

Pan-Cancer Analysis of TIGIT and Its Association with the Tumor Immune Microenvironment and Potential in Cold Tumor Therapy

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Abstract. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is an inhibitory receptor that marks exhausted and inflamed immunity and offers a practical handle to restore anti-tumor function. This study synthesizes evidence across bulk transcriptomic resources, pathology series, and single cell datasets to define TIGIT expression, ligand geography, and clinical implications. TIGIT is concentrated in activated CD8⁺ and CD4⁺ T cells, regulatory T cells, and natural killer cells. Its ligands CD155 and CD112 are widely expressed by tumor and myeloid compartments. TIGIT tracks with immune and stromal signals and shows context dependent prognostic value across histologies. These features support strategies that restore the CD226 costimulatory axis and PD-1 or PD-L1 blockade with TIGIT inhibition in ligand rich niches. In immunologically cold or immune excluded tumors, low bulk TIGIT often reflects limited lymphocyte entry rather than absence of target. Therefore, a sequence remodel first and release second. Normalizing vasculature, easing stromal and chemokine barriers, or inducing type I and type III interferon tone can prime responses to dual checkpoint therapy. Where MHC class I loss shifts surveillance toward innate cells, TIGIT blockade should be combined with natural killer supportive approaches. Together these principles outline biomarker guided and tumor microenvironment aware deployment of TIGIT centered therapy.

Keywords: TIGIT, Immune checkpoint inhibitors, Cold tumors, Tumor microenvironment.

1. Introduction

Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 and CTLA-4 have reshaped cancer therapy, but their targets remain concentrated in “hot,” T cell-inflamed tumors. However, many common solid cancers are immunologically “cold” or immune-excluded and respond poorly [1]. Here, “cold” is used to denote tumors with scant effector T-cell infiltration and a dominantly immunosuppressive microenvironment. This state is characterized by physical exclusion from fibrotic stroma, suppressive myeloid and regulatory populations, low antigen visibility, and hostile metabolism, rather than an absence of checkpoint molecules. These features, together with TGF- β -rich exclusionary stroma, underpin primary and adaptive resistance to current ICIs [1, 2]. These tumor microenvironment (TME) states provide a useful framework to localize where combination approaches are most needed.

T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a key inhibitory “brake” on anti-tumor T and NK cells, making it a promising target to address this therapeutic gap. TIGIT, as an immune checkpoint, is expressed on activated or chronically stimulated CD8⁺/CD4⁺ T cells, NK cells and regulatory T cells (Tregs). It competes with the co-stimulatory receptor CD226 (DNAM-1) for the shared ligands CD155 (PVR) and CD112 (PVRL2). Through ITIM-mediated inhibitory signaling, it suppresses T-cell receptor output and IFN- γ production, while promoting tolerogenic dendritic-cell states [3-5]. Since TIGIT often rises alongside other immune checkpoints such as PD-1, TIM-3, and LAG-3 and tracks stable ‘exhaustion’ programs, its presence usually signals an inflamed-yet-restrained state. This state indicates that immune cells remain alive but are functionally inefficient [3, 6-7].

Importantly, TIGIT acts on both innate and adaptive immune systems. On T cells, it associates with epigenetically stabilized exhaustion. For NK cells, it functions as an immune checkpoint.

Blocking TIGIT restores degranulation and IFN- γ release. This is especially vital in MHC-I-low or myeloid-rich cold tumors, where NK surveillance should compensate [8, 9]. In prototypically cold tumors such as glioblastoma, myeloid dominance and abundant ligand expression provide additional rationale to target the TIGIT–CD226–ligand axis [10].

TIGIT also shapes the suppression functions of Tregs. It marks highly suppressive Tregs and, by engaging CD155 on dendritic cells, reduces interleukin-12 and increases interleukin-10, thereby weakening effector priming [4, 11]. This, together with its role on exhausted T cells and NK cells, suggests that blocking TIGIT could relieve both T-cell dysfunction and Treg-mediated control and thereby better target cold tumors [7, 8].

Clinically results are mixed but informative. Early studies of tiragolumab alone or with atezolizumab showed acceptable safety and signals of activity, while a phase III trial in small-cell lung cancer did not improve survival, and meta-analyses emphasize context dependence [12-14]. These findings highlight a research gap: the need for a pan-cancer, TME-aware map of TIGIT that incorporates the DNAM-1 axis and links TIGIT, CD226, and ligand levels to hot, excluded, and cold states. Such a framework would help identify contexts where TIGIT combinations with PD-1/PD-L1 and microenvironment remodeling are most likely to be effective.

2. Introduction TIGIT and Immune Infiltration

2.1. Transcript-Level Landscape Across Tumor Types

Across TCGA–GTEx compendia, TIGIT mRNA is elevated in many cancers relative to normal tissues and co-varies with immune-infiltration and exhaustion program, indicating that bulk TIGIT expression primarily reflects the presence of tumor-infiltrating lymphocytes rather than tumor-cell expression [15, 16]. This result has two practical consequences. First, differences in TIGIT across tumor types often mirror variation in immune cell abundance. Second, interpretation should remain aware of sample purity. Deconvolution tools such as CIBERSORT and ESTIMATE can help distinguish genuinely low target expression from simply low lymphocyte abundance, and therefore should accompany pan-cancer comparisons [17, 18]. In this context, TIGIT correlates with other checkpoints (PDCD1, HAVCR2, LAG3) and with IFN- γ -linked inflamed signatures, consistent with the “inflamed-yet-restrained” state described in the Introduction [6, 7].

2.2. Single-Cell Resolution and Cell-of-Origin

Single-cell datasets across multiple histology show that TIGIT is mainly expressed on chronically stimulated or exhausted CD8⁺ and CD4⁺ T cells, as well as on regulatory T cells, with frequent co-expression of PD-1, TIM-3 and LAG-3 [19]. Analyses of intertumoral NK cell compartments also detect TIGIT on defined NK subsets, indicating that the pathway functions in both adaptive and innate immunity in human tumors [20]. Taken together, these observations suggest that, where lymphocytes are present, TIGIT marks effector populations that are restrained and thus potential candidates for checkpoint reversal, rather than representing a transcript produced by tumor cells.

2.3. Protein-Level Evidence

At the protein level, immunohistochemistry consistently identifies TIGIT to tumor-infiltrating lymphocytes at invasive margins and at stromal-immune interfaces, consistent with PD-1 rich T-cell niches [7, 21]. In vivo molecular imaging further supports its detectability. TIGIT-targeted PET tracers enable quantification of intertumoral TIGIT in patients and allow non-invasive stratification and longitudinal assessment [22]. Because TIGIT signaling depends on ligand availability, documenting CD155 (PVR) and CD112 (PVRL2) alongside TIGIT is informative. In pancreatic ductal adenocarcinoma, CD155 is abundantly expressed on tumor and myeloid cells, creating a ligand-rich niche that favors TIGIT over CD226 and promotes immune evasion [23]. In sum, these observations indicate that, at the protein level, TIGIT is mainly found on tumor-infiltrating lymphocytes, and its therapeutic relevance is maximized where CD155 and CD112 are abundant.

2.4. Implications for Cold Tumors

In immune-excluded or cold tumors, such as pancreatic, prostate and cholangiocarcinoma, and glioblastoma, bulk TIGIT can look modest because lymphocytes are sparse. Nevertheless, per-cell TIGIT expression on resident T and NK cells can be high, and ligands such as CD155 are often abundant in myeloid-dominant microenvironments [10, 23]. Taken together, transcript and protein data support a target-present and context-dependent view. TIGIT is detectable across cancers, and its therapeutic relevance is determined by immune content and ligand availability, which motivates subsequent analyses of the DNAM-1 axis and TME-aware contexts.

Across cancers, TIGIT is widely detectable at the mRNA level and localizes at the protein level to tumor-infiltrating lymphocytes rather than tumor cells. Bulk differences largely reflect variation in immune-cell content, necessitating purity-aware interpretation. In cold tumors, low bulk signal does not preclude meaningful TIGIT expression on the few resident lymphocytes, especially where CD155 and CD112 are present. These points justify a context-guided approach that integrates TIGIT with CD226 and its ligands, linking this axis to quantitative TME states [10, 15, 21, 23].

3. TIGIT and Immune Infiltration

3.1. Pan-Cancer Expression and Infiltration Association

Across TCGA-GTEX pan-cancer datasets, TIGIT mRNA is higher in many tumor types than in matched normal tissues from GTEx. At the bulk level, TIGIT expression correlates with leukocyte infiltration metrics, including ESTIMATE immune and stromal scores, as well as T-cell and NK-cell gene signatures [16, 24-25]. This pattern is biologically consistent, as TIGIT protein localizes to tumor-infiltrating lymphocytes rather than malignant epithelium. Thus, bulk TIGIT primarily reflects the abundance and activation state of infiltrating lymphocytes rather than tumor-intrinsic transcription [3, 21].

Prognostic signals vary by histology and by the balance between “immune presence” and “immune paralysis”. In tumors where activated infiltration is beneficial (e.g., melanoma), higher TIGIT levels can be associated with improved outcomes. By contrast, in contexts dominated by dysfunctional or Treg-skewed infiltrates (e.g., subsets of renal and uveal cancers), high TIGIT often predicts worse prognosis, suggesting that restraint outweighs infiltration in those settings [9, 16].

3.2. Immune Cell Subsets

Building on the pan-cancer data showing that bulk TIGIT mainly reflects infiltrating lymphocytes rather than tumor-intrinsic transcription, this study next examines which immune compartments express TIGIT in tumors and how this shapes function. TIGIT is enriched on activated CD8⁺ and CD4⁺ T cells, regulatory T cells, and NK cells. Its ligands CD155 and CD112 are broadly expressed on tumor cells and myeloid antigen-presenting cells. This distribution helps determine whether local immunity is constrained yet potentially reversible, or instead dominated by suppressive signals. [3, 9, 21].

3.2.1 CD8⁺ T cells

TIGIT is co-induced during chronic T-cell receptor stimulation and marks exhausted or dysfunctional CD8⁺ tumor-infiltrating lymphocytes. These cells are characterized by reduced cytokine production, diminished proliferative capacity, and stable epigenetic features despite persistent expression of activation markers [6, 26]. Single-cell studies consistently identify PD-1⁺ TIGIT⁺ CD8⁺ clusters enriched for TOX and NR4A programs, with lower expression of cytotoxic effectors and greater susceptibility to additional inhibitory signals compared with PD-1 single-positive cells [6, 9]. In bulk datasets, high TIGIT usually indicates a lymphocyte-rich yet functionally constrained tumor microenvironment, which helps explain variable responses to PD-1 monotherapy across diseases [3, 16].

3.2.2 NK cells

Activated and tumor-infiltrating NK cells express TIGIT. Engagement by CD155 or CD112 dampens NK cytotoxicity and IFN- γ production [5, 9]. The impact is greatest when MHC class I is downregulated and NK surveillance becomes a key line of defense. Cytokines such as interleukin-15 not only expand and prime NK cells, but can also upregulate inhibitory receptors including TIGIT. In preclinical models, combining cytokine-based priming with TIGIT blockade restores NK-mediated control, which suggests that TIGIT-high, NK-inflamed tumors contain an actionable yet currently suppressed innate compartment [9].

3.2.3 Regulatory T cells (Tregs)

TIGIT identifies a highly suppressive Treg subset that limits dendritic cell co-stimulation, skews cytokine production toward interleukin-10, and reduces interleukin-12 and interleukin-23, collectively suppressing Th1-oriented anti-tumor immunity [3, 9]. At the synapse, TIGIT competes with CD226 for the same ligands on myeloid and tumor cells. Because TIGIT binds CD155 with higher affinity, ligand-rich niches preferentially deliver inhibitory signals and blunt CD226-dependent co-stimulation [5]. Tumors with high TIGIT frequently show Treg-enriched signatures and reduced effective co-stimulation despite ongoing antigen exposure.

3.2.4 Myeloid-derived suppressor cells (MDSCs) and myeloid APCs

MDSCs do not depend on TIGIT to mediate suppression. They often express TIGIT ligands, especially CD155, and other myeloid antigen-presenting cells such as macrophages and dendritic cells do as well. Many tumors epithelial cells also express these ligands [9, 21, 27]. The result is a receptor-ligand expression pattern in which immune cells express inhibitory receptors while tumor or myeloid compartments provide abundant ligands. These interactions favor interleukin-10 rich niches with poor antigen presentation, which helps explain why bulk TIGIT often co-occurs with myeloid-inflamed states and MDSC signatures. Taken together, TIGIT integrates cellular composition, effector state, and the availability of co-stimulation into a single measurable signal.

3.3. Conclusion for Immune Infiltration

Pan-cancer profiling and single-cell analyses together indicate that bulk TIGIT mainly reflects the quantity and functional state of infiltrating lymphocytes rather than tumor-intrinsic transcription. TIGIT concentrates on activated CD8⁺ and CD4⁺ T cells, regulatory T cells, and NK cells, while its ligands CD155 and CD112 are common on tumor cells and myeloid antigen-presenting cells. This receptor-ligand distribution aligns with either constrained yet recoverable immunity or myeloid-dominated suppression, which helps explain histology-specific prognostic patterns and variable responses to PD-1 therapy. These features place TIGIT within an exhaustion-centered framework alongside PD-1, TIM-3 and LAG-3, setting up the next section on co-expression modules and their therapeutic implications.

4. Therapeutic Implications of TIGIT Biology

Therapeutically, TIGIT coordinates restraint across T cells and NK cells, so its biology points to where and how to intervene in solid tumors. In inflamed yet functionally arrested microenvironments, persistent antigen drives an exhaustion program, during which TIGIT is upregulated alongside PD-1, TIM-3 and LAG-3 on CD8⁺ T cells and Tregs. Concurrently, high CD155 and CD112 expression on tumor and myeloid cells biases the immunological synapse toward inhibitory TIGIT rather than co-stimulatory CD226. In colder or myeloid-heavy niches with reduced MHC class I, TIGIT also suppresses NK cytotoxicity and IFN- γ production. Overall, TIGIT functions both as a readout of an exhausted-inflamed state and as a tractable therapeutic target. Strategies that restore CD226 signaling or relieve TIGIT-mediated NK inhibition aim to convert paralyzed hot tumors, and selected cold tumors, into productive anti-tumor immunity.

4.1. TIGIT Co-expression and Exhaustion as Therapeutic Guides

A recurring feature of TIGIT in cancer is tight co-expression with other inhibitory receptors induced by persistent antigenic stimulation. Foundational and recent studies demonstrate coordinated up regulation of TIGIT alongside PD-1, TIM-3 and LAG-3 on dysfunctional or exhausted T cells in chronic infection and in tumors. This pattern reflects convergent transcriptional regulation through NFAT in combination with TOX and NR4A programs, along with partially non-overlapping signaling nodes that collectively restrain cellular function [26].

In human tumors, PD-1⁺ TIGIT⁺ CD8⁺ T cells often represent a dominant exhausted subset. The stepwise addition of TIM-3 and LAG-3 marks deeper functional impairment and a more entrenched epigenetic state. This pattern does not represent simple redundancy. PD-1 attenuates TCR and CD28 signaling. TIGIT outcompetes CD226 for CD155 and CD112 to weaken co-stimulation, and TIM-3 and LAG-3 provide additional inhibitory signals through distinct ligand systems, such as galectin-9 with CEACAM1 and MHC-II. From a therapeutic viewpoint, these co-expression layers map the position of cells along the progenitor to terminal exhaustion continuum and indicate when relieving a single brake is unlikely to be sufficient. They also motivate biomarker panels that simultaneously quantify TIGIT, PD-1, TIM-3, LAG-3 and CD226 on the same lymphocyte populations, guiding combination selection and estimating the potential for functional rescue [26].

A similar logic applies to NK cells. TIGIT is part of a broader inhibitory repertoire on activated or tumor-infiltrating NK cells, and engagement by CD155 or CD112 reduces cytotoxicity and IFN- γ production. The effect is most visible when MHC-I is reduced and NK surveillance carries more of the load. Recognizing this NK axis has practical value, as contexts with impaired T-cell surveillance may benefit from TIGIT blockade combined with NK-supportive approaches alongside T-cell-targeted strategies [5].

4.2. Implications for Combination Immunotherapy

Mechanistically, competition between TIGIT and CD226 generates a vulnerability in ligand-rich niches. Preferential engagement of TIGIT by CD155 or CD112 can blunt CD226-dependent co-stimulation, even when PD-1 is blocked. This provides a clear rationale for combining TIGIT and PD-(L)1 inhibition, particularly in tumors with abundant ligands and intact downstream co-stimulatory capacity [5].

Ex vivo and preclinical studies demonstrate that dual blockade more effectively restores proliferation, cytokine production, and cytotoxicity of human CD8⁺ tumor infiltrating lymphocytes compared with PD-1 monotherapy. The magnitude of benefit depends on the integrity of CD226 signaling, which is often diminished under chronic stimulation, and on the distribution of CD155 and CD112 across tumor and myeloid compartments, both of which vary across histology [5].

These mechanics inform biomarker strategies. Rather than quantifying TIGIT in isolation, it is informative to measure TIGIT together with CD226 on the same lymphocyte populations, and to interpret co-expression layers of PD-1, TIM-3 and LAG-3 as a proxy for positioning cells along the exhaustion continuum [26].

The ligand side of the synapse is equally important. Characterizing the abundance and spatial distribution of CD155 and CD112 on tumor cells and myeloid antigen-presenting cells helps identify niches where TIGIT preferentially outcompetes CD226, while estimating the size of the TCF1⁺ progenitor pool clarifies how much of the exhausted compartment remains amenable to rescue by checkpoint therapy [6].

In NK-biased contexts, particularly where loss of MHC class I limits T-cell surveillance, pairing TIGIT blockade with NK supportive cytokine strategies such as IL-15 or engineered IL-2 variants has restored NK function in models and represents a complementary route. More broadly, triplet or sequential combinations that include TIM-3 or LAG-3 inhibition in heavily co-inhibited states are conceptually justified, but should be guided by co-expression maps and careful management of overlapping toxicities [9].

5. Translational path for Cold Tumors

In cold tumors, low bulk TIGIT often reflects sparse lymphocyte entry rather than absence of a target. A practical sequence involves remodeling the tumor microenvironment first, followed by functional release of immune restraint. Normalizing aberrant vasculature and relieving stromal exclusion can increase lymphocyte trafficking and improve antigen presentation, creating conditions where dual checkpoint therapy can restore function. Anti-angiogenic strategies can normalize vessels and cooperate with immunotherapy. TGF- β -driven exclusion and the CXCL12 CXCR4 axis represent actionable barriers to lymphocyte infiltration. Innate agonists, such as STING, are being engineered for tumor-targeted delivery to convert non-inflamed niches into inflamed states prior to PD-1 plus TIGIT administration [2, 28-30].

5.1. NK Centered Opportunities

When MHC class I is reduced and T cell pressure is limited, the natural killer axis becomes a primary. TIGIT is expressed on activated and tumor infiltrating natural killer cells, and engagement by CD155 or CD112 suppresses degranulation and IFN- γ production. Preclinical work shows that TIGIT blockade prevents natural killer cell exhaustion and restores anti-tumor activity [8, 9].

Cytokine support can amplify responses. The interleukin-15 receptor super agonist nogapendekin alfa inbakicept expands and activates natural killer cells in humans and received regulatory approval in 2024 for BCG-unresponsive non-muscle-invasive bladder cancer [31]. Engineered interleukin-2 variants such as nemvaleukin alfa preferentially engage intermediate-affinity receptors on natural killer and CD8 T cells and have shown tolerability with early signs of activity in advanced solid tumors [32].

Innate redirection is also progressing clinically. A phase 1 study of cord-blood-derived natural killer cells precomplexed with the bispecific engager AFM13 produced encouraging responses in heavily pretreated CD30 positive lymphomas and established feasibility and safety of natural killer redirection in humans [33]. These observations support pairing TIGIT inhibition with cytokine support or redirected natural killer strategies in MHC class I low tumors with abundant CD155.

5.2. Future Directions

Prospective trials should test PD-1 plus TIGIT in settings defined by clear biological predicates such as evidence of exhausted inflammation or high ligand abundance. For cold tumors, “remodel first” strategies should be evaluated, using predefined conversion criteria based on lymphocyte infiltration and interferon-related signals prior to initiating dual blockade. In NK-biased disease, TIGIT inhibition should be paired with NK-supportive cytokines or adoptive NK strategies, incorporating NK specific pharmacodynamic endpoints that include changes in tissue-resident NK subsets, CD107a degranulation, and interferon-gamma release, while comparing sequential versus concurrent and local delivery approaches to maximize efficacy and manage toxicity. References above provide the mechanistic and translational basis for these designs.

6. Conclusion

This study introduces TIGIT as a biomarker of exhausted inflamed immunity and a tractable lever to restore anti-tumor function. Across datasets and tissues, TIGIT concentrates on activated CD8 and CD4 T cells, regulatory T cells, and natural killer cells. Its ligands, CD155 and CD112, are widely expressed by tumor and myeloid compartments. This arrangement helps explain variable prognosis across histologist and the uneven benefit from PD-1 or PD-L1 monotherapy. It supports strategies that restore the CD226 co-stimulatory axis and combine PD-1 or PD-L1 with TIGIT blockade in ligand rich niches.

For immunologically cold or immune excluded tumors, low bulk TIGIT often reflects scarce lymphocyte entry rather than true target absence. A practical sequence is remodel first and release second. Normalize vasculature, relieve stromal barriers driven by TGF- β and CXCL12, or induce

type I and type III interferon tone before dual checkpoint therapy. Where MHC class I loss shifts surveillance toward innate immunity, pair TIGIT blockade with natural killer supportive approaches such as IL-15 agents or tuned IL-2 variants, with readouts that capture tissue resident natural killer function.

Prospective trials should enrich exhaustion and inflammation signatures and high CD155 or CD112. Measure the TIGIT and CD226 balance and spatial topology. Purity and spatial heterogeneity limit broad generalization. State defined and tumor microenvironment aware endpoints are needed to deploy TIGIT centered strategies across diverse tumor contexts.

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