CD155/TIGIT, a novel immune checkpoint in human cancers (Review)

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Abstract. CD155/T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel type of immune checkpoint. CD155 is an adhesion molecule that is upregulated during tumor progression and promotes the proliferative and migratory abilities of tumor cells via various pathways. TIGIT, an inhibitory receptor, is mainly expressed on natural killer (NK), $CD8^+$ T, $CD4^+$ T and T regulatory (Treg) cells. CD155 transmits immune signals via interacting with the inhibitory checkpoint receptor TIGIT, thereby inhibiting the function of T and NK cells. Several preclinical studies have supported the use of TIGIT blockade as a monotherapy or combined with other immune checkpoint inhibitors for the treatment of advanced solid malignant tumors. The present review summarized the current knowledge on CD155/TIGIT and the lymphocyte-mediated inhibitory mechanism of CD155/TIGIT. An in-depth understanding of the role of CD155/TIGIT in tumors may aid to improve the application of immune checkpoint inhibitors in tumor therapy.

Contents

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1. Introduction

Tumor immunotherapy is a crucial treatment approach following surgery, radiotherapy and chemotherapy. Currently, immunotherapy is considered to be the most common treatment method for tumors (1). Although tumor cells cause a strong immune response, cancer persists, which may be attributed to the fact that the immune response against tumor cells is insufficient to prevent the development of cancer or that the transient immune response triggers specific immune tolerance mechanisms in tumor cells (2). A healthy immune system maintains immune balance using co-suppressing receptors and their ligands, known as immune checkpoint blockers (ICBs). Therefore, tumor cells can escape immune attacks by breaking the balance of the immune checkpoints (3). In recent years, the successful application of combined signal receptor-targeted immune therapy has attracted widespread attention (4,5). Multiple clinical studies have demonstrated that monoclonal antibodies (mAb) targeting the inhibitory receptors cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1) exhibit favorable therapeutic effects in a variety of human malignancies, including melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer and Hodgkin lymphoma (6-8). However, despite the promising results achieved by ICBs, there is still a considerable number of patients who cannot benefit from the currently available therapies (9). To further exploit the advantages of immune checkpoint inhibitor therapy, it is necessary to explore novel immune checkpoints as therapeutic targets for patients with cancer (10).

2. Structure of CD155

In recent years, nectin receptors and nectin-like molecule (NECL) proteins have received extensive attention as targets for cancer immunotherapy (11). NECLs are more extensively expressed than nectins and exert more abundant functions (12). NECL-1 and NECL-4 mediate the interaction between axons and participate in Schwann cell differentiation and myelination (12,13). NECL-2 functions as a tumor suppressor and immune surveillance modulator (14). NECL-5 serves a crucial role among NECLs due to its unique expression profile as described below. NECL-5 is also known as CD155. CD155 also serves as a poliovirus receptor (PVR), which promotes the

migration and proliferation of tumor cells (14,15). CD155 is a member of the immunoglobulin superfamily, characterized by the presence of an immunoglobulin domain V and C1-like and C2 domains in the extracellular region (16). CD155 has four splicing isoforms, defined as α, β, γ and δ. The α and δ isoforms contain a transmembrane domain, while the α isoform contains a longer C-terminal domain and an immunoreceptor tyrosine-based inhibitory motif (ITIM) necessary for the intrinsic biology of tumor cells (17). However, the β and γ subtypes lack transmembrane domains, and their biological functions have not been elucidated (17). CD155 can recruit protein-tyrosine phosphatase SHP-2 via the ITIM domain to initiate signal transduction (18,19), cell adhesion (20), motility (18,21), proliferation and survival (22). CD155 is also involved in tumor immune response. When CD155 is upregulated in different types of tumor cells, the activating receptor CD226 and the inhibitory receptors T cell immunoreceptor with Ig and ITIM domains (TIGIT) and CD96, which are expressed on the cell surface of T and natural killer (NK) cells, recognize and bind to tumor cells (23). CD155 exhibits the highest binding capacity with TIGIT, followed medium binding capacity with CD96 and the lowest binding capacity with CD226 (Fig. 1) (24,25).

3. High expression of CD155 in malignant tumors

CD155 is overexpressed in several types of cancer, including melanoma (26), lung adenocarcinoma (27), pancreatic cancer (28), ovarian cancer (29), acute myeloid leukemia (30), malignant glioma (31), cholangiocarcinoma (32) and head and neck squamous cell carcinoma (33) (Table I). Furthermore, a previous study has demonstrated that the level of soluble CD155 in the serum of patients with cancer was significantly higher compared with that of healthy volunteers and was positively correlated with tumor stage (34).

The increased expression of CD155 in tumors may be caused by different mechanisms. Firstly, the chemotherapy approach used at present to treat patients with multiple myeloma (MM) damages the DNA of tumor cells and inhibits the expression of DNA polymerase, thereby affecting the replication capacity of highly proliferating malignant cells. However, standard-dose chemotherapy usually causes a powerful immunosuppressive effect (35,36). Ataxia telangiectasia mutated (ATM) is a serine-threonine kinase activated when cells are exposed to DNA double-strand breaks. ATM is involved in cell cycle regulation, apoptosis and DNA repair (37). Similar to ATM, Ataxia telangiectasia and Rad3-related protein (ATR) serves a vital role in cell cycle signal transduction and DNA damage response (38). In MM cells treated with doxorubicin and melphalan, CD155 was upregulated at both the protein and mRNA levels, depending on the activation status of the DNA damage sensors, ATM and ATR (36).

Secondly, it has been suggested that the Ras oncogene mediates the upregulation of CD155 via the Raf/MEK/ERK/activator protein-1 signaling pathway (39). Therefore, a MEK inhibitor can block the Ras-mediated activation of the CD155 promoter. Additionally, it has been demonstrated that fibroblast growth factor also upregulates the expression of CD155 via the same signaling pathway (39).

Thirdly, sonic hedgehog (Shh), a vital morphogen, is co-expressed in the same locations with CD155 during development. The Shh signaling pathway serves an important role in cell differentiation and proliferation (40). Abnormal activation of Shh-Gli has been associated with different types of human cancer (40,41). A previous study indicated that treatment of human NTERA-2 cells with purified Shh protein upregulated the mRNA expression of CD155 (42).

Fourthly, immune cells expressing CD155 have been detected in primary tumors and tumor-infiltrating leukocytes of the draining lymph nodes; however, it seems to be mainly limited to myeloid cells (43). Stimulation of murine bone marrow-derived macrophages and B lymphocytes with lipopolysaccharide (LPS) has been indicated to upregulate the NF-κB-dependent CD155 expression *in vitro* (44-46). Furthermore, Toll-like receptor agonists, including LPS, have been reported to increase the expression of CD155 in dendritic cells (DCs) (47).

High expression of CD155 is associated with the invasive and migratory abilities of tumor cells. Focal adhesions are composed of integrins and related cytoplasmic plaque proteins, including talin, vinculin, α-actin, tenascin and paxillin and numerous protein kinases. Integrins interact with the extracellular matrix (ECM) (48). *In vitro*, ECM proteins bind to CD155, suggesting that CD155 may mediate cell-matrix interactions (20). Stimulation of CD155α with its ligand has been indicated to promote the Src kinase-mediated phosphorylation of ITIM, focal adhesion kinase (FAK) and paxillin, ultimately inhibiting cell adhesion and enhancing cell proliferation. The activation of CD155α also enhanced the platelet-derived growth factor (PDGF)-mediated cell migration. Taken together, these findings indicated that CD155 could regulate cell adhesion and movement (Fig. 2A) (18). CD155, PDGF receptor and integrin αvβ3 synergistically participate in the formation of a ternary complex on the leading edge of a cell (49-51). Ternary complexes serve a vital role in the dynamics of the leading edge. It has been demonstrated that this ternary complex promotes the activation of Src and DNA-binding protein RAP1, which in turn activates Rac and inhibits RhoA, thereby resulting in improved cell movement (16). In addition, a previous study has revealed that CD155 could regulate cell proliferation via enhancing the activation of the Ras/Raf/MEK/ERK signaling pathway (22). Protein sprouty homolog 2 (SPRY2) is a negative regulator of the growth factor-induced cell proliferation (52,53). SPRY2 is phosphorylated by the Src kinase following growth factor signaling, thereby inhibiting the activation of growth factor-induced Ras signals (52). CD155 prolongs the activation of the proliferation-associated signals induced by the inhibition of SPRY2, which is a negative regulator of the Ras/Raf/MAPK signaling pathway involved in the regulation of organogenesis, differentiation, cell migration and proliferation (54). As illustrated in Fig. 2B, SPRY2 can be released from CD155 and phosphorylated by Src to inhibit the Ras pathway and cell proliferation (16).

Additionally, CD155 promotes tumor growth. A previous study has demonstrated that CD155 enhanced the activation of the serum-induced Ras/Raf/MEK/ERK signaling pathway, upregulated cyclin D2 and E, downregulated p27Kip1 and finally inhibited the G_0/G_1 cell cycle arrest of NIH3T3 cells (Fig. 2C) (22). Furthermore, knockdown of CD155 reduced the size and weight of tumors in colon cancer models and attenuated the metastasis rate of tumors in several other mouse tumor models (6,43,55).

Table I. Expression of CD155/TIGIT in human cancers.

First author, year	Tumor type	Role	Clinical significance	(Refs.)
Bevelacqua *et al*, 2012	Melanoma	Knockout CD155, cell invasion ability is reduced	Positive: Lymph node metastasis, Breslow thickness	(26)
Nakai *et al*, 2010	Lung adenocarcinoma	-	Positive: Lymph node metastasis, TNM staging, bronchioloalveolar carcinoma ratio of tumors	(27)
Nishiwada *et al*, 2015	Pancreatic cancer	Knockout of CD155, cell proliferation is inhibited	Positive: Intra-tumoral micro vessel density; Negative: $CD4^+$ T, $CD8^+$ T, $CD45^+$	(28)
Smazynski *et al*, 2020	Ovarian cancer	-	There was a negative correlation between CD155 expression and immune infiltrating cells	(29)
Pende *et al*, 2019	Acute myeloid leukemia	-	CD155 expression promotes NK cell lysis	(30)
Gromeier *et al*, 2000	Malignant glioma	-	-	(31)
Huang *et al*, 2017	Cholangiocarcinoma	-	Positive: Vascular endothelial growth factor, microvessel density; Negative: Overall survival, disease-free survival	(32)
Wu *et al*, 2019	Head and neck squamous cell carcinoma		Negative: Overall survival	(33)
Iguchi-Manaka *et al*, 2016	Gastric cancer	-	Positive: Tumor stage	(34)
Kong *et al*, 2016	Acute myeloid leukemia	Knockdown of TIGIT, $CD8^+$ T lymphocyte apoptosis is inhibited, toxicity is increased	Positive: Primary refractory disease, leukemia relapse post-alloSCT	(58)
Chauvin *et al*, 2015 and Lee *et al*, 2019	Melanoma	TIGIT blockade enhances the production ofcytokines, promotes the proliferation of $CD8^+$ cells, increases the blocking effect of PD-1	Positive: PD-1 expression, deeper Breslow thickness, lymph node involvement, advanced stage of disease	(59,61)
Guillerey *et al*, 2018	Multiple myeloma	TIGIT blockade enhances the toxicity of $CD8^+$ T cells	Positive: Tumor progression	(60)
O'Brien *et al*, 2019	Non-small cell lung cancer	$CD8^+$ $TIGIT^+$ are highly prevalent among TILs and PBMCs in tumor patients	-	(62)
He *et al*, 2017	Gastric cancer	$CD8^+$ $TIGIT^+$ cell function failure, activation is weakened, proliferation is decreased, metabolism is impaired	-	(63)
Zhang *et al*, 2020	Hepatocellular Carcinoma	TIGIT blockade or CD155-knockdown reversed the inhibitory effect of Hepatocellular Carcinoma HCC cells on CD8 T-cell effector function	-	(64)
Degos *et al*, 2019	Endometrial Cancer	-	Positive: Lymph node metastasis	(70)

TIGIT, T cell immunoreceptor with Ig and ITIM domains; PD-1, programmed cell death-1; alloSCT, allogeneic stem cell transplantation; NK, natural killer; TIL, tumor-infiltrating lymphocyte; TNM, tumor, node and metastasis.

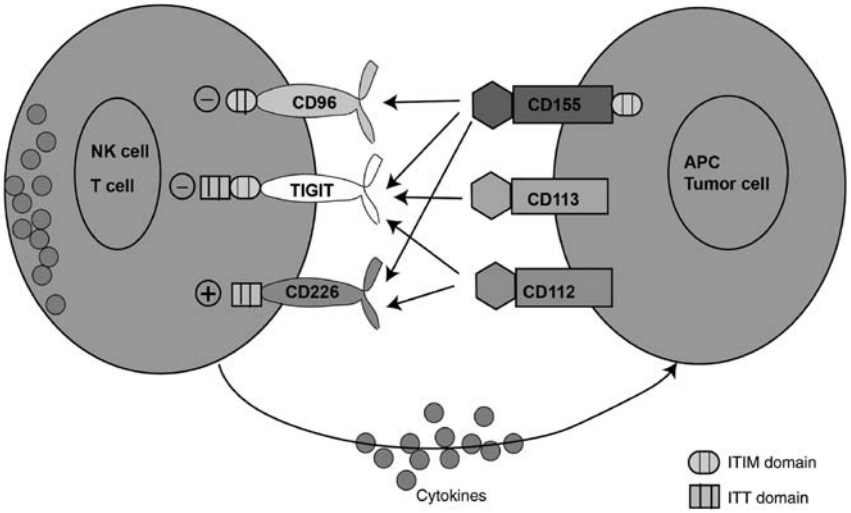

Figure 1. CD155 and TIGIT pathway. TIGIT, CD226 and CD96 are mainly expressed on T and NK cells. CD155, CD112 and CD113 are TIGIT ligands and are expressed on APCs or tumor cells. TIGIT binds to CD155 and transmits inhibitory signals via its cytoplasmic tail. CD96 can interact with CD155 to transmit inhibitory signals, while CD226 transmits activation signals into cells via its cytoplasmic tail after interacting with CD155. TIGIT, T cell immunoreceptor with Ig and ITIM domains; APC, antigen-presenting cell; NK, natural killer; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITT, immunoglobulin tail tyrosine; -, inhibition, +, activation.

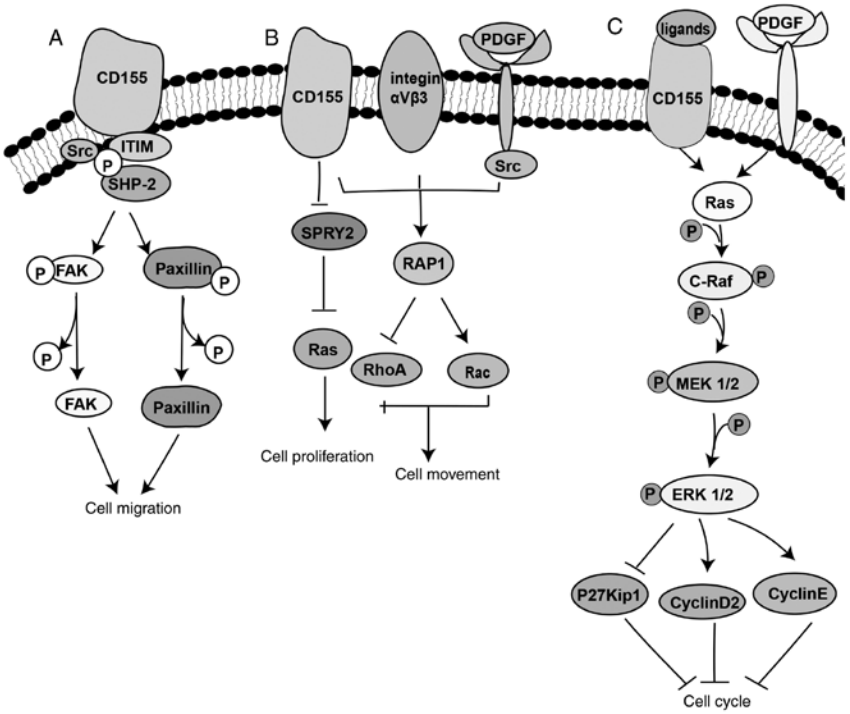

Figure 2. CD155 serves a crucial role in tumor cell invasion, migration and proliferation. (A) CD155 is phosphorylated by members of the Src kinase family, and SHP-2 is recruited into the plasma membrane. FAK is then dephosphorylated and its kinase activity is inhibited, leading to reduced cell adhesion and enhanced cell migration. (B) CD155, integrin αvβ3 and PDGF receptor form a ternary complex on the front edge of mobile cells, leading to Rac activation and RhoA inhibition. The ternary complex inhibits SPRY2 and enhances cell proliferation by inducing the activation of Ras-mediated signal transduction pathways. (C) CD155 accelerates the cell cycle via the Ras/Raf/MEK/ERK pathway. CD155 enhances Ras/Raf/MEK/ERK signaling, leading to upregulation of cyclin D2 and E and downregulation of p27Kip1. This decreases the G_0/G_1 phase of the cell cycle. FAK, focal adhesion kinase; PDGF, platelet derived growth factor; SPRY2, protein sprouty homolog 2; ITIM, immunoreceptor tyrosine-based inhibitory motif.

4. Structure of TIGIT

To identify costimulatory or inhibitory molecules on activated human T cells, Yu *et al* (24) conducted a genome search to recognize genes with immunomodulatory receptor protein domains in T helper (Th)17 cells. They identified a specific gene expressed on T and NK cells, which encoded a protein containing variable immunoglobulin domains and an ITIM, which was named TIGIT. It is considered that TIGIT is an inhibitory receptor mainly expressed on NK, $CD8^+$ T, $CD4^+$ T cells and Tregs (24). TIGIT consists of an extracellular immunoglobulin variable domain, a type I transmembrane

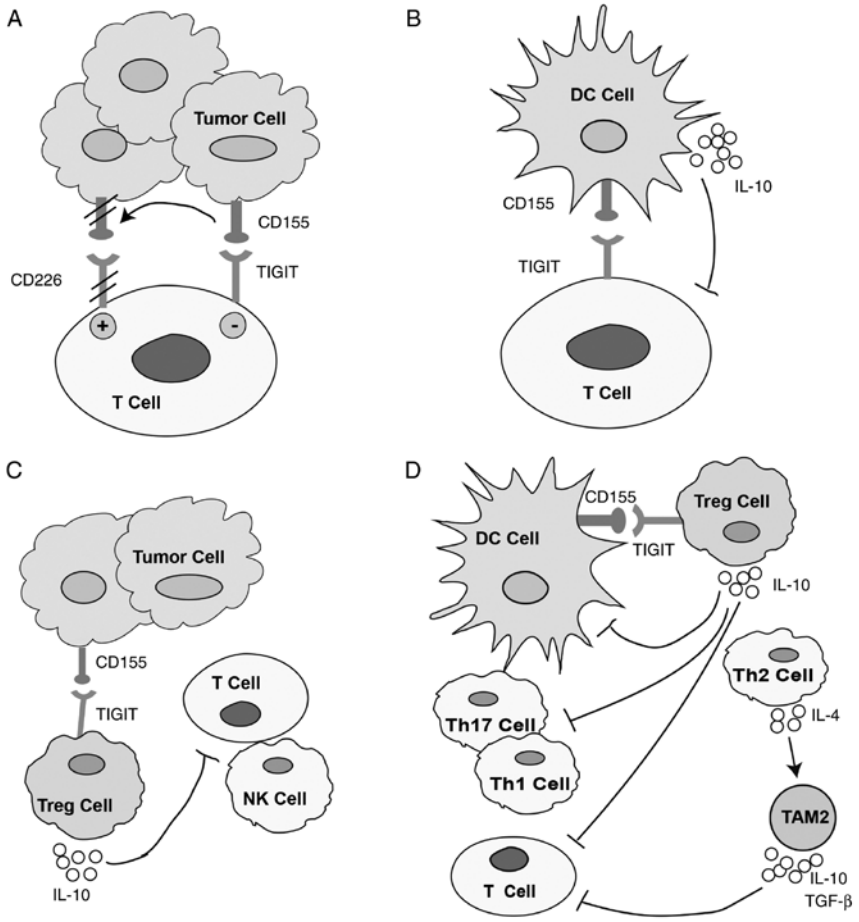

Figure 3. Inhibitory mechanism of effector T cells and NK cells mediated by CD155/TIGIT. (A) TIGIT engagement directly inhibits T cell activation and limits CD226 activity. (B) TIGIT interacts with CD155 expressed on DCs and inhibits their function, resulting in impaired T cell function. (C) TIGIT$^+$ Tregs can suppress CD8$^+$ T cell effector function. (D) TIGIT$^+$ Tregs may suppress the function of T cells and DCs. TIGIT$^+$ Tregs inhibit the development of both Th1 and Th17 cell responses. Th2 cells promote TAM2 differentiation and inhibit T cell function. TIGIT, T cell immunoreceptor with Ig and ITIM domains; DC, dendritic cell; NK, natural killer; Treg, T regulatory; Th, T helper; TAM2, type 2 tumor-associated macrophages.

domain, a short intracellular domain with an ITIM and an immunoglobulin tail tyrosine (ITT)-like motif (24). It has been indicated that TIGIT can bind to three ligands on tumor cells, namely CD155, CD112 and CD113. CD155 is a high-affinity ligand of TIGIT (Fig. 1) (24,56). TIGIT acts as a receptor for PVR and induces intracellular signaling, while it may serve as a competitive inhibitor of CD226 (24,56).

5. Role of TIGIT in malignant tumors

It has been reported that TIGIT is upregulated in tumor-infiltrating lymphocytes (TILs) in acute myeloid leukemia (AML), melanoma, multiple myeloma, non-small cell lung cancer, gastric cancer and hepatocellular carcinoma (56-64). It has been demonstrated that the expression of TIGIT was upregulated in CD8$^+$ T lymphocytes and tumor-infiltrating Tregs and NK cells (65-67). TIGIT has been associated with poor clinical outcomes in cancer. For example, the expression of TIGIT in TILs of patients with melanoma and CD8$^+$ T cells in the peripheral blood of patients with gastric cancer was associated with tumor metastasis and poor survival (62,68,69). Furthermore, a strong association between the expression of TIGIT on CD8$^+$ T cells in the peripheral blood and the recurrence of AML after transplantation has been revealed (58). In addition, a recent study on endometrial cancer demonstrated that the high expression of TIGIT on tumor-infiltrating NK cells was positively correlated with the severity of the disease (Table I) (70).

6. TIGIT suppresses the immune response

Currently, several mechanisms of the CD155/TIGIT-mediated inhibition of effector T and NK cells have been discovered. Immunoactivating receptor CD226 is a co-stimulatory molecule expressed on NK cells, T lymphocytes, monocytes and B cells, which competes with TIGIT for binding with CD155 (71). TIGIT directly interacts with CD226 on the cell surface and attenuates the ability of CD226 to form homodimers. These results indicate that TIGIT can reduce the activity of CD226 during the anti-tumor and anti-viral T cell response (57). In NK cells, TIGIT has been demonstrated to mediate inhibitory signals via ITIM (56), while its engagement could directly inhibit T cell activation and proliferation (Fig. 3A) (55,71,72). CD155 is also expressed on DCs. It has been suggested that the CD155-TIGIT interaction can regulate T cell-driven immune responses via inducing interleukin IL-10 expression in DCs. Furthermore, TIGIT-modified mature DCs can promote the production of IL-10 and attenuate that of IL-12 (Fig. 3B) (24).

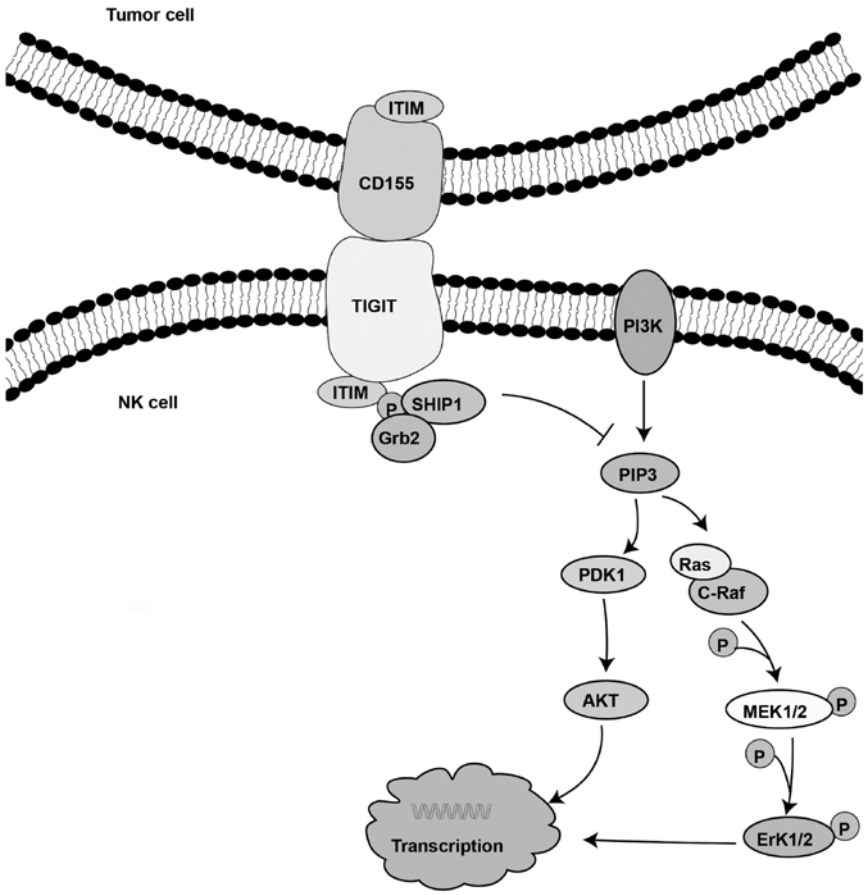

Figure 4. Inhibitory effect of CD155/TIGIT on PI3K/MAPK signaling. When CD155 binds to TIGIT, ITIM is phosphorylated and binds to cytosolic adaptor Grb2, which recruits SHIP1 to inhibit PI3K and MAPK signaling, resulting in the attenuation of NK cell function. TIGIT, T cell immunoreceptor with Ig and ITIM domains; NK, natural killer; ITIM, immunoreceptor tyrosine-based inhibitory motif; Grb2, growth factor receptor-bound protein 2; SHIP-1, SH2-containing inositol phosphatase-1; PDK-1, phosphoinositide-dependent protein kinase-1; PIP3, phosphatidylinositol (3,4,5)-trisphosphate.

TIGIT is also highly expressed in Tregs (66). Indeed, it has been revealed that compared with TIGIT$^-$ Tregs, the inhibitory effect of TIGIT$^+$ Tregs was enhanced. In addition, TIGIT$^+$ Tregs were indicated to produce a higher amount of the immunosuppressive cytokine IL-10 compared with TIGIT$^-$ Tregs, which not only contributed to immunosuppression in the tumor microenvironment but also promoted a tolerogenic phenotype in DCs (Fig. 3C) (73). Additionally, IL-10 and fibrinogen-like protein 2 (Fgl2) secreted by TIGIT$^+$ Treg cells could synergistically inhibit the secretion of IL-12 and IL-23 by activated DCs, thereby inhibiting the Th1 and Th17 immune responses (73). It has been also demonstrated that TIGIT$^+$ Treg cells secreted high amounts of Fgl2, resulting in the inhibition of Th1 and Th17 cell differentiation, but not Th2 differentiation (73-74). Th2 cells can promote type 2 tumor-associated macrophage (TAM2) differentiation by secreting IL-4. Therefore, it was demonstrated that TAM2 suppressed T cell immune responses via secreting inhibitory cytokines, such as IL-10 and TGF-β, and depleted nutrients in the microenvironment via secreting arginase 1 (Arg1), indoleamine 2 and 3-dioxygenase, further weakening T cell function (Fig. 3D) (75).

Inhibitory effect of CD155/TIGIT on PI3K/MAPK signaling. TIGIT expressed on NK cells binds with its ligand on tumor cells to directly inhibit NK cell toxicity (56). It has been reported that the decreased NK cell activity is mediated by the phosphorylation of the ITT-like domain of the cytoplasmic tail of TIGIT. Following binding of TIGIT to its ligand, the ITT-like motif is phosphorylated at Tyr225. Subsequently, the complex binds to the cytosolic adaptor growth factor receptor-bound protein 2 (Grb2) and recruits SH2-containing inositol phosphatase-1 (SHIP-1), which in turn promotes signal inhibition, thereby attenuating the cytotoxic activity of NK cells (76). It has also been demonstrated that TIGIT recruits SHIP-1 to prematurely terminate the activation of AKT, ERK and MEK, thereby inhibiting NK cell cytotoxicity (Fig. 4) (76).

Inhibitory effect of CD155/TIGIT on NF-κB signaling. β-arrestins are common inhibitory protein. The interaction of β-arrestins and with their partners can regulate cell positioning, translocation and stability, while they are also involved in the regulation of the immune response (77). Emerging evidence has suggested that IκBα can directly interact with β-arrestin 2 to prevent phosphorylation and degradation of IκBα (77). Furthermore, TNF receptor-associated factor 6 (TRAF6) serves an important role in NF-κB signal transduction (77-79). Therefore, a previous study demonstrated that β-arrestin 2 could bind to the ITT-like motif of phosphorylated TIGIT, recruit SHIP-1 and reduce TRAF6 autoubiquitination, thereby preventing NF-κB activation and inhibiting IFN-γ production. However, SHIP-1 silencing could restore IFN-γ production (Fig. 5A) (77).

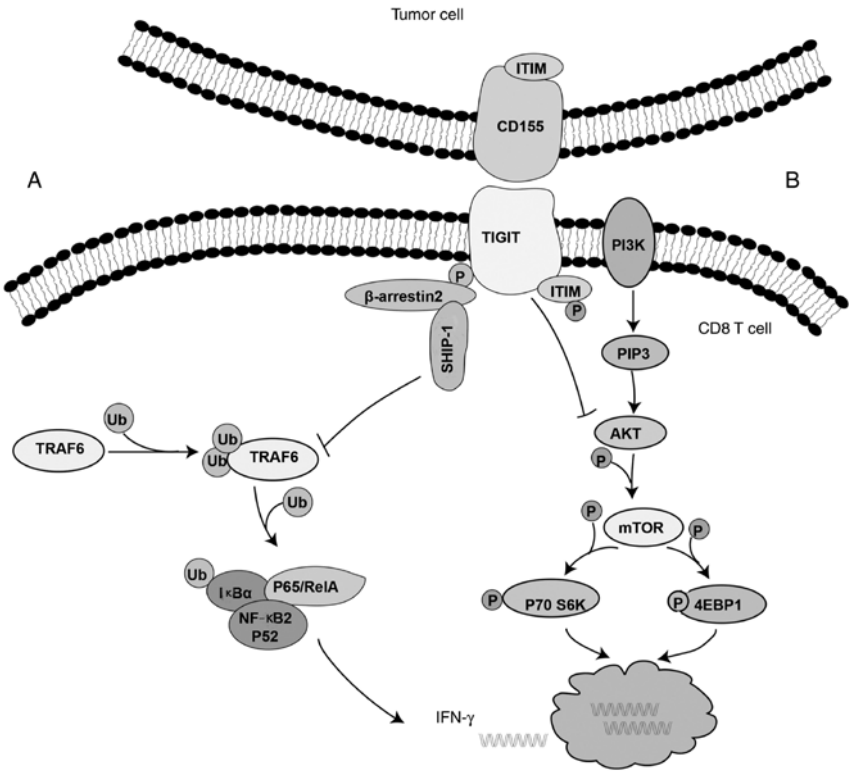

Figure 5. Inhibitory effect of CD155/TIGIT on AKT/mTOR and NF-κB signaling. (A) Following CD155 binding to TIGIT, cytoplasmic TIGIT is phosphorylated. Phosphorylated TIGIT recruits β-arrestin 2, which subsequently recruits SHIP1. SHIP1 reduces TRAF6 autoubiquitination to inhibit NF-κB activation, and ultimately inhibit IFN-γ production in NK cells. (B) Phosphorylated TIGIT following interaction with CD155 inhibits AKT, p70S6K and 4EBP1 phosphorylation in $CD8^+$ T cells. This causes the inhibition of $CD8^+$ T cell metabolism and cytokine production. TIGIT, T cell immunoreceptor with Ig and ITIM domains; ITIM, immunoreceptor tyrosine-based inhibitory motif; SHIP-1, SH2-containing inositol phosphatase-1; PIP3; phosphatidylinositol (3,4,5)-trisphosphate; TRAF6, TNF receptor-associated factor 6; 4EBP1, 4E binding protein 1; K, kinase.

Inhibitory effect of CD155/TIGIT on AKT/mTOR signaling. It has been reported that the CD155/TIGIT interaction reduces the activation of the AKT/mTOR pathway, resulting in the inhibition of metabolism and cytokine production. In a co-culture system of the human gastric cancer cells SGC7901 with $CD8^+$ T cells, downregulation of CD155 in SGC7901 cells increased the phosphorylation of AKT, p70S6 kinase and 4E binding protein 1 in $CD8^+$ T cells (63). In addition, glucose uptake, lactic acid production and IFN-γ secretion were also increased. Furthermore, TIGIT has been indicated to inhibit the metabolic pathway in $CD8^+$ T cells (63). TIGIT blockade was demonstrated to promote the activation of the AKT/mTOR pathway, leading to metabolism upregulation and cytokine production in $CD8^+$ T cells. These findings indicated that CD155/TIGIT signaling in $CD8^+$ T cells reduced the activation of the AKT/mTOR pathway, thereby resulting in metabolism downregulation and suppression of cytokine production (Fig. 5B) (63).

7. TIGIT immunotherapy

In mouse tumor models, TIGIT deficiency significantly attenuated the proliferation of B16F10 melanoma and MC38 colon cancer cells, compared with wild-type controls (65). In addition, a recent study has demonstrated that the serum levels of monoclonal immunoglobulin proteins in TIGIT-deficient mice increased, thus reducing the tumor burden and prolonging the survival period of mice, suggesting that TIGIT inhibited the anti-tumor responses in multiple myeloma. Importantly, blocking TIGIT with monoclonal antibodies could enhance the function of $CD8^+$ T effector cells and inhibit the development of multiple myeloma (60). Furthermore, it was demonstrated that treatment with anti-TIGIT could significantly delay tumor growth in a mouse model of transgenic head and neck squamous cell carcinoma and enhance the anti-tumor immune response via activating $CD8^+$ T effector cells and reducing the number of Tregs. *In vitro*, co-culture studies revealed that anti-TIGIT treatment could significantly eliminate the immunosuppressive ability of myeloid suppressor cells via downregulating Arg1 and preventing Treg inhibition by reducing the secretion of TGF-β1 (33). In AML, TIGIT downregulation using the small interfering RNA technology, could inhibit the immunosuppressive effect of $TIGIT^+$ $CD8^+$ T cells in the blood, thereby resulting in increased secretion of IFN-γ and TNF-α and decreased apoptosis (58).

8. Anti-TIGIT combination immunotherapy

A clinical trial has indicated that the mismatch repair status can predict the clinical benefit of treatment with the anti-PD-1 mAb pembrolizumab. However, one third of patients still did not respond to anti-PD-1 therapy (80). Preclinical studies on the effect of TIGIT on regulating anti-tumor immune responses indicated that TIGIT combined with current immunotherapy was a promising target. For example, it has been suggested that a combined treatment approach with TIGIT and PD-1 or T-cell immunoglobulin mucin receptor 3 (TIM-3) on malignant

Table II. Currently registered clinical trials.

Trial sponsor	Agent	Clinicaltrials.gov identifier	Type of trial	Combination immunotherapy	Condition or disease
Multiple myeloma Research Consortium	TIGIT inhibitor (BMS-986207)	NCT04150965	Phase I/II	Elotuzumab, anti-LAG3 antibody (BMS-986016)	Multiple myeloma, relapsed refractory multiple myeloma
Innovent Biologics (Suzhou) Co., Ltd.	Anti-TIGIT antibody (IBI939)	NCT04353830	Phase I	Anti-PD-1 antibody (Sintilimab)	Advanced malignancies
Compugen Ltd.	TIGIT inhibitor (COM902)	NCT04354246	Phase I	-	Advanced cancer
Compugen Ltd.	TIGIT inhibitor (BMS-986207)	NCT04570839	Phase I/II	Anti-PD-1 antibody (nivolumab), anti-PVR antibody (COM701)	Endometrial neoplasms, ovarian cancer, solid tumors
Hoffmann-La Roche	Anti-TIGIT antibody (tiragolumab)	NCT04543617	Phase III	Anti-PD-1 antibody (atezolizumab)	Esophageal squamous cell carcinoma
BeiGene	Anti-TIGIT antibody (BGB-A1217)	NCT04047862	Phase I	Anti-PD-1 antibody (tislelizumab)	Metastatic solid tumors
Genentech, Inc.	Anti-TIGIT antibody (MTIG7192A)	NCT03563716	Phase II	Anti-PD-1 antibody (atezolizumab)	Non-small cell lung cancer
EMD Serono, Inc.	TIGIT inhibitor (M6223)	NCT04457778	Phase I	Anti-PDL1/TGF-β antibody (bintrafusp alfa)	Metastatic solid tumors
Hoffmann-La Roche	Anti-TIGIT antibody (tiragolumab)	NCT04256421	Phase III	Anti-PD-1 antibody (atezolizumab), carboplatin, etoposide	Small cell lung cancer
Hoffmann-La Roche	Anti-TIGIT antibody (tiragolumab)	NCT04294810	Phase III	Anti-PD-1 antibody (atezolizumab)	Non-small cell lung cancer

TIGIT, T cell immunoreceptor with Ig and ITIM domains; PD-1, programmed cell death-1; PDL1, programmed death-ligand 1; PVR, poliovirus receptor; LAG3, lymphocyte-activation gene 3.

tumors was more beneficial compared with a single-targeted one (11,65). Treatment of patients with TIGIT/PD-1 co-blockade also enhanced the expansion and cytotoxicity of $CD8^+$ T cells in gastric cancer (63), non-Hodgkin lymphoma (81) and glioblastoma (82) compared with a single blockade therapy. Furthermore, the combination of anti-TIGIT therapy with other immune checkpoint inhibitors has been also examined in mouse models. For instance, treatment of $TIGIT^{-/-}$ mice with anti-TIM-3 antibodies significantly reduced tumor growth compared with $TIGIT^{-/-}$ deficiency alone (65). Blocking TIGIT could also increase the cytokine expression (such as TNF-α, IFN-γ and IL-2) of $TIGIT^+$ cells; however, this was less effective than the combined blockade of TIGIT, PD-1 and TIM-3 (83).

9. Conclusion

Immunotherapy can provide an important anti-tumor response in patients with advanced and metastatic tumors. However, even in sensitive types of tumors, a large proportion of patients does not respond to these therapies. Therefore, novel immune targets as a supplement to immunotherapy are urgently needed. TIGIT is considered a promising target that exhibits an immunomodulatory role in several processes involved in carcinogenesis (84). It is hypothesized that the combined application of anti-TIGIT and anti-PD-1 will have a synergistic effect similar to that of the combined application of anti-PD-1 and anti-CTLA-4 antibodies in melanoma, which can increase the response rate to therapy (85). A growing number of preclinical studies have indicated that combining anti-TIGIT with other immunological agents can increase the anti-tumor response in patients (Table II). Therefore, more favorable results in future studies based on the application of anti-TIGIT therapy are anticipated.

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Availability of data and materials

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Authors' contributions

LL wrote the manuscript; XWY and YS designed and drew the figures; SH and JHZ edited the figures; YZZ conceived and designed the study. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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