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# Pathway Analysis of Tumor Immunity by TIGIT and Recent Scientific Research Results

Xiaoyuan Liu *

Department of Life Sciences, Hebei Agricultural University, Hebei, 071000, China

* Corresponding author: danghui@ldy.edu.rs

**Abstract.** The T cellular immune receptor with immunoglobulin and TIGIT, an immunoreceptor tyrosine-based inhibitory motif, is a recently identified immune checkpoint molecule primarily found on the outer membrane of T cells and natural killer (NK) cells. It is mediated by binding to ligands such as CD155 inhibits T and NK cells' Immune response and influences of tumor microenvironment. At present, many studies have identified the main pathway and mechanism of TIGIT control, and some drug companies have developed anti-Tigit drugs and put them into clinical trials. The application of TIGIT antibody to the treatment of malignant tumors has shown broad prospects in tumor immunotherapy. However, many studies have limitations, The research on TIGIT is less extensive and detailed compared to PD-1/PD-L1, and there is still uncertainty regarding the impact of the TIGIT pathway on various cancers, which requires further investigation by researchers. This study examined previous research on the structure and pathway of TIGIT, and successfully identified the structure of TIGIT and the ligands associated with its primary pathway. Based on the research on its signaling pathway and the results of its clinical trials in some cancers, the paper summarized its four main pathways, three mechanisms of action and recent research results. On this basis, I put forward my personal speculation. This paper focuses on the structural composition, ligand types and pathway analysis of TIGIT, providing a basic reference for further exploration of the action pathway of TIGIT in the future. However, the summary of the TIGIT pathway is not complete and needs further exploration by researchers.

**Keywords:** TIGIT; CD155; tumor cell; regulatory t cells; immune checkpoint.

## 1. Introduction

In the field of tumor treatment, there has been a significant advancement in recent years with the introduction of immunotherapy [1]. Immunotherapy enhances the ability of the host's immune system to respond to tumor antigens and boost anti-tumor activity by inhibiting the interaction between inhibitory receptors on immune cells and inhibitory ligands on tumor cells. This approach, also known as immune checkpoint targeted therapy, is currently at the forefront of tumor therapy research. Targeting immune checkpoints such as programmed death receptor 1 (PD-1)/ programmed death ligand 1 (PD-L1) or cytotoxic T lymphocyte-associated protein 4 (CTLA-4) in tumor immunotherapy has shown significant clinical effectiveness, although the overall response rate is limited. Therefore, there is an urgent need to identify new immune checkpoints that offer higher overall response rates. In 2009, the discovery of T-cell immunoglobulin and immunoreceptor tyrosine inhibitory motif structure (TIGIT) added a new immune checkpoint molecule to the field. [2]. Multiple research studies have discovered that TIGIT exhibits elevated expression levels within various tumor models and individuals affected by cancer, thus demonstrating an association with disease prognosis. The immune checkpoint mechanism assumes a crucial responsibility in governing immune functionality and upholding immune equilibrium [3]. Multiple research studies have discovered that TIGIT exhibits elevated expression levels within various tumor models and individuals affected by cancer, thus demonstrating an association with disease prognosis. The immune checkpoint mechanism assumes a crucial responsibility in governing immune functionality and upholding immune equilibrium. In addition, the role of other immune checkpoints in tumors cannot be ignored, and researchers are constantly discovering new immune checkpoints and exploring their mechanisms of action, which are constantly summarized through clinical trials. In the T cell immunoglobulin and ITIM domains,

it is an emerging immune checkpoint protein [4], which is mainly expressed in Tregs, activated T cells, and NK cells. Recent research has provided evidence that the TIGIT pathway is intricately connected to the formation and progression of cancerous growths. Taking aim at TIGIT or employing a strategy that obstructs the interaction between TIGIT and its ligand can effectively restore the levels of T cells that have been reduced. [5], which is represented by enhanced proliferation capacity, cytokine secretion capacity and cytotoxicity, thereby inhibiting tumor growth, and is highly likely to become a potential target for tumor immunotherapy, which is expected to make up for the shortcomings of the above-targeted therapies. In this review, the structure, expression, signaling pathway, immunomodulatory mechanism and immunotherapy of TIGIT and its ligands are reviewed. Organization of the Text

## 2. TIGIT Domain

### 2.1. TIGIT structure

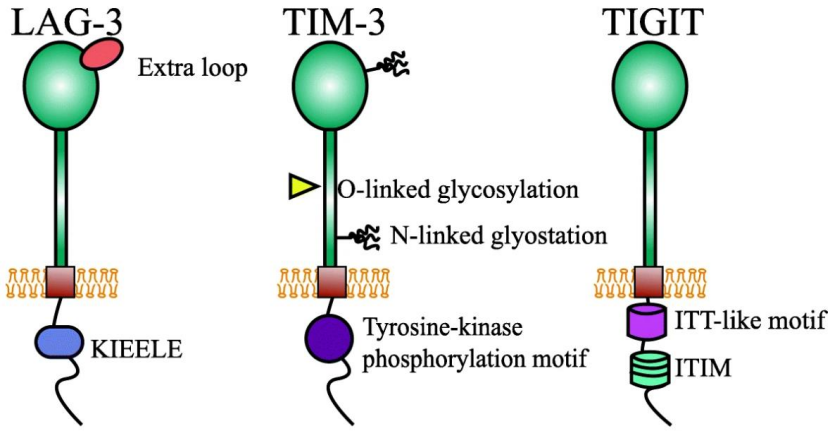


**Figure 1.** TIGIT structure diagram [6]

As shown in Figure 1, Liu et al. clearly pointed out the structure of TIGIT [7] ligands and expression sites. TIGIT comprises an extracellular domain that has an immunoglobulin variable domain, a transmembrane domain of type I, and a short intracellular domain that contains an immunoreceptor tyrosine inhibitory motif (ITIM) as well as an immunoglobulin tyrosine tail (ITT)-like motif. By means of its cytoplasmic tail's ITIM structure, TIGIT has the ability to transmit inhibitory signals to both NK cells and T cells. The main expression of TIGIT occurs in CD4+ T cells, CD8+ T cells, and NK cells, and it interacts with a variety of receptors in order to regulate immune system functionality.

### 2.2. Receptor and expression

In order to get a clearer picture of the complex regulatory network involved in TIGIT,this paper refer to the research results of Zhu Zhu et al., and conclude that TIGIT is involved in a sophisticated regulatory network that includes several inhibitory receptors (including CD96 and CD112R), one competitive co-stimulatory receptor (CD226), and multiple ligands (such as CD155 and CD112). The inhibitory receptor and co-stimulatory receptor both compete for the same ligand, illustrating the intricate regulatory network of TIGIT. [3]. TIGIT-related ligand structure (FIG. 2) [8]. There are three main ligand types of TIGIT. The terms used to refer to cluster of differentiation 155 (CD155), CD112 and CD113 remain the same.[9]. Among them, CD155 is the homologous ligand with the highest affinity for TIGIT in humans and mice.

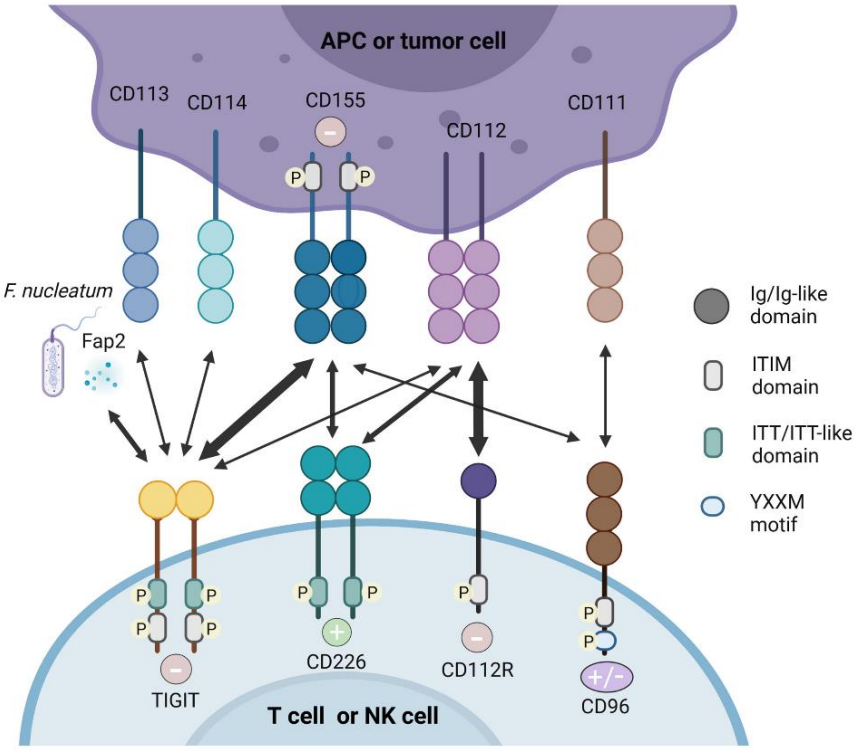


**Figure 2.** TIGIT ligands and their regulatory networks [8]

Also known as PVR, stalk protein-like protein 5 (Necl5) and tumor-associated glycoprotein E4 (Tage4). A crucial component in tumor development and progression is CD155, an adhesion protein that spans the cell membrane and falls under the immunoglobulin superfamily. CD155 comprises a transmembrane area, an extracellular region featuring three IG-like rings, and a cytoplasmic region. Specifically found on the surface of tumor cells or anti progenitor cells, CD155 actively stimulates cell proliferation and migration, thus contributing significantly to tumor formation and growth. Non-immune cells, such as those found in the kidney, lung, pancreas, and other areas, also express a small amount of CD155 on their surface. Oyama et al.'s research revealed a correlation between high levels of CD155 expression and the invasion and spread of lung cancer. Additionally, CD155-positive patients responded less favorably to PD-L1 inhibitors compared to those who were PD-L1 negative. Furthermore, increased CD155 expression was found to be indicative of a poor prognosis for patients. CD112, also known as PVR L2 and NECTIN-2, is expressed on antigen presenting cells and tumor cells, and is present on a wide range of cell types in both the hematopoietic and non-hematopoietic systems. It belongs to the nectin family.[9]. CD112 binds to the cluster of differentiation 112 receptor (CD112R) or TIGIT to inhibit T cell proliferation. CD113 is only expressed on the surface of non-hematopoietic cells. TIGIT has weak affinity with CD112 and CD113.

Dendritic cells (DC), T cells, B cells, and macrophages predominantly express CD155, and it is also found in non-hematopoietic tissues. Hematopoietic tissues show widespread expression of CD112, while CD113 is limited to non-hematopoietic tissues. Both CD155 and CD112 are significantly upregulated in various human malignancies [10].

### 2.3. Correlation path

After learning the above basic properties of TIGIT, this paper began to explore it signaling pathway. Four pathways related to tumor microenvironment were found and summarized after a lot of reference (Figure 3): 1) TIGIT binds to CD155 and directly inhibits the functions of T cells and NK cells; 2) When TIGIT binds to CD155 on dendritic cells (DC), it enhances the release of IL-10, a molecule that promotes immune suppression, while reducing the secretion of IL-12, a pro-inflammatory cytokine. Additionally, TIGIT hinders the functioning of T cells [2].

3) TIGIT exhibits a greater capacity to bind CD155 or disrupt the homologous dimer of CD226 compared to CD226 itself. This interference inhibits CD226-mediated activation of T cells. 4) TIGIT acts on regulatory T cells (Tregs) to enhance immunosuppressive function. It can be seen that the effect function of the immune pathway regulated by TIGIT is to inhibit the occurrence of immune response and promote the immune escape of tumor cells.

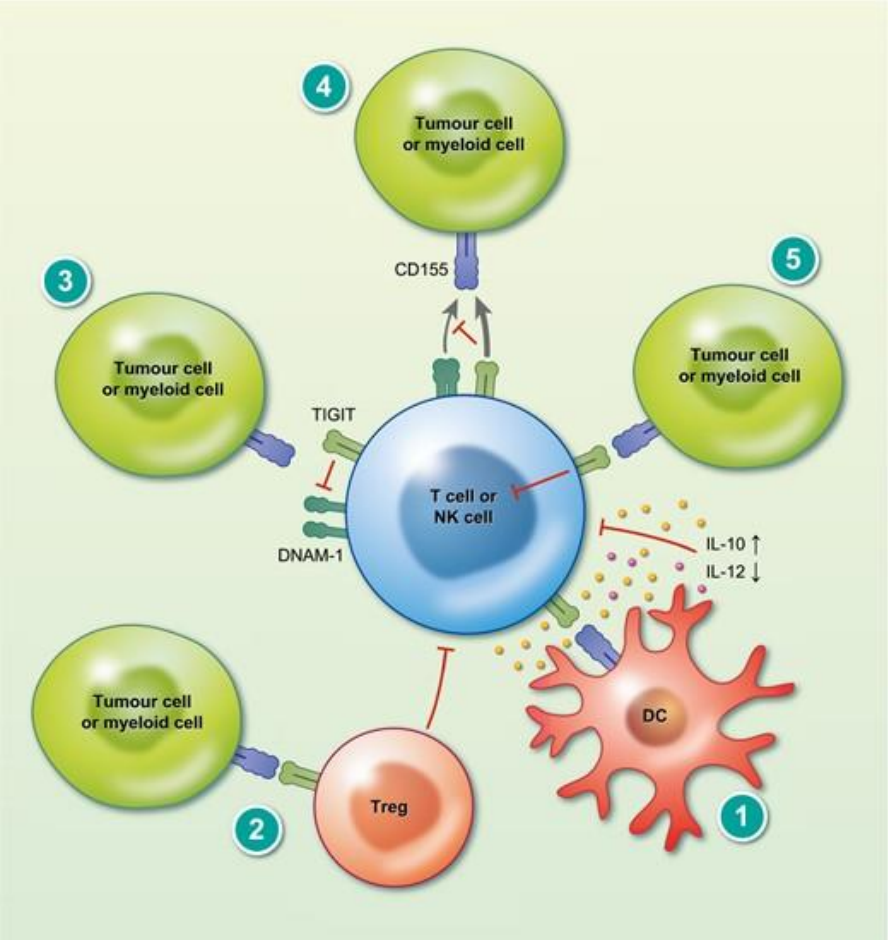


**Figure 3.** TIGIT pathways [2]

According to the above pathways, the immune regulatory mechanism of TIGIT can be analyzed, and three regulatory mechanisms of TIGIT inhibiting the normal work of the immune system can be summarized by referring to the findings of Zhu Zhu, Wang Rong, Wu Jieqiong et al:

1) TIGIT/CD155 exerts direct or indirect immunosuppressant effects. TIGIT acts indirectly on T cells by binding to CD155 on DC and regulating the cytokines produced by DC, resulting in immunosuppression [11]. Studies have found that TIGIT binds with CD155 of DC to promote the formation of immune-tolerant DC, reduce the expression of IL-12 and increase the secretion of IL-10, thus inhibiting the activation of T cells and inhibiting the production of INF-γ [12] Referring to the study of Zhou et al., it was found that IL-12, IFN-γ and IL-10 have feedback regulatory mechanisms: INF- boosts the synthesis of IL-12, while IL-10 can hinder the synthesis of IL-12.

Studies have found that the mobile antibody against TIGIT proves that TIGIT can directly inhibit T cell response independently of antigen presenting cells (APC) [11]. According to the microarray analysis of T cells, TIGIT has the ability to directly impact T cells by diminishing the activation signal generated by TCR, thus impeding the function and growth of T cells. Moreover, when the TIGIT/ poliovirus receptor (PVR) signaling pathway is activated, TIGIT's ITT-like motifs trigger the recruitment of GrB2 and SHIP-1, initiating negative signaling that diminishes cytokine production and the ability of NK cells to destroy CD155+ tumor cells.

2) By competing with the co-stimulating receptor CD226 for the CD155 receptor, TIGIT indirectly causes T cell failure, as it antagonizes CD226-mediated costimulatory signals. [13]. Research has demonstrated that CD226 is crucial in controlling the function of T cells mediated by TCR and that it attaches to CD155 and CD112 on the outer layer of cancer cells. It serves as a mediator for NK cells and CD8+ T cells in destroying tumor cells. CD226's co-stimulatory signals strengthen the secretion of INF- in naïve T cells, while the majority of INF- and IL-17 secreting cells exhibit elevated levels of CD226. Simultaneously, CD226 also joins with CD155, amplifying the capability of CD4+ T cells to generate pro-inflammatory substances. at the same time, TIGIT and CD226 interact directly on the cell surface, destroying the homologous dimer of CD226, making it unable to normally bind to CD155 [13]. These findings indicate that the expression of TIGIT and CD226 is crucial in determining the effector function of T cells and NK cells, promoting the rejection of tumors through T-cell activity.

3) TIGIT stimulates Treg to produce cytokines that can inhibit T cell proliferation [14]. Tregs are essential in maintaining T cell homeostasis and preventing autoimmune diseases, among other things. As an activated Treg subgroup, TIGIT+Treg has high expression of Treg characteristic genes, high inhibition and stability, and is enriched in tumors. After being activated, TIGIT-positive Tregs produced IL-10 and Fgl2, which enhanced the suppressive effect of cytokines on the proliferation of effector T cells. Additionally, it was observed that TIGIT expression in Tregs of melanoma patients was elevated, while the expression of CD226, a competing co-stimulatory receptor, was reduced. This resulted in an increased TIGIT/CD226 expression ratio, which exerted a certain regulatory influence on the immunosuppressive function and stability of Tregs. Blocking TIGIT by activating CD226 in Tregs prevented tumor development, suggesting a potential foundation for novel cancer therapies.

## 3. Recent research and speculation

### 3.1. Anti-Tigit monoclonal antibody therapy

Many immune checkpoints are activated by ligand-receptor interactions and are easily blocked by antibodies [15]. Studies have shown that anti-Tigit monoclonal antibody (mAb) therapy has great therapeutic potential in a wide range of malignant tumors [16]. Zhou et al. [17] used CT26 and MC38 subcutaneous tumor mouse models with TIGIT knockout and found that NK cells and CD8+ T cells had enhanced IFN-γ secretion, slowed down tumor growth, and prolonged survival. In both the E0771 breast cancer model and the methylcholine-induced fibrosarcoma model, it was observed that the administration of anti-Tigit mAb alone resulted in the delaying of tumor growth, decreased metastasis, enhanced survival rates, and the restoration of NK cells and CD8+ T cells that infiltrate the tumor. [16]. In a head and neck squamous cell carcinoma model, anti-Tigit mAb therapy delayed tumor growth by enhancing CD8+ T cell response and eliminating the immunosuppressive ability of Treg and MDSC [18]. In the multiple myeloma mouse model, TIGIT is highly expressed in 30% to 40% of fork-head transcription factor P3 (FOXP3) Treg cells, and the expression of TIGIT is correlated with myeloma burden. Targeting TIGIT can significantly reduce tumor burden [19].

### 3.2. Combination Therapy

Wu et al. 's related studies in head and neck squamous cell carcinoma (HNSCC) showed that TIGIT was abnormally highly expressed on tumor-infiltrating CD8 + and CD4 + T cells, and was correlated with PD-1 expression. Xu et al, in their study, found that CD155 was present in both tumor cells and mesenchymal immune cells [18]. Furthermore, they observed a correlation between CD155 expression and tumor pathological grade as well as lymph node metastasis. Patient survival rates were significantly lower in individuals with high levels of CD155 expression [20]. It was found that coexpression of TIGIT and PD-1 was detected on the surface of CD8+ TIL when analyzing relevant immune checkpoints in small cell lung cancer (SCLC). The co-expression of multiple immune inspection sites on T cells suggests that tumor cells can evade the attack of the immune system through multiple pathways, and it also means that drugs targeting these different pathways may have

synergistic anti-tumor effects. Yu et al. used anti-Tigit and PD-1 antibodies separately or in combination to treat CT26 model mice with colon cancer, and found that blocking with anti-Tigit or anti-PD-1 antibodies alone was not enough to inhibit tumor growth. However, anti-PD-1 /TIGIT dual antibody can significantly inhibit tumor growth [11].

### 3.3. Research on anti-Tigit drugs

mAb is the main type of anti-TIgit antibody drugs. The expert family WO2009126688, which was the first to publicly open TIGIT target, publicly opened TIGIT monoclonal antibody. The patent family has a total of 72 extended families, of which, the United States, Europe, and Japan have been granted protection. The claim granted by China to the isofamily (CN102057272B) is to claim protection against: an anti-Tigit antibody or its antigen-binding fragment containing six complementarity determining region with a specifically defined amino acid sequence. This is also the most important way to write the application for TIGIT monoclonal antibodies, that is, to define antibodies by CDR, the variable region refers to the sequences of amino acids or nucleotides in the heavy and light chains [21]. The use of a combination therapy involving antibodies and chemotherapy agents can often result in a synergistic effect and the targeting of multiple effects. This leads to a more effective treatment outcome. Compugen's patent application, WO2022069940, focuses on the combination therapy using anti-PVrig antibodies, anti-Tigit antibodies, and anti-PD-1 antibodies to treat various types of cancer. The specific composition and proportion of the antibody preparation are detailed in the patent claim. GENENTECH INC's patent application, WO2016011264, focuses on a method of treating cancer using TIGIT inhibitors in combination with antineoplastic agents, which can be chemotherapy agents, growth inhibitors, targeted therapeutic agents, T cells with chimeric antigen receptors, antibodies or their fragments that bind to antigens, antibody-drug conjugates, angiogenesis inhibitors, antitumor agents, cancer vaccines, adjuvants, or their combinations [21].

### 3.4. Future Outlook

Based on the above knowledge of the mechanism of action of TIGIT in immune regulation, the following clinical application is speculated:

1) According to the feedback regulation mechanism of IL-12, IFN-γ and IL-10, the content of IFN-γ in the internal environment can be supplemented externally, and the production of IL-12 can be increased through feedback regulation, thus reducing the secretion of IL-10, and the patient's T lymphocytes can be activated again; 2) According to the fact that TIGIT can destroy the dimer of CD155 and CD226, TIGIT inhibitors can be used to weaken the destruction of the dimer, thus reactivating the function of the immune system; 3) Cut off the signaling pathway between TIGIT and Treg, prevent Treg from producing IL-10 and Fgl2, and restore the function of the immune system.

## 4. Conclusion

In this paper, the structure, ligand, pathway and mechanism of action of TIGIT are comprehensively introduced, the recent drug production and scientific research results of TIGIT in cancer are summarized, and feasible treatment schemes are speculated based on the above knowledge. This article summarizes the above contents and provides basic theoretical support for the study of TIGIT, a summary of recent studies and personal prediction for readers' reference and innovation. The TIGIT pathway plays a significant role in the development and progression of tumors, making it a promising target for tumor immunotherapy. Therefore, it is crucial to study and investigate this pathway from various angles, including targeted therapy and combination chemotherapy. However, because a large number of receptors and ligands in the TIGIT pathway co-regulate TIGIT to regulate the immune system, more time and effort are needed to clarify this complex pathway. Moreover, the chemotherapeutic drugs and clinical studies targeting TIGIT are not comprehensive, and further drug development and multi-faceted clinical trials are still needed. It is hoped that researchers will break this difficulty as soon as possible, so that TIGIT pathway can become an effective target for cancer treatment, and fill the gap in immune pathway research in cancer treatment.

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