

The CD155-TIGIT Signaling Axis in NK Cell Immune Evasion in Tumors: Mechanisms, Synergy with TGF- β , and Combined Intervention Strategies

Shuyu Liu

Department of Clinical Medicine, Zhengzhou University, Zhengzhou, 450000, China

lsy17390990773@outlook.com

Abstract. Although significant progress has been made in cancer immunotherapy, the issue of immune resistance has become an increasingly important issue. NK cell dysfunction is the key factor contributing to poor treatment response. The CD155-TIGIT signaling axis serves as the core pathway mediating tumor cell immune evasion, however, the outcome of clinical trials concerning about T cell immunoreceptor with Ig and ITIM domains (TIGIT) blockade alone in Phase III settings has failed to meet expectations. It suggests the existence of synergistic inhibitory mechanisms. This review systematically integrates and finds that TGF- β not only directly suppresses NK cell function but also upregulates cluster of differentiation 155 (CD155) expression on tumor cells through both classical and non-classical pathways. Therefore, it is able to amplify TIGIT-mediated negative signaling. More notably, a positive feedback loop may exist between CD155 and TGF- β , mutually reinforcing each other to form an immunosuppressive circuit. The clinical challenges of TIGIT inhibitors highlight the need for combination intervention strategies. At present, the precise molecular mechanisms and general relevance of this feedback loop remain to be explored. Based on these gaps, this review discusses four key parts: the inhibitory effects of the CD155-TIGIT axis on NK cells; the dual suppressive mechanisms of TGF- β and their positive feedback loop; current clinical challenges in targeting these pathways; and combined intervention strategies of TIGIT/TGF- β bispecific antibodies. The aim is to provide theoretical guidance for optimizing NK cell-based cancer immunotherapy.

Keywords: NK Cells, Immune Escape, CD155-TIGIT, TGF- β , Immunotherapy.

1. Introduction

Cancer immunotherapy has made great progress and changed tumor treatment modalities. However, the issue of immune resistance has become a new challenge, and greatly reduces the effect of these therapies. NK cell dysfunction is the key reason for poor outcomes and low response rates. Therefore, understanding the causes and molecular mechanisms of NK cell dysfunction can help overcome immunotherapy resistance.

The CD155-TIGIT signaling axis is the major pathway in tumor immune evasion. CD155 is highly expressed on many tumor cells and delivers inhibitory signals when it binds to the TIGIT receptor on NK cells [1]. At the same time, the activating receptor CD226 competes with TIGIT for CD155 binding, forming a balance in immune regulation [2]. Monoclonal antibodies targeting TIGIT, such as Tiragolumab, showed promise in early-phase II trials (for example, the CITYSCAPE trial reported an 18.2% increase in objective response rate). However, later phase II trials (like SKYSCRAPER-01) did not meet expected results, with no significant improvement in overall survival [3]. This raises some key questions: Why is blocking the CD155-TIGIT axis alone not effective? Do other co-inhibitory pathways also play a role?

TGF- β is a key immunosuppressive factor in the tumor microenvironment. It not only directly suppresses NK cell function, but also increases CD155 expression on tumor cells through pathways such as Smad and ERK1/2 [4], further enhancing the inhibitory effect of the CD155-TIGIT axis. Importantly, recent studies suggest a possible interaction between the CD155-TIGIT axis and TGF- β : TGF- β upregulates CD155, and in turn, CD155 may boost TGF- β activity [5]. This suggests a positive feedback loop in which the two pathways reinforce each other and together lower NK cell

immune surveillance. However, this idea is still at an early stage of validation, and its general relevance and detailed molecular mechanisms need to be further studied.

Although two pathways mentioned have been reported, how they work together to suppress NK cells, the validation of the positive feedback loop, and the clinical translation of combined targeting strategies are still not systematically reviewed. Unlike previous reviews, this paper is the first to systematically integrate the cooperative inhibitory effects of the CD155-TIGIT axis and TGF- β on NK cells, and to propose a combined immunotherapy strategy targeting the positive feedback loop. Based on this, this paper summarizes combination strategies to provide a theoretical possibility for optimizing NK cell-based cancer immunotherapy.

2. Inhibitory Effect of the CD155-TIGIT Signaling Axis on NK Cell

2.1. Expression and Regulation of CD155 in Tumor Cells

CD155 is highly expressed in many types of tumor cells. For example, in a mouse model of pancreatic ductal adenocarcinoma (PDAC), CD155 expression was significantly higher than that of PD-L1 and was also much higher than its expression in healthy pancreatic tissue of mice. This suggests that CD155 may act as an immune evasion pathway independent of PD-L1 [1]. In hepatocellular carcinoma (HCC), deleting the CD155 gene helped the PD-L1/PD-1-targeted immunotherapy work better, further confirming the important role of CD155 in tumor immune evasion [6]. At the same time, several mechanisms in the tumor immune microenvironment regulate CD155 expression. For example, IL-22 not only acts on tumor cells to increase CD155 expression on the surface and promote tumor immune evasion, but also reduces immune killing by lowering CD226 expression on immune cells [7]. In addition, METTL1 increases the expression of PKM2 dimers by mediating methylation of PKM mRNA, and these dimers can also upregulate CD155 expression [8]. Since CD155 is the main ligand for TIGIT, its high expression provides the molecular basis for TIGIT-mediated NK cell inhibition.

2.2. Structure of TIGIT and Its Inhibitory Signaling Pathway

TIGIT, CD155, and CD226 all belong to the immunoglobulin superfamily. TIGIT is a co-inhibitory receptor mainly expressed on NK cells and T cells. Studies show that CD155 is highly expressed on the surface of circulating tumor cells (CTCs), and its binding to the TIGIT receptor on NK cells helps CTCs escape immune surveillance. Importantly, CTCs bind to TIGIT but not to other immune receptors such as CD96 or CD226 [9]. This suggests that the specific binding between CD155 and TIGIT plays a central role in tumor immune evasion.

2.3. Competitive Balance between TIGIT and the Activating Receptor CD226

CD226 is a co-stimulatory receptor. Studies have found that its expression is downregulated in non-small cell lung cancer [2], which is the opposite phenomenon of the high CD155 expression on tumor cells, suggesting a possible antagonistic relationship between the two. In addition, both tumor-infiltrating lymphocytes (TILs) and tumor cells can express TIGIT and CD226, but CD155 is expressed only on tumor cells. The cell type-specific expression of CD155 further supports an antagonistic relationship between CD155 and CD226 in the tumor microenvironment. Also, as mentioned earlier, IL-22 has opposite effects on CD155 and CD226: it upregulates CD155 expression and downregulates CD226 expression [7].

Therefore, it can be suggested that when the balance tilts toward CD226, immune surveillance is favored; when it tilts the other way, immune evasion is strengthened. The specific mechanism is shown in Figure 1.

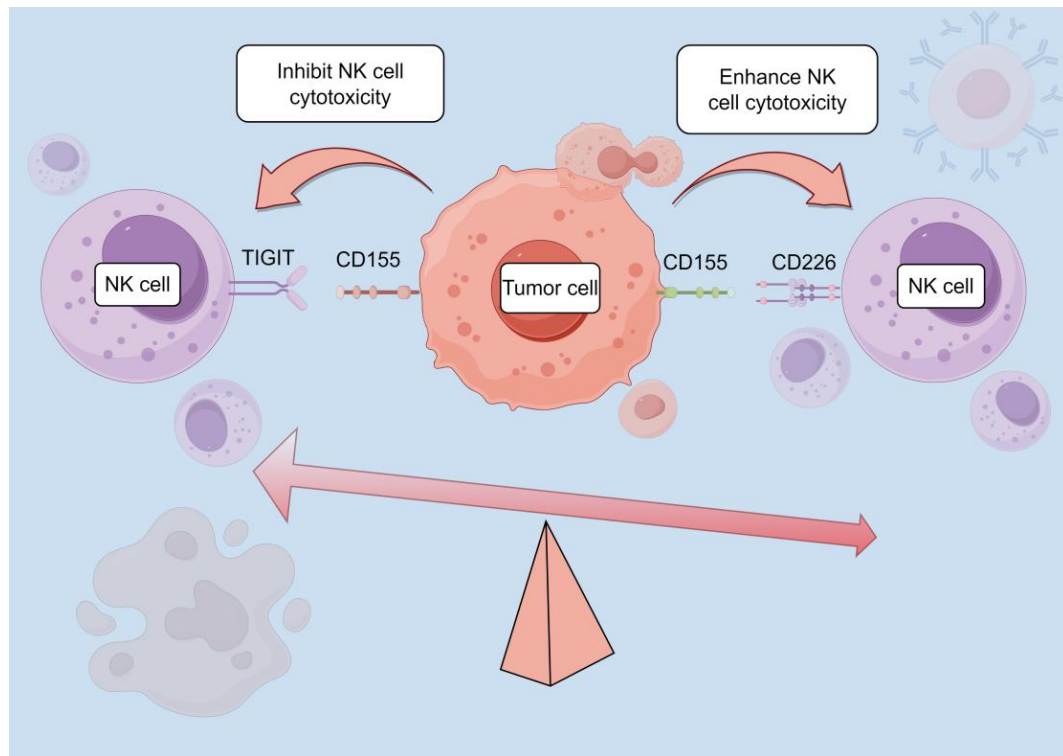


Fig. 1 Competitive binding of CD155 to CD226 and TIGIT (Picture credit: Original)

3. Inhibitory Effect of TGF- β on NK cells

3.1. Direct Inhibition of NK cells by TGF- β

Studies show that TGF- β inhibits NK cells through multiple mechanisms. By binding to the TGF- β receptor complex on NK cells, TGF- β can activate both the classical Smad/SMAD4 signaling pathway [10] and non-classical pathways, interfering with NK cell immune surveillance. For example, after TGF- β binds to its receptor, it induces phosphorylation of Smad2/3, then forms a complex with SMAD4 and enters the nucleus. Finally, they inhibit the transcription of key factors such as T-bet [10]. In addition, TGF- β downregulates the expression of several key activating receptors on NK cells, including NKp30, NKG2D [11], and CD226.

3.2. Indirect Inhibition: Enhancing TIGIT Signaling by Upregulating Cd155 Expression on Tumor Cells

The regulation of CD155 expression by TGF- β has been confirmed in multiple tumor models. TGF- β can regulate CD155 not only through the classical Smad pathway but also through non-classical pathways such as ERK1/2.

3.2.1. Classical Smad pathway

First, TGF- β binds to the TBR1 receptor on tumor cells, recruits and phosphorylates TBRI, then phosphorylates downstream Smad2/3 proteins. Second, phosphorylated Smad2/3 and Smad4 form a trimeric complex and enter the nucleus. Finally, this complex directly binds to the Smad binding element (SBE) in the CD155 gene promoter region, promoting CD155 transcription and expression [5]. This mechanism has been validated in triple-negative breast cancer (TNBC): high CD155 expression is positively correlated with TGF- β /Smad3 signaling activity, and knocking down CD155 significantly reduces Smad3 phosphorylation and the expression of its downstream genes [5].

3.2.2. Non-canonical ERK1/2 pathway

In addition to the Smad pathway mentioned above, TGF- β can also regulate CD155 expression through non-classical pathways. In tongue squamous cell carcinoma cells (TSCCA, CAL27), TGF- β secretion significantly increases CD155 protein levels, and this effect can be blocked by U0126, a specific inhibitor of the ERK1/2 pathway. Studies show that TGF- β can lead to ERK1/2 phosphorylation and entry into the nucleus by activating the Ras/Raf/MEK/ERK cascade. It then phosphorylates various transcription factors (such as c-Fos, c-Jun, and Elk-1). These transcription factors may bind to AP-1 sites in the CD155 promoter region and work together to promote its transcription. Of note, the inhibitor of the Smad pathway does not significantly affect this process, suggesting the existence of a regulatory pathway independent of Smad [4].

In summary, TGF- β can upregulate CD155 expression through mechanisms including the classical Smad pathway and the non-classical ERK1/2 pathway. These pathways may work together or independently in different tumor types to enhance the negative effect of the CD155-TIGIT signaling axis on NK cells. As the main ligand of TIGIT, increased CD155 expression further amplifies TIGIT-mediated inhibitory signals on NK cells. Therefore, TGF- β not only directly inhibits NK cells but also indirectly amplifies the negative effect of the CD155-TIGIT signaling axis through multiple pathways.

3.3. Positive Feedback Regulation: Bidirectional Interaction between Cd155 and TGF- β

As mentioned above, TGF- β can upregulate CD155 expression on tumor cells through pathways such as Smad and ERK1/2. However, recent studies suggest that there may be a bidirectional interaction between CD155 and the TGF- β signaling pathway. It means that CD155 can enhance TGF- β signaling activity in turn and then form a positive feedback loop.

In colorectal cancer (CRC), researchers used flow cytometry to analyze tumor-associated macrophages (TAMs) and found that CD155 in TAMs can upregulate TGF- β expression, thereby enhancing the immune evasion of circulating tumor cells (CTCs). Mechanistic studies show that TGF- β induces STAT3 activation, and STAT3 then mediates CTC migration and invasion. In this way, it increases the release of matrix metalloproteinases (MMPs) in CTC, promoting CTC invasion and migration, and ultimately enabling tumor immune evasion. In addition, after inhibiting TGF- β , the expression levels of pSTAT3 and MMPs in CRC cells were significantly reduced, and the migration and invasion abilities of CTCs were also markedly decreased [12].

A similar bidirectional interaction can also be confirmed in TNBC. Studies show that CD155 interacts with the TGF- β /Smad3 pathway, and knocking down CD155 can inhibit TGF- β /Smad3 signaling activity [5]. Analyzing from the mechanistic perspective, this positive feedback loop may operate through the following steps, as shown in Figure 2. First, TGF- β upregulates CD155 transcription through the Smad and ERK1/2 pathways [4]. Second, the highly expressed CD155 promotes TGF- β secretion through some mechanism [12]. Third, the enhanced TGF- β signaling further upregulates CD155 expression, thus forming a closed loop.

Of note, although current evidence strongly suggests a positive feedback loop between CD155 and TGF- β , the specific molecular mechanisms still need to be clarified. At present, several questions require further investigation: the regulatory mechanism of CD155 promoting TGF- β secretion, the general relevance of this loop in different tumor types, and whether this positive feedback can be disrupted by TIGIT blockade alone. The answers to these questions will provide a stronger theoretical basis for combination strategies targeting both TIGIT and TGF- β .

4. Clinical Problems of Current Drugs Targeting the Tigit-Cd155 Immune Checkpoint

4.1. Current Clinical Challenges

Nowadays, drugs targeting the TIGIT-CD155 immune checkpoint have become one of the key approaches in cancer treatment. Data shows that these drugs can inhibit tumor immune evasion to some extent and improve quality of life and life expectancy.

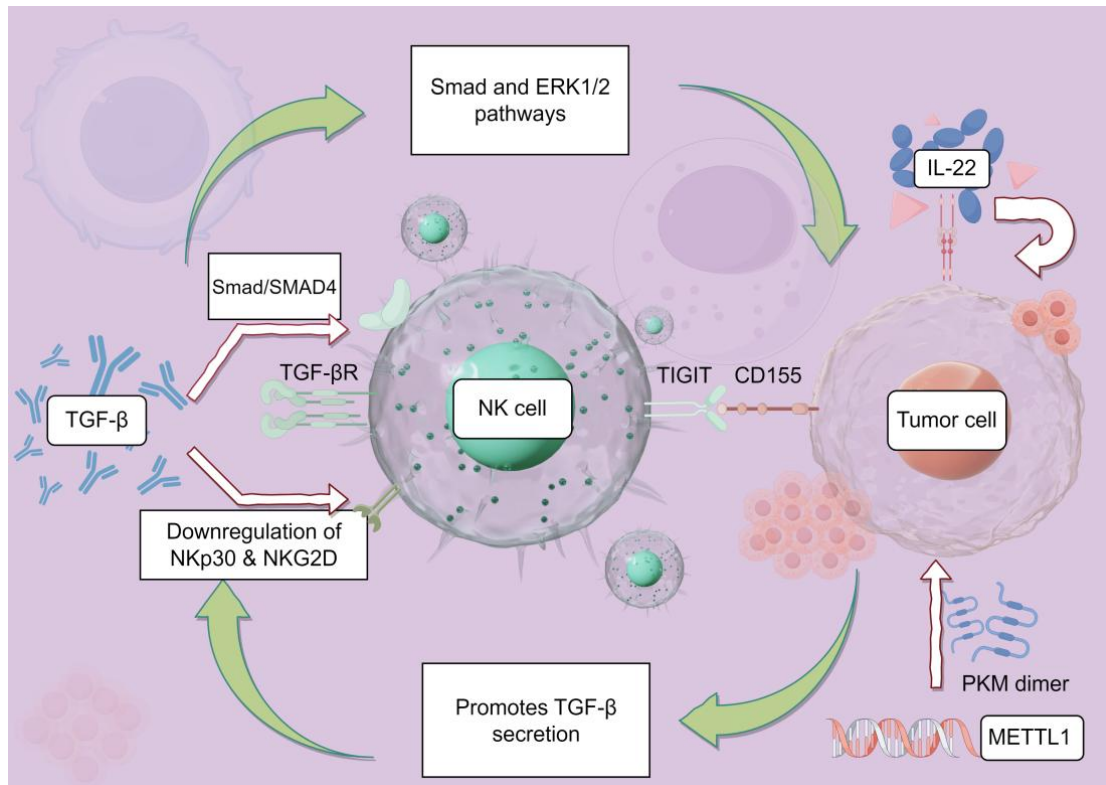


Fig. 2 Positive feedback loop between TGF-β and CD155-TIGIT axis (Picture credit: Original)

In early clinical studies, the CITYSCAPE trial (Phase II) showed that in NSCLC patients with PD-L1 $\geq 50\%$, treatment with Tiragolumab plus Atezolizumab (anti-PD-L1) increased the objective response rate (ORR) from 21% to 37%, and extended median progression-free survival (PFS) from 5.6 months to 7.0 months [3]. These positive results led to the launch of several Phase III trials. However, later Phase III trial results were disappointing. In the SKYSCRAPER-01 trial (NSCLC, PD-L1 $\geq 50\%$), the median overall survival (OS) in the Tiragolumab plus Atezolizumab group was 23.1 months, compared to 16.9 months in the control group (HR = 0.87, P = 0.22), which did not meet the expected results [3].

4.2. Possible Causes of Failure to Meet Expectations

The clinical problems faced by drugs that only block the CD155-TIGIT signaling axis may be related to three important factors: molecular pathways, the tumor microenvironment, and experimental models.

Studies have shown that the CCNC gene is a transcriptional repressor of the CD155 molecule, and clinical data indicates a negative correlation between the two. CCNC inhibits the activity of FOSL2 and downregulates CD155 expression. When CCNC is knocked out, FOSL2 activity increases, and CD155 expression also increases. These results suggest that people with low CCNC expression may be resistant to drugs targeting the CD155-TIGIT immune checkpoint [13]. In addition to genetic individualization and diversity, the killing effect of NK cells on tumors is itself affected by multiple factors and is often weakened by various factors. As mentioned earlier, TGF-β can dually inhibit NK cell killing by directly suppressing NK cells and indirectly enhancing the negative effect of the

CD155-TIGIT signaling axis. At the same time, experimental methods and model selection may also mislead the evaluation of this target's efficacy. Evidence shows that results obtained using rhesus monkeys as a study model differ from actual clinical outcomes. There is a difference in rhesus monkeys because they have an amino acid change at position 119. It means that TIGIT can be cleaved and shed by plasmin, but it can still bind to CD155 and TIGIT antibodies and neutralize their function. Thereby it leads to unnecessary drug consumption [14]. So, this result may affect data such as pharmacokinetic parameters and explain why the experimental data looked great but the clinical efficacy was poor. In summary, molecular resistance, microenvironment suppression, and model selection together form the deeper reasons for the clinical challenges of TIGIT inhibitors, highlighting the need for combination strategies.

5. Combined Intervention Strategies Targeting TGF- β and the TIGIT-CD155 axis

5.1. Molecular Mechanisms

As mentioned earlier, there is a positive feedback loop between TGF- β and the TIGIT-CD155 signaling axis. Targeting both pathways together has a clear molecular basis, which can be understood from three levels. First, anti-TIGIT antibodies can directly block the binding between CD155 and TIGIT, thereby relieving tumor immune evasion mediated by this signaling axis. Second, anti-TGF- β not only directly blocks the inhibitory effect of TGF- β on NK cells, but also blocks its upregulation of CD155, fundamentally weakening the driving force of the positive feedback loop. Finally, blocking both pathways together can activate a dual inhibitory effect and jointly restore the immune surveillance function of NK cells.

5.2. Current Clinical Studies

Based on this synergistic logic, bispecific antibodies have become a highly promising research direction. AK130 (Lucorafusp Alfa) is the first bifunctional antibody fusion protein targeting TIGIT and TGF- β to enter registrational clinical trials. Its structure consists of an anti-TIGIT antibody fused with the extracellular domain of the TGF- β receptor II. It allows it to simultaneously block the TIGIT-CD155 signaling axis and neutralize TGF- β , achieving a “one drug, two targets” synergistic effect. In September 2025, the Phase II study of AK130 combined with Ivonescimab (a PD-1/VEGF bispecific antibody) completed dosing of the first patient with advanced pancreatic cancer. This marks the entry of this combination strategy into the clinical validation phase, providing a new treatment option to overcome TIGIT inhibitor resistance [15].

6. Conclusion

This review systematically summarizes the literature and finds that the CD155-TIGIT signaling axis is one of the core mechanisms that inhibit the immune surveillance function of NK cells. Meanwhile, CD226 competes with TIGIT, forming a balance in immune regulation. At the same time, TGF- β not only directly inhibits NK cell activity but also upregulates CD155 expression on tumor cells through pathways such as Smad and ERK1/2, thereby amplifying the negative effect of the CD155-TIGIT signaling axis and producing a dual inhibition of NK cells. This review is the first to systematically integrate the dual and synergistic inhibition model of NK cells by the CD155-TIGIT axis and TGF- β . It also proposes the possible mechanism of a positive feedback loop between the two, in which TGF- β upregulates CD155 expression, and the highly expressed CD155 in turn enhances TGF- β signaling activity, forming a positive feedback immunosuppressive loop. Current evidence partially supports this hypothesis in models such as triple-negative breast cancer and colorectal cancer, but its general relevance and specific molecular mechanisms still need further validation. However, there are still few studies focusing on the synergistic effects of both pathways. In addition, the controversial efficacy of TIGIT inhibitors in clinical trials suggests that multiple

factors, including the heterogeneity of the tumor microenvironment, may affect treatment outcomes. Therefore, combined targeting of the TIGIT-CD155 signaling axis and TGF- β has broad clinical potential and may help reverse the clinical immune resistance. Future research could focus on various aspects related to this positive feedback loop, such as the detection of molecular markers to assess and predict clinical efficacy, the use of bispecific antibodies, and reversal strategies for immune resistance. In summary, the combined blockade strategy targeting CD155/TIGIT and TGF- β has the potential to reverse immunotherapy resistance and provides a new direction for optimizing NK cell-based immunotherapy.

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