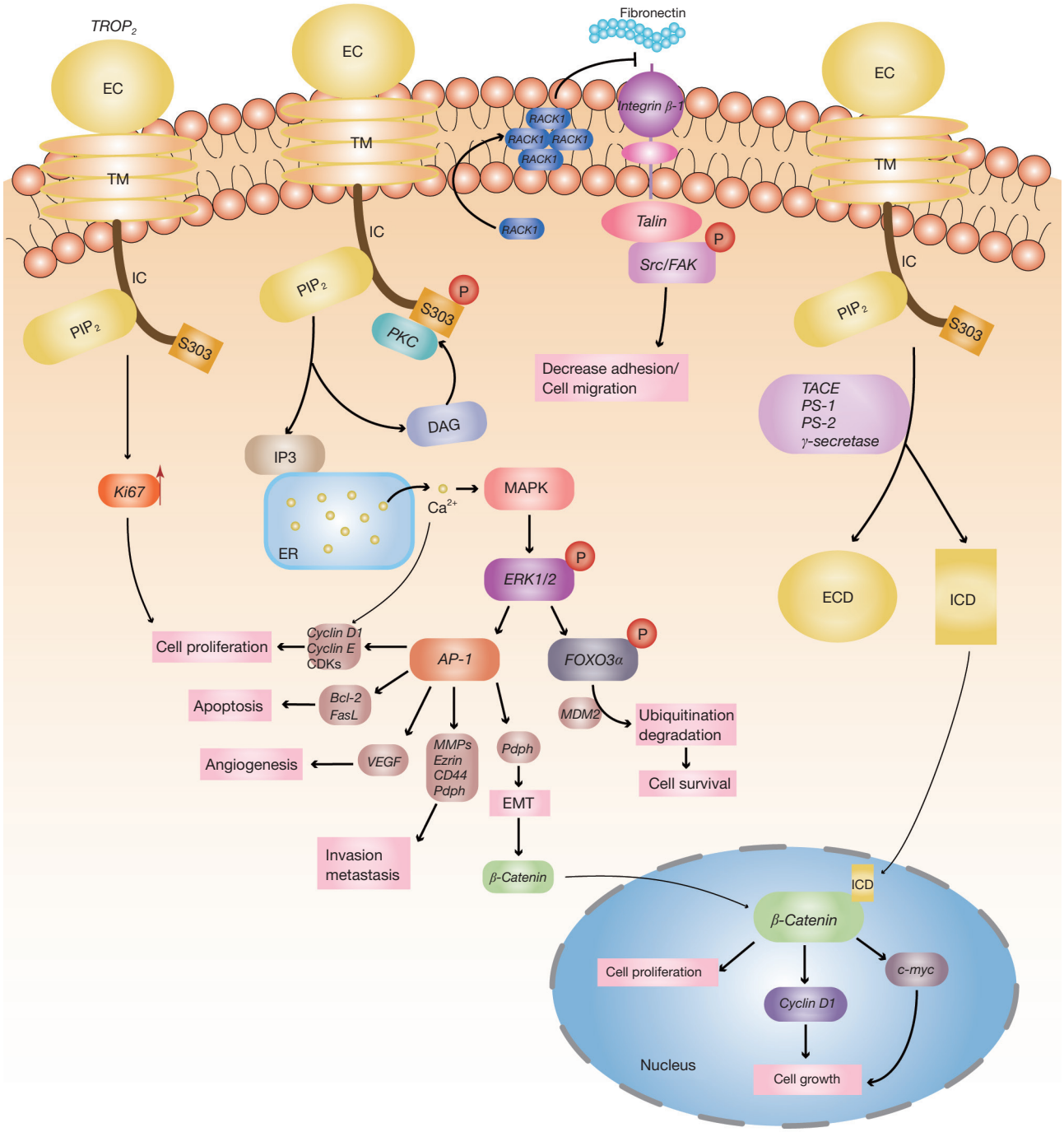

Figure 4 *TROP2* signaling network based on the literature we reviewed. Once S303 at the *TROP2* cytoplasmic tail is phosphorylated by *PKC*, PIP2 is further hydrolyzed into IP3 and DAG. IP3 releases Ca^{2+} from the endoplasmic reticulum, which stimulates MAPK signal transduction and cell cycle progression. The increase in free Ca^{2+} and DAG could activate more *PKC* through a positive feedback mechanism. Increased *PKC* may lead to further phosphorylation of *TROP2*. EC, extracellular; ECD, extracellular domain; IC, intracellular; ICD, intracellular domain; TM, transmembrane helix; PIP2, phosphatidylinositol 4,5-biphosphate; IP3, inositol 1,4,5-triphosphate; DAG, diacylglycerol.

and *CD44*.

Furthermore, *AP-1* can also cause epithelial-to-mesenchymal transition (EMT) via *Pdpn*; EMT allows for the nuclear translocation of *β-catenin*, which is conducive to cell proliferation. *TROP2* can promote the proliferation of tumor cells by upregulating the expression of the proliferation marker *Ki-67*, whereas the proliferation of tumor cells is disturbed when the *TROP2* gene is knocked down (29,31).

TROP2 promotes tumor invasion and metastasis

TROP2 enriches the *RACK1* on the cell membrane, which reduces the binding of fibronectin to *integrin β-1*. *TROP2* forms a complex with *integrin β-1* and talin proteins, resulting in the activation of downstream *Src* and *FAK*. *TROP2* reduces tumor cell adhesion and promotes metastasis through the *integrin β-1-RACK1-Src/FAK* signal transmission axis (32).

TROP2 as a prognostic biomarker

Through the GEPIA database, we found that a high level of *TROP2* is potentially related to better overall survival (OS) in lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), KICH, KIRP, and acute myeloid leukemia (LAML), while a low level of *TROP2* is potentially related to better OS in LUAD, ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), and skin cutaneous melanoma (SKCM). Furthermore, high levels of *TROP2* are associated with better disease-free survival (DFS) in KICH, KIRP and UCEC, while low levels of *TROP2* are associated with better DFS in OV, PAAD, and READ (*Figure 5*). The obvious correlation between *TROP2* levels and cancer aggressiveness and recurrence risk suggests its utility as an independent prognostic indicator for patients (33).

The expression of *TROP2* can be used as a unique prognostic biomarker of lymph node metastasis, degree of differentiation, and tumor size (34). *TROP2* overexpression is also increased in HNSC and is related to the degree of tissue differentiation and lymph node metastasis (35,36). High expression of TROP2 protein is associated with high aggressiveness in ovarian cancer (37). Elevated levels of *TROP2* are also correlated with poor patient outcomes and a more aggressive clinical course in prostate cancer (38,39). In general, *TROP2* overexpression often correlates with an unfavorable prognosis and increased risk of metastasis (1,11,40,41), while downregulation is correlated with poor prognosis in some types of cancer (42). Importantly, the hypermethylation of the *TACSTD2* gene promoter explains the low expression of *TROP2* in this type of cancer (43). Nevertheless, the prognostic value of *TROP2* may also depend on its cellular localization within tumors, which requires further research (44).

TROP2 in cancer therapy

As a transmembrane protein whose ECD is overexpressed in a variety of tumors, *TROP2* seems to be an exceptionally promising candidate for immunotherapeutic strategies (45). Various forms of drugs have been rapidly developed, including monoclonal antibodies (mAbs), bispecific antibodies, antibody-drug conjugates (ADCs), virus-like particles (VLPs), as well as antibody drugs combined with traditional chemotherapy, immunotherapy, radioimmunotherapy, photoimmunotherapy, and nanoparticles that target *TROP2* (46-49).

mAbs

Anti-*TROP2* mAbs with high affinity can recognize different regions of the *TROP2* molecule and can be used in the treatment and diagnosis of various types of cancer. hRS7 is a humanized IgG1 mAb directed against *TROP2*, which was originally raised against human non-small cell carcinoma of the lung (50) and is reactive with several cancers. For example, unlike *TROP2*-negative endometrial endometrioid carcinoma (EEC) cell lines, the EEC primary cell line was found to be highly sensitive to hRS7-mediated antibody-dependent cellular cytotoxicity *in vitro* (47). *TROP2*-positive cell lines have also exhibited high sensitivity to hRS7 antibody-dependent cell-mediated cytotoxicity (ADCC) in carcinomas of the uterus, cervix, and ovary (46,51-53). The hRS7 antibody internalizes when bound to *TROP2*, which enables direct intracellular delivery of cytotoxics (54). In the absence of hRS7 or the presence of rituximab control antibodies, the cytotoxicity of chemotherapy-resistant ovarian cancer is negligible (51).

Bispecific antibodies

TF12 is a trivalent bispecific antibody that consists of two anti-TROP-2 Fab fragments and one antihistamine-succinyl-glycine (HSG) Fab fragment (55). The characteristics and potential for pre-targeted radioimmunoimaging and radioimmunotherapy with TF12 and ^{111}In-IMP288, a radiolabeled hapten-peptide, in mice with human prostate cancer have been investigated. *TROP2*-expressing prostate cancer can be pre-targeted efficiently with TF12, with

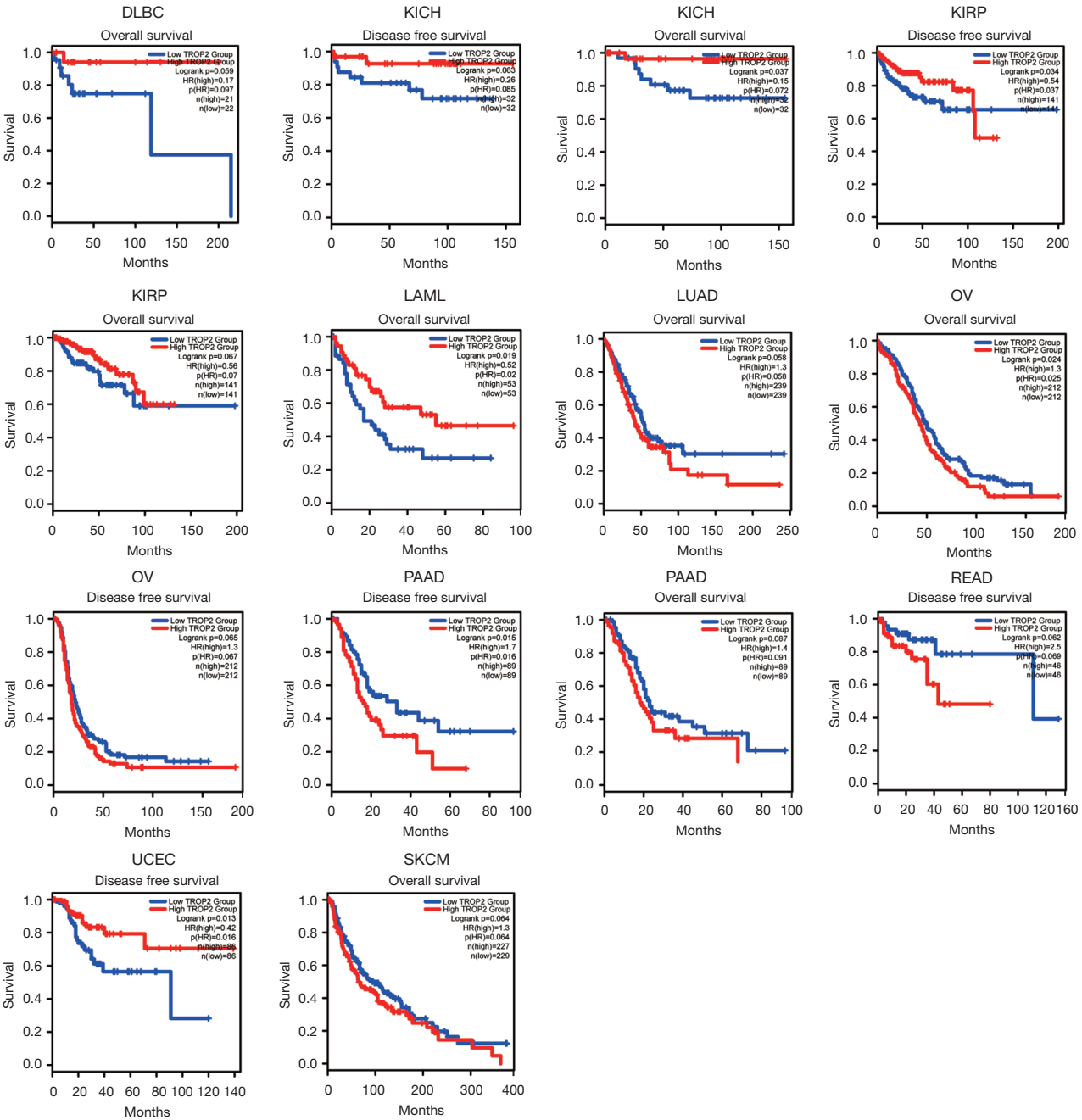

Figure 5 Survival plot based on the GEPIA database. GEPIA, Gene Expression Profiling Interactive Analysis.

a very rapid uptake of ^{111}In-IMP288, sensitive immuno-positron emission tomography (immunoPET), and effective therapy (56). Furthermore, TF12 is sufficiently preserved on the cell surfaces of several epithelial cancers, making it suitable for pre-targeted imaging and treatment of various TROP-2-expressing cancers (57).

(E1)-3s is a T-cell-redirecting trivalent bispecific antibody comprising an anti-CD3 scFv covalently linked to a stabilized dimer of a TROP-2-targeting Fab using Dock-and-Lock (DNL). This covalent combination was designated (X)-3s using the DNL method, in which the code "(X)" denotes a stabilized tumor-associated antigen (TAA)-specific Fab dimer that is fused site-specifically to an scFv of Okt3, indicated as "3s" (58). Bispecific antibody-

mediated bidirectional phagocytosis occurs between target cells and T cells and involves immune synapses (59). (E1)-3s effectively induces T-cell-mediated killing of *TROP2*-expressing pancreatic and gastric cancers (60), validating *TROP2* as a candidate tumor-associated antigen for cancer therapy.

Human Fab antibody

The ECD of *TROP2* was chosen as the antigen to isolate a human naive Fab antibody from the phage library using phage display technology. *TROP2* Fab inhibits proliferation, induces apoptosis, and terminates the migration of MDA-MB-231 cells in a concentration-dependent manner (45). Compared with the control group, *Bcl-2* expression was significantly downregulated, while *Bax* expression was significantly upregulated after treatment with *TROP2* Fab in nude mice. Therefore, *TROP2* Fab represents a promising chemotherapeutic agent for *TROP2*-expressing breast cancer (45,61).

ADCs

The utility of anti-*TROP2* antibodies coupled with other chemotherapeutic drugs has been confirmed in various preclinical studies. Based on the previous *TROP2*-Fab antibody, a new *TROP2*-IgG antibody was constructed via the eukaryotic expression system and then coupled with an SN-38, such as hRS7-CL2A-SN-38, which has been shown to exert significant specific anticancer effects in a variety of tumor cell lines (45). SN-38, the active metabolite of the topoisomerase inhibitor irinotecan, has a derivative, CL2A, which has been successfully conjugated to hRS7.

Sacituzumab govitecan (IMMU-132), hereinafter referred to as sacituzumab, is coupled with the humanized antibody hRS7 as the carrier of *TROP2* targeting with SN-38 (27). The United States Food and Drug Administration (FDA) approved the application of sacituzumab on December 26, 2019, for triple-negative breast cancer (TNBC) patients who have received two or more prior therapies (NCT01631552) (4,62-64). Sacituzumab is currently undergoing various clinical trials for different malignancies, including metastatic breast cancer, urothelial cancers, gastric cancer, non-small cell lung cancer, and castration-resistant prostate cancer (44,49,64-68) (*Table 2*). In April 2022, the Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) guidelines recommended that sacituzumab be included in the advanced rescue treatment of TNBC. The treatment of tumor-bearing mice with hRS7-SN-38 (either with CL2-SN-38 or CL2A-SN-38) significantly inhibited tumor growth in five different tumor models. It is well tolerated in monkeys and worthy of further study in human clinical trials (68). In fact, a smaller dose of SN-38 administered by sacituzumab govitecan is considerably more effective than a larger dose of irinotecan or a combination of hRS7 IgG and SN-38 (68).

A site-specific *TROP2*-ADC, RN927C (also known as PF-06664178) is composed of a humanized anti-*TROP2* hIgG1 antibody conjugated with a cleavable proprietary microtubule inhibitor (MTI) linker payload, PF-06380101 (22). Upon binding to the extracellular portion of *TROP2* on the cell surface, RN927C is internalized and transported to the lysosome, where PF-06380101 is released and induces mitotic arrest, followed by cell death (22). Indeed, RN927C has shown a potent cell-killing effect in a variety of tumor cell lines and patient-derived xenograft tumor models, including pancreatic cancer and TNBC (22).

Datopotamab deruxtecan (Dato-DXd) is another *TROP2*-directed ADC with a potent DNA topoisomerase I inhibitor (DXd) (3). The topoisomerase I inhibitor is linked to the *TROP2* mAb by a tetrapeptide-based linker (69). Dato-DXd is bound specifically to *TROP2* and is internalized into tumor cells, where lysosomal enzymes break the linker to release DXd, which induces DNA damage and apoptosis in *TROP2*-expressing tumor cells. The DNA damage of *TROP2*-expressing xenograft tumors induced by accumulated DXd is unique, and neither the isotype control IgG-ADC nor the anti-*TROP2* antibody displayed this effect (70). Dato-DXd is currently being investigated in a phase I clinical trial in patients with TNBC (NCT03401385) and will be a valuable treatment option for patients with *TROP2*-expressing tumors (3).

Ranpirnase (Rap) is an amphibian RNase with antitumor activity, minimal toxicity, and negligible immunogenicity (71). A Rap fusion protein constructed through hRS7 has the potential to inhibit chronic lymphocytic leukemia and Raji Burkitt lymphomas (72). The DNL method has been applied to construct a class of novel IgG-Rap immunoRNases, named (Rap)2-E1-(Rap)2 or 2L-Rap(Q)-hRS7, which are made of Rap(Q), a mutant Rap with the putative N-glycosylation site removed, and the anti-*TROP2* antibody hRS7 (73). (Rap)2-E1-(Rap)2 has made considerable progress in enhancing the potency of Rap, which significantly suppressed tumor growth in nude mice bearing Calu-3 human non-small cell lung cancer xenografts and improved the survival rate of tumor-bearing mice (71,73).

Table 2 Clinical trials of sacituzumab govitecan (IMMU-132)

Clinical trials	Cancers	Phase	Status
NCT01631552	Refractory metastatic epithelial cancers	I & II	Completed
NCT02574455	Refractory/Relapsed metastatic TNBC	III	Completed
NCT03337698	Metastatic NSCLC	I & II	Recruiting
NCT03424005	Metastatic or advanced TNBC	I & II	Active, not recruiting
NCT03547973	Metastatic urothelial carcinoma	II	Recruiting
NCT03725761	Metastatic castration-resistant prostate cancer	II	Recruiting
NCT03901339	HR+/HER2– metastatic breast cancer	III	Active, not recruiting
NCT03964727	Metastatic NSCLC; head and neck Squamous cell carcinoma; endometrial cancer	II	Recruiting
NCT03992131	Ovarian cancer; TNBC; urothelial carcinoma; solid tumor	Ib & II	Terminated
NCT03995706	Glioblastoma; metastatic brain tumors	I	Recruiting
NCT04039230	Metastatic breast cancer	I & II	Recruiting
NCT04230109	Invasive localized TNBC	II	Active, not recruiting
NCT04251416	Endometrial carcinoma	II	Recruiting
NCT04319198	Metastatic solid tumor	IV	Enrolling by invitation
NCT04448886	Metastatic HR+/HER2– breast cancer	II	Recruiting
NCT04454437	Metastatic TNBC	II	Active, not recruiting
NCT04468061	PD-L1-negative metastatic TNBC	II	Recruiting
NCT04527991	Locally advanced or metastatic unresectable urothelial cancer	III	Recruiting
NCT04559230	Glioblastoma	II	Recruiting

TNBC, triple-negative breast cancer; NSCLC, non-small cell lung cancer; HR+, hormone receptor-positive; HER2–, human epidermal growth factor-2 negative; PD-L1, programmed death-ligand 1.

Combination therapies with ADCs and various compounds

A previous study revealed that the overexpression of one or more efflux pumps in the superfamily of ATP-binding cassettes (ABCs) may induce drug resistance in cancer cells (74). Since SN-38 is susceptible to multiple ABC transporters (75), some patients with metastatic triple-negative breast cancer (mTNBC) showed early disease progression, thus failing IMMU-132. Treatment with known ABCG2 inhibitors (such as fumitremorgin C, Ko143, and YHO-13351) restored the toxicity of SN-38, while the combination of YHO-13351 and IMU-132 improved the therapeutic efficacy and median survival of mice bearing human gastric cancer xenografts (76). ABCG2 plays a key role in inducing SN-38 resistance in various cancer cells, and disturbances in DNA topoisomerase I (Top1) are a potential source of cellular SN-38 resistance (76).

The mutation and degradation of Top1 is the main molecular mechanism of Top1 resistance to camptothecin, especially for SN-38 (77,78). Interestingly, the poly ADP-ribose polymerase (PARP) enzyme was found to catalyze binding between the ADP-ribose polymer and Top1, which reduced the efficacy of camptothecin (79). The combination treatment of sacituzumab govitecan and PARP inhibitors (olaparib, rucaparib, or talazoparib) showed synergistic growth inhibition and antitumor effects in mice bearing human TNBC tumor xenografts (80). A phase I/II clinical trial (NCT04039230) involving patients with mTNBC is currently ongoing.

Immunotherapy, radioimmunotherapy, and photoimmunotherapy

The adoptive transfer of antigen-specific cytotoxic T lymphocytes (CTLs) is a promising anticancer immunotherapy (81). *TROP2* has been verified as a potential target molecule for presentation to human CTLs, and

TROP2-specific CTLs exhibit highly specific cytotoxicity to transfected target cells (82).

Radioimmunotherapy (RAIT) is a therapeutic modality that is based on selectively targeting ionizing radiation to tumor sites using tumor-targeting mAbs tagged with radionuclides (83). ^{131}I-IMP-R4-hRS7 is an hRS7 monoclonal antibody labeled with radioactive iodine, and ^{131}I-IMP-R4 was evaluated for preclinical RAIT in breast cancer (84,85). ^{131}I-IMP-R4 is an improved residual form of ^{131}I, which has the advantage of a longer residence time in tumors compared to conventional radioiodinated mAbs (86). Radiolabeled hRS7 has been demonstrated to have a tumor-targeting ability and significant antitumor efficacy in animal models. Compared to direct conventional ^{131}I-hRS7, ^{131}I-IMP-R4-hRS7 exhibited considerably better tumor growth control in athymic mice bearing human breast cancer xenografts (86), which provides a significant therapeutic advantage. RAIT has been combined with the humanized antibody 90Y-hPAM4 targeted antigen in pancreatic cancer, while the conjugate hRS7-SN-38 has been shown to target *TROP2* in cancer cells (72). This combination therapy was found to be significantly more effective than using RAIT alone (72). In addition, radiolabeled ^{111}In-HRS7 and ^{89}Zr-HRS7 preferentially and specifically accumulated in prostate cancer xenografts and were clearly visualized through immunoPET and immunoSPECT; thus, they will be beneficial for guiding clinical cancer therapy (87).

Photoimmunotherapy (PIT) is a new type of tumor-specific treatment utilizing mAb-photosensitizer conjugates and near-infrared (NIR) light irradiation (88). A newly developed human anti-*TROP2* mAb conjugated with photosensitizer IR700 (*TROP2*-IR700) has been successfully used to treat pancreatic cancer and cholangiocarcinoma cells under near-infrared irradiation (89). *TROP2*-IR700 could cause rapid and selective cell death when exposed to NIR light. *TROP2*-targeted PIT significantly inhibited the growth of xenograft tumors in pancreatic cancer and cholangiocarcinoma and is expected to be an attractive cancer-specific treatment (89).

VLPs

VLPs are highly immunogenic and versatile immunostimulants that can be used as cancer vaccines by binding exogenous proteins to their cell membranes (90). VLPs can induce the production of m*TROP2*-specific cytotoxic T lymphocytes and antibodies without the induction of autoimmunity. The combination of VLP immunization with gemcitabine treatment has shown an improved effect, significantly increasing the survival of tumor-bearing mice. Chimeric *TROP2* VLPs will be a novel immunotherapeutic approach that could potentially be used as an alternative treatment option (90).

Anti-*TROP2* antigen-conjugated nanoparticles (ST-NPs)

TROP2-targeted therapy also includes nanoparticles bound to anti-*TROP2* antibodies. ST-NPs are potential nanocarriers consisting of carboxymethyl glucan (CMD) derivatives and bioreducible disulfide bonds loaded with doxorubicin (DOX), called DOX-ST-NPs, which are utilized for the targeted delivery of anticancer drugs to TNBC (91). After binding to *TROP2*, the nanoparticles enter cells via endocytosis and release DOX. Compared to the control nanoparticles, which lack disulfide bonds or anti-*TROP2* antibodies, *TROP2*-expressing TNBC cell lines have higher selectivity and toxicity to DOX-ST-NPs. Therefore, ST-NPs might be a promising nanocarrier for targeted TNBC therapy (91).

Furthermore, the delivery of apoptotic activator 2 nanoparticles via liposomes targeting the *TROP2* antigen is a possible approach for the intelligent killing of human gastric adenocarcinoma cells (AGS) (92). AGS cells have been treated with apoptosis activator 2-loaded liposomes that targeted the cell surface *TROP2* antigen in cancer cells and significantly increased cell apoptosis (92).

Chimeric antigen receptor T (CAR-T) cell therapy

CAR-T cell therapy, a type of adoptive cell therapy, has been successfully used when treating lymphoma malignancies, but not nearly as successful in treating solid tumors. One study showed that a novel bispecific *TROP2*/PD-L1 CAR-T cell can target *TROP2*/PD-L1 and show a killing effect on gastric cancer, thus improving the killing effect of CAR-T cells in solid tumors (93). The CD27-based *TROP2* CAR-T cells showed a higher antitumor activity in mouse tumor models (94). There is no denying that *TROP2* is a promising target for CAR-T cell therapy. We are still waiting for further clinical trials, *TROP2*-CAR-T therapy is just around the corner (95).

Conclusions

In recent years, research has been conducted to identify cancer-specific proteins that can be used for targeted therapy (96-100). The *TROP2* oncogene represents an ideal

target for the development of ADC drugs. In this review, we found that *TROP2* is highly expressed in a variety of malignant tumors and plays roles in cell proliferation, adhesion, migration, EMT, apoptosis, and targeted therapy by interacting with or binding to several molecules. *TROP2* is involved in survival signaling and is a prognostic predictor in patients with several types of cancer. Briefly, *TROP2* can be used as a new target for tumor-targeted therapies and has considerable research value and development prospects for research into new antitumor drugs. The development of novel *TROP2*-targeting therapies for advanced cancers that do not pose a risk of toxicity to normal tissues is essential. Combination therapies, such as agents targeting *TROP2* coupled with conventional chemotherapy, immunotherapy, radioimmunotherapy, and nanoparticles, have substantial potential and are worthy of further study in preclinical and clinical studies.

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Footnote

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