Unlocking New Frontiers: Novel Immune Targets for Next-Gen Cancer Immunotherapy

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November 15, 2024

Title: Unlocking New Frontiers: Novel Immune Targets for Next-Gen Cancer Immunotherapy

Type of article - Review article

Running title: Novel Immune targets

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Declaration:

Conflict of Interests: None

Funding: None

Data availability statement: Data sharing is not applicable to this article as no new data were created or analysed in this study.

Acknowledgements: NIL

Competing interests: The author(s) declared no potential conflicts of interest.

This paper has been prepared by the above mentioned authors and reviewed and agreed upon for submission. The requirements for authorship as stated above in this document have been met, and that each author believes that the manuscript represents honest work.

CRediT author statement

Niti Sureka : Data curation.

Sufian Zaheer : Conceptualization; Visualization; Supervision; data curation; resources; writing—original draft; writing—review and editing.

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Abstract

Cancer immunotherapy represents a transformative strategy in modern oncology, utilizing the body's immune system to recognize and eliminate malignant cells with precision. Unlike traditional therapies, which often directly target the tumor, immunotherapy enhances the immune system's inherent ability to differentiate between healthy and cancerous cells, leading to more targeted and potentially longer-lasting therapeutic effects. The advent of immune checkpoint inhibitors (ICIs), particularly those targeting the PD-1/PD-L1 and CTLA-4 pathways, has marked a significant breakthrough in this field, yielding substantial clinical success in various cancer types. However, the therapeutic landscape is still challenged by issues such as the development of resistance mechanisms, heterogeneity in patient responses, and the limited efficacy of current ICIs across all tumor types.

Given these challenges, there is a critical need to identify and validate new immune targets that can synergize with existing therapies or function independently to overcome resistance and improve patient outcomes. This review provides a comprehensive overview of the latest research efforts focused on uncovering novel immune targets. By expanding the repertoire of immune targets, these discoveries aim to enhance the effectiveness of cancer immunotherapy, offering hope for more personalized and resilient treatment options. The integration of these novel targets into clinical practice could not only extend the benefits of immunotherapy to a broader spectrum of cancers but also mitigate some of the current limitations, paving the way for more durable and effective therapeutic strategies in the fight against cancer.

Keywords: Cancer immunotherapy; Immune Checkpoints; Co-Stimulatory Molecules; **TAM Receptors; CD73, Adenosine pathway**

Introduction: Cancer immunotherapy represents a groundbreaking strategy in contemporary oncology, utilizing the body's immune system to target and eliminate malignant cells. Unlike traditional treatments that directly target tumors, immunotherapy aims to stimulate or enhance the immune system's ability to recognize and eliminate cancer cells, offering the potential for more durable and targeted therapeutic outcomes [1]. Immunotherapy, including adoptive cell transfer (ACT) and immune checkpoint inhibitors (ICIs), is a cancer treatment that harnesses the power of the immune system to target and eliminate tumor cells. Used either on its own or alongside traditional treatments such as radiotherapy and chemotherapy, this approach has become a standard and highly successful option for treating many cancers [2,3].

Notably, immune checkpoint inhibitors (ICIs) that target PD-1/PD-L1 and CTLA-4 have gained prominence in clinical practice [2,3]. These therapies have achieved significant success by effectively releasing the brakes on the immune response, allowing the immune system to detect and attack tumors that previously evaded detection. Despite these advancements, challenges remain, such as the emergence of resistance mechanisms and the varying effectiveness of treatment across different types of cancer. This resistance, which can be primary (intrinsic) or acquired (secondary), is driven by complex cellular and molecular processes.

The TME is often immunosuppressive, containing regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) that inhibit T-cell activity. These cells secrete immunosuppressive cytokines, such as TGF-β and IL-10, which dampen the anti-tumor immune response. The abundance of these immunosuppressive cells and molecules can lead to primary resistance to ICIs by preventing effective T-cell infiltration and activation [2,3]. Tumor cells and immune cells in the TME can upregulate PD-L1 in response to interferon-gamma (IFN-γ) produced by activated T cells. This adaptive resistance mechanism creates a feedback loop where increased PD-L1 binding to PD-1 on T cells suppresses

their activity. This adaptive response, particularly in tumors with high PD-L1 expression, is associated with resistance to PD-1/PD-L1 inhibitors [3,4]. Certain genetic alterations in tumors, such as mutations in JAK1/2 and loss of PTEN, have been associated with ICI resistance. JAK1/2 mutations can disrupt IFN-γ signaling, leading to impaired antigen presentation and immune evasion. Additionally, epigenetic changes, such as DNA methylation and histone modifications, can silence genes involved in antigen presentation and immune recognition, further contributing to immune evasion [2,3,4].

Consequently, there is a pressing need to identify novel immune targets that can complement existing therapies, broaden the spectrum of cancers that can be effectively treated, and improve overall treatment outcomes. This review critically examines the latest advancements in the field, focusing on the discovery and exploration of new immune targets for cancer immunotherapy.

2. Emerging Immune Checkpoints

Emerging immune checkpoints represent a new frontier in cancer immunotherapy, offering novel targets to enhance the body's immune response against tumors. While therapies targeting well-known checkpoints such as PD-1/PD-L1 and CTLA-4 have revolutionized cancer treatment, many patients still experience resistance or limited efficacy [2, 5]. To address these challenges, researchers are exploring additional inhibitory and stimulatory pathways that regulate immune cell function. Immune checkpoints like TIGIT, LAG-3, VISTA, TIM-3 and others, are increasingly being recognized for their significance in regulating immune responses within the tumor microenvironment (TME) [Table 1] [6]. These emerging targets are drawing attention due to their potential to influence the effectiveness of cancer immunotherapies by modulating the immune system's ability to recognize and attack tumor cells (Figure 1) [6, 7, 8]. By targeting these novel checkpoints, either alone or in combination with existing therapies, there is potential to overcome resistance mechanisms, treat a broader range of cancers, and ultimately improve patient outcomes.

2.1 TIGIT (T Cell Immunoreceptor with Ig and ITIM Domains)

TIGIT (T cell immunoreceptor with Ig and ITIM domains) also known as WUCAM (Washington University Cell Adhesion Molecule), Vstm3 , and VSIG9, is an inhibitory receptor of the Ig superfamily, found on the surface of activated CD8+ T and CD4+ T cells, regulatory T cells (Tregs), follicular T helper cell and natural killer (NK) cells [9, 10]. However, expression of tigit is weak on naïve T cells. TIGIT is a member of the continually growing family of poliovirus receptor (PVR)-like proteins [11]. TIGIT is composed of an extracellular immunoglobulin variable domain, a type I transmembrane domain, and a short intracellular domain containing one immunoreceptor tyrosine-based inhibitory motif (ITIM) and one immunoglobulin tyrosine tail (ITT)-like motif [11, 12]. TIGIT is expressed on natural killer (NK) cells and T cells, including CD4+ T cells, CD8+ T cells, and regulatory T cells (Tregs) [13, 14]. While TIGIT expression is typically low in naive cells, both T cells and NK cells have been shown to upregulate TIGIT upon activation [12, 13, 14].

Its primary role is to regulate immune responses, maintaining a balance to prevent over activation that could lead to autoimmunity [13, 14]. TIGIT competes with the co-stimulatory receptor CD226 (DNAM-1) for binding to the same ligands, primarily CD155 and, to a lesser extent, CD112 and CD113, which are expressed on antigen-presenting cells (APCs) including dendritic cells, macrophages [10], and various tumor cells including melanoma [15], colon cancer [16], pancreatic cancer [17], lung adenocarcinoma [18], and glioblastoma [19].

When TIGIT binds to CD155 on APCs or tumor cells, it transmits inhibitory signals to the T cells and NK cells, leading to a suppressed immune response . This suppression helps tumors evade the immune system, contributing to tumor growth and progression [9, 10]. The engagement of TIGIT with CD155 also inhibits the activation and function of CD226 (DNAM-1) in a cell-intrinsic manner , further dampening immune responses [20, 21].

Elevated levels of TIGIT have been observed in the cellular microenvironment of various cancers including melanoma [10], non-small-cell lung carcinoma (NSCLC) [22], colorectal adenocarcinoma [23], gastric cancer

[24], breast cancer [25], acute myeloid leukaemia (AML) [26] and multiple myeloma (MM) [27], correlating with an unfavorable prognosis for cancer patients. Numerous studies have documented increased TIGIT expression on CD8+ T cells, alongside reports of elevated TIGIT levels on tumor-infiltrating regulatory T cells (Tregs) and NK cells [28, 29, 30]. Several studies have revealed that high TIGIT expression on tumor-infiltrating lymphocytes (TILs) correlates with poor clinical outcomes in cancer [31, 32, 33]. Sun et al showed that, high TIGIT expression in lung adenocarcinoma was linked to advanced TNM staging, lymphoid metastasis, distant metastasis, and low expression of antitumor immunity-related genes [34]. A study by Liu et al revealed that, in patients with hepatocellular carcinoma, high TIGIT expression in CD8+ T-cell populations in peripheral blood is inversely correlated survival. [35]. Further in melanoma patients, an elevated TIGIT/CD226 ratio in Tregs is associated with higher Treg frequencies in tumors and poorer clinical outcomes [29] . In endometrial cancer, increased levels of TIGIT on NK cells residing within tumors have been linked to the severity of the disease [36]. A study by Kong et al., noted that, TIGIT expression on $CD8^+$ T cells from peripheral blood collected from patients with AML was increased and was associated with poor prognosis [26] . However as revealed by Ma et al., Increased TIGIT expression in gastric cancer appears to be a positive indicator. It is associated with an active immune landscape, improved survival, greater sensitivity to immunotherapy, and a favorable prognosis. Patients with high TIGIT expression respond better to immunotherapy compared to those with low TIGIT expression [37].

Preclinical studies have shown that blocking TIGIT can enhance the activity of T cells and NK cells [27, 30]. This blockade prevents TIGIT from binding to CD155, thereby allowing CD226 to interact with CD155 unimpeded. The interaction of CD226 with CD155 provides stimulatory signals that promote T cell and NK cell activation, proliferation, and cytotoxic activity against tumor cells. However, single TIGIT blockade is found to be insufficient in suppressing the growth of tumors in several experimental tumor models [21, 38, 39].. Several groups have shown that, combining TIGIT blockade with inhibitors of the PD-1/PD-L1 pathway, another critical immune checkpoint pathway, shows synergistic effects. Blocking both TIGIT and PD-1/PD-L1 pathways can significantly enhance anti-tumor immunity by unleashing T cell and NK cell responses, leading to more effective tumor eradication [39, 40, 41]. Zhang et al, observed that while a single TIGIT inhibitor only upregulated IFN-γ and TNF-α, the combination of anti-TIGIT and anti-PD-1 inhibitors significantly upregulated IL-2, IFN-γ, and TNF-α in CD4+ and CD8+ T cells. This combination could enhance the anti-leukemia immune response. [42]. In the MC38 model, the combined blockade of TIGIT and PD-1 resulted in significantly enhanced effector functions of both CD4+ and CD8+ T cells compared to blocking either pathway alone. Additionally, this dual blockade achieved a 100% cure rate [43].

These findings have generated significant interest in the potential therapeutic use of TIGIT inhibitors in cancer immunotherapy [44, 45]. Clinical trials are ongoing to evaluate the safety and efficacy of TIGIT blockade, both as monotherapy and in combination with PD-1/PD-L1 inhibitors, in various types of cancer [NCT04952597, Ociperlimab (anti-TIGIT antibody) + tislelizumab (PD-1 inhibitor) + chemoradiotherapy or Tislelizumab + chemoradiotherapy] [NCT04995523, AZD2936 (bispecific, humanized IgG1 targeting PD-1 and TIGIT)] [NCT04746924, ociperlimab+ tislelizumab or Pembrolizumab] [NCT03563716, Tiragolumab (TIGIT inhibitor) + atezolizumab] [NCT04256421, Tiragolumab + atezolizumab + chemotherapy or Atezolizumab + chemotherapy] [NCT04294810, Tiragolumab + atezolizumab or Atezolizumab] [NCT04672356 , IBI939 (anti TIGIT monoclonal antibody) + sintilimab (PD-1 blocker)]. The results of these trials, may pave the way for new treatment strategies that improve the outcomes for patients with cancer by utilizing the power of the immune system. A recent clinical trial discovered that Elraglusib (9-ING-41) decreased TIGIT expression on CD8+ T cells, thereby exerting an inhibitory effect on melanoma [46]. In CITYSCAPE trial (phase 2 study) , patients with chemotherapy-naive, PD-L1-positive, recurrent, or metastatic non-small cell lung cancer (NSCLC), the combination of tiragolumab (anti-TIGIT inhibitory immune checkpoint agents) and atezolizumab (anti-PD-L1) demonstrated a clinically meaningful improvement in objective response rate and progression-free survival compared to placebo plus atezolizumab [40].

2.2 LAG-3 (Lymphocyte Activation Gene-3)

LAG-3 (Lymphocyte Activation Gene-3) is a 55 kDa type I trans-membrane glycoprotein consisting of four

extracellular immunoglobulin (Ig)-like domains (D1–D4) , a inter-connecting peptide, and an intracellular region that transmits inhibitory signals to the T cell upon binding to MHC class II and other ligands [47, 48]. It is expressed on activated T cells, some activated B cells, Tregs, natural killer (NK) cells, plasmacytoid dendritic cells and neurons, and subjected to epigenetic regulation [48, 49, 50]. Research on LAG-3 knockout mice and LAG-3 antibodies has shown that LAG-3 primarily plays a role in negatively regulating the activation, proliferation, effector function, and homeostasis of T cells [51, 52, 53]. LAG-3 has structural similarities to the CD4 co-receptor, including a similar domain architecture and approximately 25% amino acid sequence identity. It binds to MHC class II but has distinct functional properties [53, 54]. .

The primary/ canonical ligand for LAG-3 is MHC class II molecules, which are expressed on antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B cells [55, 56]. Other LAG-3 ligands include galectin-3 (Gal-3), fibrinogen-like protein 1, α-synuclein and Liver Sinusoidal Endothelial Cell Lectin (LSECtin) [57]. LAG-3 binds to MHC with a higher affinity than CD4, thereby disrupting CD4–MHC-II interactions [58]. When LAG-3 binds to MHC class II molecules, it transmits inhibitory signals to the T cells, leading to reduced T cell proliferation, cytokine production, and overall activity. This interaction helps maintain immune homeostasis and prevents excessive immune responses that could lead to tissue damage or autoimmunity [57, 59].

In the context of cancer, the inhibitory signals delivered by LAG-3 is seen to contribute to the immune evasion mechanisms of tumors [60, 61]. Tumor cells and the TME can exploit LAG-3 to suppress anti-tumor immune responses, allowing tumors to grow and spread unchecked. Therefore, targeting LAG-3 has emerged as a promising strategy in cancer immunotherapy [62]. The co-expression of LAG-3 and PD-1 in T cells serves as a biomarker for significant T-cell dysfunction in cancer and is linked to resistance against anti-PD-1/anti-PD-L1 immunotherapies [58, 63]. In a study involving three distinct transplantable tumors, Woo et al. demonstrated that the immune inhibitory molecules LAG-3 and PD-1 work together to regulate T-cell function, thereby facilitating tumor immune escape [64]. Wang et al documented that, high expression of LAG-3 in residual tissues, especially in combination with PD-L1, was associated with poor prognosis in 148 pre- and 114 post-neoadjuvant chemotherapy (NACT) specimens of human Triple-Negative Breast Cancer (TNBC) tissue [65].

Preclinical studies and early-phase clinical trials had shown potential of LAG-3 inhibitors, particularly in combination with other checkpoint inhibitors such as PD-1/PD-L1 inhibitors [66, 67]. LAG-3 targeting molecules include: anti-LAG-3 monoclonal antibodies, bispecific molecules, LAG-3 fusion protein and CAR-T cells [68]. Wierz et al. documented that, dual blockade of PD-1 and LAG-3 immune checkpoints restricts tumor development in a murine model of chronic lymphocytic leukemia [67]. In mouse models, Thudium et al., documented that simultaneous blockade of LAG-3 and PD-1 using surrogate antibodies led to enhanced antitumor activity that surpassed the effects observed with blockade of either receptor alone [69]. In a study by Matsuzaki et al., dual blockade of LAG-3 and PD-1 during T-cell priming significantly enhanced the proliferation and cytokine production of NY-ESO-1 ("cancer-testis" antigen) -specific CD8+ T cells in epithelial ovarian cancer [63]. In a phase 1 clinical trial involving patients with stage-IV renal cell carcinoma, the administration of IMP321—a recombinant soluble LAG-3 Ig fusion protein that activates dendritic cells via MHC class II, resulted in the induction of effector CD8+ T cells in all patients. Additionally, high doses of IMP321 led to reduced tumor growth and improved progression-free survival [NCT00351949] [66]. RELATIVITY-047 (NCT03470922), a phase II/III trial demonstrated that the combination of relatlimab (LAG-3 inhibitor) and nivolumab (PD-1 blocking antibody) is a well-tolerated regimen that provides superior progression-free survival compared to nivolumab monotherapy in patients with unresectable or metastatic melanoma [70]. In March 2022, the U.S. FDA approved the fixed-dose combination of relatlimab and nivolumab for treating unresectable or metastatic melanoma in adult patients and pediatric patients aged 12 years and older, weighing at least 40 kg [71]. Relatlimab, the first LAG-3 inhibitor to be approved, marks the third immune checkpoint inhibitor to enter clinical practice following PD-1 and CTLA-4 inhibitors [71].

2.3 VISTA (V-domain Ig Suppressor of T Cell Activation)

V-domain Ig. suppressor of T Cell Activation (VISTA; gene *Vsir* ; also known as Dies-1, Gi24, BH-75, D1α, and PD-1H) is an emerging immune checkpoint receptor that has garnered attention for its role in regulating immune responses, particularly within the TME [72, 73, 74].. It is a type I transmembrane protein consisting of 279 amino acids (AAs). It includes an extracellular IgV domain comprising 162 AAs, a transmembrane domain spanning 21 AAs, and a cytoplasmic domain containing 96 AAs [75]. VISTA exhibits the highest sequence homology with PD-1 [73]. However, unlike PD-1, VISTA lacks a conventional immunoreceptor tyrosine-based inhibition motif (ITIM) or immunoreceptor tyrosine-based switch motif (ITSM) within its cytoplasmic domain. Instead, the intracellular tail of VISTA contains two putative binding sites for protein kinase C (PKC) and a proline-rich motif that likely serves as docking sites for signaling molecules. These features suggest that VISTA has the potential to function both as a receptor and a ligand [73]. VISTA is predominantly expressed on myeloid cells, including monocytes, macrophages, dendritic cells, microglia, neutrophils, and tumoral cells as well as on certain subsets of tumor-infiltrating lymphocytes (TILs) [72, 76]. Human VISTA has two confirmed binding partners (ligands) with immunosuppressive functions: P-selectin glycoprotein ligand-1 (PSGL-1), V-Set and Immunoglobulin domain containing 3 (VSIG3) and galectin-9 . Additionally, there are less well-confirmed ligands: VSIG8 and FOXD3 [75, 77, 78].

The main role of VISTA is to uphold an immunosuppressive environment, which is essential for preventing excessive immune responses, thereby maintaining the body's homeostasis and protecting against autoimmune tissue damage [73, 74]. However, in the context of cancer, this immunosuppressive function can be hijacked by tumors to evade immune detection and destruction. VISTA achieves this by delivering inhibitory signals to T cells, dampening their activation, proliferation, and effector functions [79]. Studies have demonstrated that tumor-infiltrating immune cells, such as CD11b+Gr1+ myeloid cells and FoxP3+ Tregs, can exhibit increased expression of VISTA, thereby dampening anti-tumoral immune responses. Additionally, the hypoxic conditions within the TME can induce overexpression of VISTA, facilitating immune evasion by tumor cells [74, 80]

VISTA is structurally similar to other immune checkpoint molecules but operates through distinct mechanisms [81]. It can act both as a receptor and as a ligand, engaging in interactions that suppress T cell activity [78]. When VISTA is expressed on antigen-presenting cells (APCs), it interacts with counter-receptors on T cells, leading to the inhibition of T cell activation. This interaction effectively suppresses the immune response by preventing the T cells from mounting a robust attack against antigens, including those presented by tumor cells [78, 79]. Conversely, when VISTA is expressed on T cells, it can receive inhibitory signals from its ligands present on APCs. This bidirectional inhibitory signaling further enhances immune suppression by dampening the activation and function of T cells [78, 79].

VISTA is often significantly upregulated in tumor-infiltrating immune cells across various cancers, including gastric cancer [82], colorectal cancer [83], melanoma [84], prostate cancer [85], TNBC [86], and acute myeloid leukemia [87]. However, the significance of VISTA expression in the TME for patient survival remains controversial, and further research is required to assess VISTA expression and function within the TME . Recent studies on non-small cell lung cancer(NSCLC) [88], esophageal adenocarcinoma [89], endometrial carcinoma [90], and breast cancer [86] have confirmed that high levels of VISTA ecpression in immune cells are associated with a better prognosis. However, a study by Kuklinski et al. on cutaneous melanoma found a negative correlation between VISTA expression in immune cells and prognosis [84]. Similarly in Ovarian Cancers, Liao et al., observed that high expression of VISTA on immune cell was significantly associated with poor prognosis [91]. In renal cell carcinoma (RCC), the presence of VISTA-positive immune cells in the venous tumor thrombus, but not in the primary RCC, was associated with a poor prognosis [92]. Additionally, recent observations have revealed that VISTA can also be expressed on tumor cells in various cancers, including ovarian [93], endometrial [93], gastric cancer [94], hepatocellular carcinoma [95] and small cell lung cancer [88].

Preclinical studies have demonstrated that blocking VISTA can reinvigorate exhausted T cells and promote their proliferation and cytotoxic activity against tumor cells. Blocking VISTA by anti-VISTA mAb can also inhibit the recruitment of MDSCs and increases dendritic cells [96]. In a study by Le Mercier et al.,

VISTA monoclonal antibody (mAb) treatment enhanced the infiltration, proliferation, and effector function of tumor-reactive T cells within the TME. VISTA blockade also altered the suppressive nature of the TME by decreasing the presence of monocytic myeloid-derived suppressor cells and increasing the presence of activated dendritic cells within the TME. Additionally, VISTA blockade impaired the suppressive function and reduced the emergence of tumor-specific Foxp3+CD4+ Tregs [80]. In the CT26 colorectal cancer model, treatment of small tumors with anti-VISTA alone led to a reduction in tumor growth. When used in combination therapy for large CT26 tumors, anti-PD-1/CTLA-4 alone was met with complete adaptive resistance. However, the addition of anti-VISTA to the regimen resulted in the rejection of half the tumors. They observed that single-cell RNA sequencing (scRNA-seq) of tumor-specific CD8+ T cells demonstrated that anti-VISTA therapy activated T-cell pathways. This was achieved by promoting co-stimulatory genes and reducing regulators of T-cell quiescence [74]. CA-170, a small molecule inhibitor targeting PD-L1 and VISTA, demonstrated robust restoration of T cell proliferation and effector functions inhibited by PD-L1/L2 and VISTA. It also showed significant anti-tumor efficacy in several immunocompetent mouse tumor models [97]. This has led to increased interest in developing VISTA-targeted therapies as a novel approach in cancer immunotherapy. The first anti-VISTA antibody to undergo human testing is CI-8993. CI-8993 is designed with putative binding sites at four residues within the C-C' loop of VISTA and has been demonstrated to block interactions with both PSGL-1 and VSIG-3. It features an active IgG1 Fc domain that enhances interactions with Fc gamma receptors and myeloid cells, supporting antibody-dependent cell cytotoxicity (ADCC) [98]. Further anti-VISTA antibodies BMS767) and HMBD-002 are in preclinical development [99]. Mehta et al., used yeast surface display to engineer an anti-VISTA antibody, SG7, which binds with high affinity to VISTA in mice, humans, and cynomolgus monkeys. SG7, as a monotherapy and even more effectively in combination with anti-PD1, slows tumor growth in multiple syngeneic mouse models [99].

In particular, combining VISTA inhibitors with other immunotherapies, such as PD-1/PD-L1/ CTLA-4 inhibitors, holds significant promise [78]. In a murine model of colon cancer, Dr. Lines and her team documented that anti-VISTA treatment enhanced immune cell density within the TME, with increased post-treatment infiltration of NK cells, along with CD45+, CD8+, and CD4+ T cells. Significant synergy was noted when anti-PD-1 and anti-CTLA-4 treatments were combined, compared to monotherapy. This combination resulted in further tumor growth reduction and diminished the suppressive nature of myeloid cells within the TME [74]. The rationale for combination therapy is that simultaneously targeting multiple immune checkpoints can produce synergistic effects, leading to a more robust and sustained anti-tumor immune response [100]. For instance, while PD-1/PD-L1 inhibitors work by lifting the "brakes" on T cells, VISTA inhibitors can further enhance T cell activation by disrupting additional inhibitory pathways. This multi-faceted approach can potentially overcome resistance mechanisms that limit the effectiveness of single-agent therapies. Clinical trials are currently underway to evaluate the safety and efficacy of VISTA inhibitors, both as monotherapies and in combination with other checkpoint inhibitors [101]. Several VISTA-targeting inhibitors are being tested in phase I and II trials in patients with advanced, metastatic or unresectable solid tumors (NCT04475523) (NCT05082610) (NCT04564417). A phase 1 dose-escalation study (NCT04475523) is currently being conducted in patients with advanced, treatment-resistant solid tumors to evaluate CI-8993 (anti-VISTA antibody). So far, the safety data suggests that the treatment is manageable, with no dose-limiting side effects noted up to a dose of 0.6 mg/kg [102]. In a phase II TRIAL, oral dual inhibitor targeting both VISTA and PD-L1, known as CA-170, exhibited a clinical benefit rate of 75% and achieved a median progression-free survival (PFS) of 19.5 weeks in a cohort of eight previously treated non-squamous NSCLC patients [103].

2.4 TIM-3 (T cell Immunoglobulin and Mucin-domain containing-3)

TIM-3 (T cell Immunoglobulin and Mucin-domain containing-3), discovered in 2002, is a member of the TIM family of immunoregulatory proteins [104, 105]. TIM member family protein is characterized by a common structural organization that includes an amino-terminal immunoglobulin variable domain (IgV domain) with five noncanonical cysteines, a mucin stalk, a trans-membrane domain, and a cytoplasmic tail [105]. Nuclear factor of activated T cells (NFAT) signaling has been demonstrated to influence the regulation of Tim-3 in CD8+ T cells [106]. Tim-3 expression is also regulated by at least three transcription factors: NFIL3, T-bet,

and STAT3 [107].

TIM-3 is an inhibitory receptor expressed on various IFNγ-producing immune cells, including CD4 + T cells, CD8 + T cells,, natural killer (NK) cells, FoxP3 + Treg cells, dendritic cells, macrophages and monocytes [108, 109]. TIM-3 plays a critical role in regulating immune responses and maintaining immune homeostasis. It is involved in suppressing immune responses and inducing immune tolerance, primarily by depleting CD8(+) T-cells. While this function can help prevent autoimmunity, it is detrimental in the context of cancer [105, 108, 110]. TIM-3 protein also has a role in efferocytosis [111, 112]. Fourcade et al. observed that in melanoma patients, the upregulation of Tim-3, in conjunction with PD-1, results in a subset of CD8+ T cells that are highly non-responsive [113].

TIM-3 interacts with several ligands, the most well-studied of which is galectin-9 (gal-9). Other ligands include phosphatidylserine (PtdSer), high mobility group protein B1 (HMGB1), and, cancer-embryonic antigen cell adhesion molecule 1 (CEACAM1) [105, 107]. These ligands attach to different regions on the TIM-3 extracellular immunoglobulin V domain [105, 107, 114]. The interaction between TIM-3 and its ligands transmits inhibitory signals to immune cells, leading to the suppression of their activation and effector functions [107]. For instance, the binding of galectin-9 to TIM-3 on T cells can induce cell death or exhaustion, a state where T cells lose their ability to proliferate and produce cytokines in response to antigen stimulation [115].

In cancer, TIM-3 expression is often upregulated on T cells within the TME. This upregulation contributes to the immune evasion mechanisms of tumors by suppressing the anti-tumor immune response. High levels of Tim-3 expression are associated with the suppression of T cell responses and T cell dysfunction, also known as T cell exhaustion, which is a gradual loss of T cell function in a hierarchical manner during tumor development [114]. TIM-3 activates the IL-6-STAT3 pathway, which directly suppresses CD4+ T cells and inhibits Th1 polarization (development [114]. TIM-3 is also expressed on other immune cells in the TME, including Tregs and myeloid-derived suppressor cells (MDSCs), further contributing to an immunosuppressive environment [116].

Blocking TIM-3 has emerged as a promising strategy to rejuvenate exhausted T cells and enhance anti-tumor immunity [114]. By inhibiting the interaction between TIM-3 and its ligands, TIM-3 blockade can restore the function of exhausted T cells, increasing their proliferation, cytokine production, and cytotoxic activity. Preclinical studies have shown that TIM-3 blockade can enhance anti-tumor immunity. A study by Ngiow et al. observed that anti-mouse TIM-3 monoclonal antibodies (mAb) used against experimental and carcinogen-induced tumors enhance CD8+ and CD4+ T cells IFN-γ-mediated antitumor immunity and suppress established tumors [117]. A study by Kikushige and Miyamoto, in xenograft models reconstituted with human acute myeloid leukemia leukemic stem cells (AML LSCs) or hematopoietic stem cells (HSCs), a TIM-3 mouse IgG2a antibody with cytotoxic activities eliminated AML LSCs in vivo, while preserving normal human hematopoiesis [118].

When used in combination with other ICIs, such as PD-1/PD-L1 inhibitors, TIM-3 blockade has demonstrated synergistic effects [119]. The rationale for this combination therapy is that targeting multiple inhibitory pathways can produce a more comprehensive and potent reactivation of T cells. PD-1/PD-L1 inhibitors lift the suppression mediated by the PD-1 pathway, while TIM-3 blockade further enhances T cell function by targeting a different inhibitory mechanism [120, 121]. Sakuishi et al. observed that T cells expressing Tim-3 also co-express PD-1, with Tim-3+ PD-1+ TILs representing the predominant fraction of T cells infiltrating tumors, in mice bearing solid tumors. These Tim-3(+)PD-1(+) TILs display the most profound exhausted phenotype characterized by an inability to proliferate and produce IL-2, TNF, and IFN-γ. Their research also documented that simultaneous targeting of the Tim-3 and PD-1 pathways reverses T cell exhaustion and restores anti-tumor immunity more effectively than targeting either pathway alone [119]. In their study, Zhou et al. identified a distinct phenotype of exhausted T cells in mice with advanced acute myelogenous leukemia (AML), characterized by concurrent expression of Tim-3 and PD-1. This co-expression escalated as AML advanced. PD-1+ Tim-3+ CD8+ T cells exhibited impaired production of IFN-γ, TNF-α, and IL-2 in response to AML cells expressing PD-1 ligand (PDL1) and Tim-3 ligand (galectin-9). Zhou et al.

further demonstrated that individually blocking the PD-1/PDL1 or Tim-3/galectin-9 pathway failed to rescue mice from AML-induced mortality. However, a synergistic effect was observed in reducing tumor burden and mortality when both pathways were simultaneously targeted [122]. In a work by Fourcade et al., dual blockade of PD-1 and Tim-3 enhanced the expansion and cytokine production of vaccine-induced CD8(+) T cells in vitro [123]. In a murine model of ovarian cancer, Guo et al. noted that either anti-TIM-3 or CD137 mAb alone was unable to prevent tumor progression in mice bearing established tumor, however, combined anti-TIM-3/CD137 mAb significantly inhibited the growth of these tumors with 60% of mice tumor free 90 days after tumor inoculation. Therapeutic efficacy was associated with a systemic immune response with memory and antigen specificity [124].

Ongoing clinical trials are assessing the safety and efficacy of TIM-3 inhibitors, both as standalone treatments [NCT04823624, MBG453] [NCT04623892, TQB2618] [NCT03489343, Sym023], and in combination with other checkpoint inhibitors [NCT03680508, TSR-022 (cobolimab, TIM-3 binding antibody) and TSR-042 (dostarlimab, PD-1 binding antibody)] [NCT04139902, anti-PD-1/anti-TIM-3 combination (TSR-042 / TSR-022)] [NCT03708328, TIM-3/PD-1] . The results of these trials will provide important insights into the potential of TIM-3 inhibitors as a new class of immunotherapies.

2.6 B7-H3 (CD276) and B7-H4

B7-H3 (also known as CD276) and B7-H4 (also known as B7S1, B7x, or Vtcn1)) are members of the B7 family of immune checkpoint molecules, which play crucial roles in regulating immune responses [149, 150]. These proteins are involved in maintaining immune homeostasis by delivering co-stimulatory or co-inhibitory signals to T cells and other immune cells upon interaction with their respective receptors [149, 150].

B7-H3 is a type I trans-membrane protein, discovered in 2001, that is widely expressed on both tumor cells and immune cells within the TME but but seldom in normal cells [151]. Its expression pattern varies across different cancer types but is notably upregulated in many solid tumors, including colorectal cancer, gastric cancer, esophageal cancer [152], pancreatic cancer [153], prostate cancer [154], ovarian cancer [155], and breast cancer [156].

Initially at the time of its discovery, it was reported that B7-H3 exerted a co-stimulating effect on the proliferation of both $CD4^+$ and $CD8^+$ T cells [157, 158, 159], but latter on a larger majority of studies has revealed that B7-H3 induces a more robust immune evasive effect when deregulated in cancers. Suh et al. discovered that murine B7-H3 inhibits T cell proliferation when mediated by antibodies targeting the T cell receptor or allogeneic antigen-presenting cells [160]. Veenstra et al. in their study observed that B7-H3 is responsible for providing a negative costimulatory signal [161]. In osteosarcoma and hypopharyngeal squamous cell carcinoma, B7-H3 expression showed a negative correlation with the presence of circulating CD8+ tumor-infiltrating lymphocytes, suggesting its involvement in tumor immune evasion [162, 163]. A study conducted by Cong et al. found that elevated levels of CD24 and B7-H3 were associated with a poor prognosis in breast cancer patients [156]. Another study identified B7-H1 and B7-H3 as independent predictors of poor prognosis in patients with non-small cell lung cancer [164]. Additionally, a study on clear cell renal cell carcinoma patients demonstrated that higher cytoplasmic expression of B7-H3 was significantly associated with increased nucleolar grade, lymph node invasion (LNI), invasion of Gerota's fascia, and tumor necrosis [165]. Hence, B7-H3 has garnered attention as a potential therapeutic target due to its role in promoting tumor immune evasion. In cancer, B7-H3 can exert immunosuppressive effects through multiple mechanisms. It can deliver inhibitory signals to T cells, leading to decreased T cell activation, proliferation, and cytokine production.Moreover, B7-H3 expression on tumor cells can directly promote their survival and resistance to immune-mediated destruction [166]. B7-H3 is also seen to induce drug resistance in various cancers [167, 168]. Targeting B7-H3 with specific inhibitors or blocking antibodies has shown promise in preclinical studies and early clinical trials. In vitro and in vivo studies have shown, that experimental depletion or blocking of B7-H3, enhance the anti-tumor immune response and inhibit tumor cell proliferation and migration [169, 170, 171, 172].) Attempts are being made to target B7-H3 via.,**monoclonal antibodies, bispecific antibodies,** antibody–drug conjugates (ADCs), **CAR T cells and CAR NK cells, and B7-H3 small-molecule inhibitors** [166, 172, 173]. Through these modalities, several clinical trials are in progress

: targeting B7-H3 with monoclonal antibody (MGA271) [NCT01391143] [NCT02923180] [NCT02982941] [NCT02381314], targeting B7-H3 with bispecific antibodies [NCT02628535] [NCT03406949], targeting B7-H3 through ADC therapies [NCT05280470] [NCT04145622] [NCT03729596] [NCT02475213], targeting B7-H3 with CAR T cells [NCT04385173] [NCT04077866] [NCT04185038] [NCT04432649] [NCT04637503] [NCT05143151] [NCT05190185], targeting B7-H3 with CAR NK cells [NCT04630769] [NCT03056339] and radioimmunotherapy [NCT04022213] [NCT04167618] [NCT04743661] [NCT03275402]. Preliminary data from some of the clinical trials have shown promising results [174, 175].

B7-H4 is another member of the B7 family that functions as a negative regulator of T cell responses [176, 177]. It is primarily expressed on tumor cells and certain immune cells, such as macrophages and dendritic cells, within the TME [177, 178]. Similar to B7-H3, B7-H4 expression is upregulated in several cancers, including melanoma, colorectal, prostate, ovarian , breast cancer, urothelial lung and renal cell carcinoma [178, 179, 180, 181, 182]. Its expression is associated with various adverse clinicopathological features, such as larger tumor size, higher primary tumor classification, elevated TNM clinical stage, reduced tumor-infiltrating lymphocyte counts, and decreased survival rates [178, 179, 180, 181, 182]. The interaction of B7-H4 with its receptor(s) on T cells leads to inhibitory signals that dampen T cell activation and effector functions. This results in reduced T cell proliferation, cytokine secretion, and cytotoxic activity against tumor cells. B7-H4 suppresses T-cell proliferation and IL-2 production by disrupting the activation of ERK, JNK, and AKT pathways [183]. Additionally, B7-H4 can promote tumor immune evasion by modulating the function of antigen-presenting cells and enhancing the recruitment of Tregs, which suppress anti-tumor immune responses [184]. A study by Sica et al., noted that administration of B7-H4 Ig into mice impairs antigen-specific T cell responses whereas blockade of endogenous B7-H4 by specific monoclonal antibody promotes T cell responses [176]. In their study, Zhou et al. observed that B7-H4 was highly expressed in breast carcinomas. They found that B7-H4 surface expression on tumor cells was inversely correlated with CD8+ T lymphocyte infiltration, and these tumor cells exhibited enhanced growth in immunocompetent mice [177]. In human cervical cancer, a study found that B7-H4 promotes the proliferation of Tregs and the secretion of IL-10 and TGF-β1 [185]. Similarly, in colorectal cancer, Treg cell proliferation was increased along with cancer tolerance under influence of B7-H4 [182]. Various approaches, including monoclonal antibodies and fusion proteins that block the B7-H4 pathway, are being developed and evaluated in preclinical and clinical settings [186]. The development of an anti-B7-H4 monoclonal antibody for cancer treatment has been completed in preclinical studies [178].

2.8 Siglec-15 (Sialic acid-binding Ig-like lectin 15)

Sialic acid-binding Ig-like lectin 15 (Siglec-15) is an emerging immune checkpoint receptor that has gained attention for its role in regulating immune responses within the TME [208]. Dr. Takashi Angata characterized Siglec-15 in 2007, identifying it as one of the most evolutionarily conserved Siglecs in vertebrates, distinctively distant from other members of its family phylogenetically [209]. It belongs to the Siglec (sialic acid-binding immunoglobulin-like lectin) family of proteins, which are characterized by their ability to bind to sialic acids present on glycoproteins and glycolipids [209, 210]. It contains only a V-set immunoglobulin (Ig) structural domain and a C2-set immunoglobulin, which has a high structural similarity to PD-L1 [208].

Siglec-15 is predominantly expressed on tumor-associated macrophages (TAMs) and other myeloid cells within the TME. It is also expressed on cancer cells [211, 212]. TAMs are a crucial component of the innate immune system and play diverse roles in tumor progression, including promoting immunosuppression and facilitating tumor growth [213].. The expression of Siglec-15 on TAMs contributes to the creation of an immunosuppressive TME by dampening anti-tumor immune responses. Chen et al. conducted research on Siglec-15 expression in tumor tissues from 60 human glioma patients and GL261 tumor models. Their findings indicated that elevated Siglec-15 levels in tumor tissues were associated with poorer survival outcomes in glioma patients. Additionally, Siglec-15 was mainly expressed on peritumoral CD68+ tumor-associated macrophages [214]. Activated macrophages expressing Siglec-15 have been shown to enhance TGF-β secretion via the DAP12-Syk pathway and suppress CD4+ and CD8+ T cell activity by binding to their respective receptors. This process contributes to tumor progression by modulating intratumoral microenvironments

through TGF-β. [215]. Another study found that inhibiting Siglec-15 expression in cultured osteosarcoma cells reduced the DUSP1-mediated suppression of p38/MAPK and JNK/MAPK expression. Additionally, DUSP1 overexpression facilitated the proliferation, migration, and invasion of osteosarcoma cells. The group concluded that Siglec-15 promotes the malignant progression of osteosarcoma cells by suppressing DUSP1-mediated suppression of the MAPK pathway [216]. Data analyzed from 13 observational studies involving 1,376 patients revealed that Siglec-15 expression is significantly associated with poor outcomes in human solid tumors. However the authors of this meta-analysis concluded that further studies are needed to determine the prognostic value of Siglec-15 in solid tumors [217]. Bioinformatics analyses revealed that elevated Siglec-15 levels are associated with poor clinical prognosis and shorter recurrence times in glioma patients. and high Siglec15 expression was related to M2 tumor-associated macrophages (TAMs), N2 tumor-infiltrating neutrophils and suppressive tumor immune microenvironment [218]. However, some studies have observed an opposite or equivocql relationship regarding prognosis. According to Chen et al., positivity for Siglec-15 is associated with a good prognosis in pancreatic ductal adenocarcinoma (PDAC) [211]. Shafi et al., in their study using quantitative immunofluorescence (QIF), assessed Siglec-15 expression in lung, breast, head and neck squamous, and bladder cancers. They observed increased expression in both tumor and immune cells. Importantly, they found that Siglec-15 expression was not prognostic for either overall survival (OS) or progression-free survival (PFS) [212].

The ligands of Siglec-15 are less characterized. The interaction of Siglec-15 with its ligands (CD44, CD11b, Muc5B) or other components of the T cell receptor (TCR) and immune synapse, triggers inhibitory signals that suppress immune activation and effector functions [219, 220]. This includes reducing the production of pro-inflammatory cytokines and inhibiting the cytotoxic activity of T cells and NK cells against tumor cells. Moreover, Siglec-15 expression on TAMs can promote their polarization towards an M2-like phenotype, which further supports tumor growth and immune evasion [221]. Siglec15 interacts with sialic acids expressed on pancreatic ductal adenocarcinoma (PDAC) cells, particularly ∝-2,3-linked sialic acids, to induce SYK phosphorylation in tumor-associated macrophages (TAMs). This interaction further promotes the production of immunoregulatory cytokines and chemokines by TAMs. In vivo studies have shown that SIglec15-positive TAMs exhibit an M2-like phenotype, which accelerates tumor growth and contributes to an immunosuppressive microenvironment. These effects were significantly reduced when a SYK inhibitor was administered, indicating the potential therapeutic benefit of targeting this pathway [222].

In the context of cancer, targeting Siglec-15 has emerged as a potential therapeutic strategy to reprogram the immunosuppressive TME and enhance anti-tumor immunity [222, 223]. Siglec15 is rising as a promising immunotherapeutic target in glial, bladder, breast, gastric, colon and pancreatic cancers. Preclinical studies have shown that blocking Siglec-15 using monoclonal antibodies or other inhibitors can alleviate immune suppression and promote immune surveillance against cancer cells. A study by Sun et al documented that Siglec-15 blocking mAbs significantly slowed down the tumor growth in mice [224]. According to a study by Wang et al., genetic ablation or antibody blockade of Siglec-15 enhances anti-tumor immunity within the TME and inhibits tumor growth in certain mouse models. [208].

By inhibiting Siglec-15, researchers also aim to shift TAMs towards an M1-like phenotype, which is associated with anti-tumor activity and the promotion of T cell-mediated immune responses [222].

Clinical trials are underway to evaluate the safety, efficacy, and optimal dosing of Siglec-15 inhibitors as monotherapy and in combination with other immunotherapies or standard treatments. Considering the preclinical functional activity and expression pattern of Siglec-15, the safety of a humanized anti-Siglec-15 monoclonal antibody, designated NC318, was assessed in a phase I clinical trial (NCT03665285) involving patients with advanced solid tumors, Result demonstrated improved outcomes for those treated with the Siglec-15 inhibitor NC318 (NCT03665285). A Phase 2 clinical trial evaluating the combination of the anti-Siglec-15 antibody NC318 with pembrolizumab (NCT04699123) has shown promising clinical activity in patients with advanced non-small cell lung cancer (NSCLC) refractory to PD-1 axis inhibitors.

2.9 CD96 (TACTILE: T cell activation, increased late expression)

A team of researchers from, Stanford University school of medicine, discovered CD96, an immunoglobulin superfamily (IgSF) member in 1992 [225]. CD96, also known as T cell activation increased late expression (TACTILE), is an emerging immune checkpoint receptor that plays a significant role in regulating immune responses, particularly in the context of cancer immunotherapy [226]. It is a type I transmembrane glycoprotein expressed on various immune cells, including T cells, natural killer (NK) cells, and subsets of dendritic cells and monocytes [226, 227, 228]. The primary function of CD96 is to modulate immune cell activation and effector functions through its interactions with ligands such as CD155 (Necl5, poliovirus receptor, PVR) [227]. CD155 is expressed on both tumor cells and antigen-presenting cells (APCs), where it acts as a binding partner for CD96, as well as for other immune checkpoint receptors like TIGIT and CD226 (DNAM-1) [229, 230]. CD96 shares similarities with TIGIT in terms of its binding competition with CD226 for CD155 [229]. This competition is crucial in regulating the balance between stimulatory and inhibitory signals that control immune responses. CD226 is an activated receptor on the surface of T and natural killer (NK) cells. In vivo experiments have demonstrated that CD226 mediates the phosphorylation of FOXO1 and activates NK cells through its interaction with CD155-expressing tumor cells [231]. CD112 is usually down regulated in tumor tissue [232]. However, when CD96 binds to CD155, it delivers inhibitory signals that dampen immune cell activation and cytotoxicity, thereby contributing to immune evasion by tumors [233].

In cancer, elevated CD96 expression has been observed on exhausted T cells and dysfunctional NK cells within the TME, correlating with reduced anti-tumor immunity and poorer prognosis [226]. A study by Xu et al. demonstrated that, high infiltration of CD96-positive cells predicted poor prognosis and reduced survival benefits from fluorouracil-based adjuvant chemotherapy in the Zhongshan Hospital (ZSHS) cohort [234]. A study by Sun et al. documented that human CD96 is associated with natural killer cell exhaustion and can predict the prognosis of human hepatocellular carcinoma [235]. The Cancer Genome Atlas (TCGA) data revealed that CD96 expression was notably elevated in high-grade gliomas, isocitrate dehydrogenase (IDH)-wildtype gliomas, and gliomas of the mesenchymal molecular subtype, in a work by Liu et al. [236]. However few study demonstrate that CD96 functions as a co-stimulatory receptor to enhance $CD8^+$ T cell activation and effector responses [237].

Therefore, targeting CD96 presents an attractive strategy to restore immune cell function and enhance anti-tumor responses. Preclinical studies have demonstrated that inhibiting CD96 can lead to enhanced NK cell and T cell activity against tumor cells [226]. Combining CD96 inhibition with other immunotherapies, such as PD-1/PD-L1 inhibitors or TIGIT blockade, holds promise for synergistically enhancing anti-tumor immunity. In three different tumor models, a study demonstrated that co-blockade of CD96 and PD-1 effectively inhibited lung metastases, significantly enhancing local NK cell IFN-γ production and infiltration [238]. A compelling study by Mittal and his team demonstrated that combining anti-CD96 with anti-PD1 and anti-TIGIT therapies yielded superior antitumor responses in various experimental mouse tumor models. These results were observed regardless of the Fc receptor engagement ability of the anti-TIGIT isotype [239]. Clinical trials are underway to evaluate the safety, efficacy, and therapeutic potential of CD96 inhibitors as monotherapy and in combination with other treatments (NCT04446351) (NCT03739710) [240].

2.10 CD112R (PVRIG: Poliovirus receptor-related immunoglobulin domain-containing)

CD112R, also known as PVRIG (Poliovirus receptor-related immunoglobulin domain-protein), is an emerging immune checkpoint receptor that plays a significant role in regulating immune responses, particularly in the context of cancer immunotherapy. It is a type I transmembrane glycoprotein expressed on various immune cells, including T cells, natural killer (NK) cells, and subsets of myeloid cells [241, 242]. It was initially named and described by Zhu et al. in 2016 [241]. The primary ligand for CD112R is CD112 (**PVRL2,** nectin-2), a member of the nectin family of adhesion molecules. CD112 is expressed on both tumor cells and antigen-presenting cells (APCs), where it serves as a binding partner for CD112R. The interaction between CD112R and CD112 delivers inhibitory signals that modulate immune cell activation and effector functions [242].

In cancer, CD112R expression has been observed on exhausted T cells and dysfunctional NK cells within the TME. Studies have shown that CD112R exhibits high expression on NK cells in ovarian, endometrial, kidney,

prostate, lung, and breast cancers [243]. In a group of 60 ovarian cancer patients, elevated CD112 expression correlated with lymph node metastasis and residual tumor presence following surgery [243]. High expression of CD112R has also been noted in liver metastases from colorectal cancer [244]. Karabulut et al. noted that serum levels of CD112R have diagnostic value, with higher levels correlating with an adverse prognostic impact on progression-free survival (PFS) in patients with early-stage colorectal carcinoma [245]. A study by Murter et al. showed that enhanced CD8+ T-cell effector function inhibited tumor growth more effectively in PVRIG-/- mice compared to wild-type mice [246]. Preclinical studies have demonstrated that CD112R blockade independently or in combination with other therapy, can lead to enhanced cytotoxicity and cytokine production by T cells and NK cells, which are crucial for recognizing and eliminating cancer cells. Blocking CD112R enhanced T-cell function, in an ex vivo study using tumor-derived T cells. When combined with TIGIT or PD-1 blockade, this effect was further enhanced [247]. A preclinical study by Xue et al. noted that, IBI352g4a, a novel humanized anti-PVRIG antibody with Fc-competent function, induced significant NK cell activation in TILs (single dose), and also T-cell activation was observed after the second dose by blocking the interaction between PVRIG and its ligand PVRL2 [248]. Blockade of CD112R separately, or in combination with TIGIT signaling sensitizes human natural killer cell functions in post-trastuzumab therapy resistant breast cancer [249]. Clinical trials are currently underway to evaluate the safety, efficacy, and therapeutic potential of CD112R inhibitors (NCT04570839 PVRIG inhibitor + BMS-986207 (TIGIT inhibitor) and nivolumab) (NCT03667716, CD112R inhibitor (COM701) +/- PD-1) [10].

2.11 HHLA2 (HERV-H LTR-associating 2)

HHLA2 (HERV-H LTR-associating 2; Human endogenous retrovirus-H Long repeat-associating 2; also called B7 homolog 5 [B7-H5]) is a member of the B7 family of immune checkpoint molecules that has garnered attention for its role in regulating immune responses, particularly in the context of cancer immunotherapy. It is a type I transmembrane glycoprotein that is expressed on various immune cells and tumor cells within the TME [250]. The discovery of HHLA2 as an immune checkpoint protein is relatively recent (1999) [251], and its precise functions are still being elucidated. However, studies have shown that HHLA2 plays a role in immune regulation by interacting with its receptors on T cells and other immune cells. It is constitutively expressed on the surface of human monocytes and can be induced on B cells [250]. HHLA2 molecule is also highly expressed in tumor associated macrophages (TAMs) [252].

HHLA2 interacts with **KIR3DL3** (killer cell Ig-like receptor with three Ig domains and a long cytoplasmic tail, also known as also known as KIRC1, KIR44, and KIR3DL,) and **TMIGD2** (T cell membrane protein with immunoglobulin and ITIM domains 2) at different sites to exhibit both inhibitory and stimulatory functions, respectively. Despite the presence of TMIDG2, the inhibitory function mediated by the KIR3DL3-HHLA2 interaction predominates. [253, 254]. Therefore, tumors may escape immune surveillance through the KIR3DL3-HHLA2 pathway by suppressing CD4 and CD8 T-cell activation and effector functions in the presence of T-cell receptor signaling. This includes reducing T-cell proliferation, cytokine production, and cytotoxic activity against tumor cells. [254, 255]. KIR3DL3-HHLA2 pathway also inhibits the cytotoxicity of an NK-cell [254].

In cancer, HHLA2 expression has been observed on various types of tumors, including osteosarcoma [256], renal cell carcinoma [257], pancreatic cancer [258, 259], melanoma [260], hepatocellular carcinoma [261], ovarian cancer [262], gastric cancer [263], colorectal cancer [264] and lung cancer [265]. Elevated levels of HHLA2 have been associated with poorer prognosis, highlighting its role as a potential target for therapeutic intervention [250, 256, 257, 261, 263, 264, 265, 266]. However, better survival and prognosis is also reported with overexpression of HHLA2 in some studies [252, 258, 260, 262,].

Targeting HHLA2 with specific inhibitors or blocking antibodies represents a novel strategy to enhance anti-tumor immunity. Considering the beneficial role of the TMIGD2 receptor, an ideal therapeutic approach would involve selectively blocking the interaction between HHLA2 and KIR3DL3 [255]. Monoclonal antibody targeting the HHLA2/KIR3DL3 pathway, which block the inhibitory activity of KIR3DL3 while preserving the immune-stimulatory effects of HHLA2 via TMIGD2 have shown promising results in pre-clinical studies [253]. A study by Wei et al. revealed that KIR3DL3 blockade inhibits tumor growth in multiple

humanized mouse models [255]. However, study by Wang et al. showed (unexpected function) targeting TMIGD2 signaling with anti-TMIGD2 monoclonal antibodies diminishes leukemia stem cell self-renewal and decreases leukemia burden in AML patient-derived xenograft models, while having minimal impact on normal hematopoietic stem and progenitor cells [267]. Clinical trials are underway to evaluate the safety, efficacy, and therapeutic potential of HHLA2 inhibitors in various cancers. In July 2023, a multicenter first-in-human study, (Phase I clinical trial, NCT06240728) commenced to evaluate NPX887, a antagonistic immunoglobulin G1 (IgG1) monoclonal antibody targeting HHLA2 (B7-H7)\ KIR3DL3 interaction. This antibody aims to reactivate exhausted T and NK cells in HHLA2-positive solid tumors. The trial focuses on recurrent or metastatic solid tumors, including renal cell carcinoma (RCC), non-small and small cell lung carcinoma, colorectal carcinoma (CRC), and TNBC.

3. Novel Co-Stimulatory Molecules

Co-stimulatory molecules are a diverse group of proteins expressed on the surface of antigen-presenting cells (APCs) and other cells involved in immune responses. They play a crucial role in amplifying or reducing (Secondary signals), the initial activation signals delivered to T cells by the T cell receptor (TCR) following its interaction with an antigen/major histocompatibility complex (MHC), thereby influencing T cell differentiation and outcome. [268, 269]. Hence, co-stimulatory molecules provide secondary signals to T cells in addition to the primary signal delivered through the T cell receptor (TCR) interaction with antigen-presenting molecules (e.g., MHC molecules).

The primary function of co-stimulatory molecules is to ensure that T cell activation occurs appropriately in response to pathogens or other stimuli (Figure 2). Without adequate co-stimulation, T cells may become tolerant or undergo apoptosis (cell death) instead of becoming activated and mounting an immune response [268, 270] Traditionally, the best-known co-stimulatory molecules belong to the CD28 family, such as CD80 (B7-1) and CD86 (B7-2), which interact with CD28 on T cells to promote activation [268, 271].

However, ongoing research has identified several novel co-stimulatory molecules that expand our understanding of immune regulation and offer new opportunities for therapeutic interventions (Figure 2). These novel co-stimulatory molecules can be classified into different families based on their structural and functional characteristics. For example, members of the TNF receptor superfamily (e.g., OX40, 4-1BB) and the TNF ligand superfamily (e.g., CD40, CD27) have emerged as important regulators of T cell responses [268, 271, 272] Other families include adhesion molecules (e.g., ICOS, LFA-1) and receptors involved in cytokine signaling (e.g., IL-2R, IL-7R) [273, 274]. These co-stimulatory molecules are mainly categorized into two groups: the immunoglobulin superfamily (IgSF) include CD28, inducible co-stimulator (ICOS) and CD226. and the tumor necrosis factor receptor superfamily (TNFRSF) including OX40 receptor (CD134; TNFRSF4), CD27, 4-1BB (CD137; TNFRSF9), and glucocorticoid-induced TNFR-related (GITR) protein (CD357; TNFRSF18), death receptor 3 and CD40) [275, 276]. Additionally,**cell adhesion molecules including CD2 and LFA-1 (Lymphocyte Function-Associated Antigen 1) act as** co-stimulatory molecules [277].

The roles of these co-stimulatory molecules vary widely. Some enhance T cell activation and effector functions, promoting immune responses against infections and tumors. Others regulate immune tolerance and prevent excessive immune activation, thereby maintaining immune homeostasis and preventing autoimmune diseases [268].

3.1 ICOS (Inducible T-cell CO-Stimulator)

Inducible T-cell CO-Stimulator (ICOS, cluster of differentiation (CD278)), a member of the IgSF, is a pivotal co-stimulatory receptor expressed on activated T cells (activated CD4 and CD8 T cells), belonging to the CD28 family of molecules. ICOS is also constitutively expressed by $FOXP3^{+}CD25^{+}CD4^{+}$ Treg [278]. ICOS was first identified in humans and shortly after in mice [279, 280]. It shares significant homology with the co-stimulatory molecule CD28 and the immune-attenuator CTLA-4 [279]. It plays a crucial role in regulating immune responses by providing additional signals that amplify T cell activation and function [279, 280].

ICOS is typically up-regulated following T cell activation and interacts with its ligand, ICOS ligand (ICOSL),

primarily expressed on antigen-presenting cells (APCs) such as dendritic cells, macrophages, B cells, and somatic cells, including tumour cells in the TME. [281, 282, 283, 284]. The interaction between ICOS and ICOSL elicits a range of activities across different T cell subpopulations, including T cell activation and effector functions. When this interaction is prolonged, it also mediates suppressive activities through regulatory T cells. [285]. The ICOS/ICOSL axis may influence both anti-tumor T cell responses and pro-tumor responses due to its association with the suppressive activity of Tregs, thus exhibiting a dual effect [286]. The signaling pathway triggered by ICOS engagement leads to enhanced production of cytokines such as interleukin-4 (IL-4), interleukin-10 (IL-10), and interferon-gamma (IFN-γ), which are critical for shaping immune responses [285].

In the context of cancer immunotherapy, ICOS/ICOSL axis has been demonstrated to promote anti-tumor T cell responses when activated in Th1 and other Teff cells, or to promote protumor responses when triggered in Tregs [285, 287]. Combining ICOS agonists with ICIs, such as antibodies targeting PD-1 or CTLA-4, have shown to potentiate the effect of inhibitory checkpoint blockade in preclinical studies [288, 289]. A study by Fan et al. observed that in mouse models of melanoma and prostate cancer, simultaneous CTLA-4 blockade and ICOS engagement through tumor cell vaccines engineered to express the ICOS ligand enhanced antitumor immune responses both quantitatively and qualitatively, significantly improving tumor rejection [288]..Both agonistic (GSK3359609, JTX-2011) and antagonistic (MEDI-570, KY1044) monoclonal antibodies (mAbs) targeting the **ICOS/ICOSL** pathway are being explored for cancer immunotherapy in clinical trials [285]. INDUCE-2 (NCT03693612) a Phase I/II, open-label clinical trial, in patients with advanced solid tumors, anti-ICOS agonist (feladilimab) , administered alone or combined with an anti-CTLA-4 antibody tremelimumab, showed promising outcomes in tolerability, toxicity profile, but showed limited efficacy [290]. The Phase I/II ICONIC Trial investigated the ICOS agonist Vopratelimab, both as a monotherapy and in combination with nivolumab, in patients with advanced solid tumors. The trial demonstrated a favorable safety profile for Vopratelimab alone and in combination with nivolumab, particularly in patients with high ICOS CD4 T-cell populations [291]. ICOS mAbs are unlikely to be used as monotherapy because they do not independently induce satisfactory cytotoxic immune responses [285].

3.2 OX40 (CD134)

OX40 (also known as CD134 or or TNFRSF4) is a co-stimulatory receptor expressed primarily on activated T cells (regulatory T phenotypes constitutively and by effector T cells after activation), belonging to the tumor necrosis factor receptor (TNFR) superfamily [275]. Its interaction with its ligand, OX40 ligand (OX40L), which is expressed on antigen-presenting cells (APCs) and other cell types (vascular endothelial cells, mast cells, and some T cells.), plays a critical role in regulating immune responses [275, 292].

Upon binding to OX40L, OX40 signaling delivers potent co-stimulatory signals to T cells. These signals promote T cell activation, expansion, survival, and differentiation into effector and memory T cells. OX40 signaling also enhances the production of cytokines such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), which are crucial for orchestrating effective immune responses against pathogens and tumors [292, 293].

Agonistic antibodies or other agents (OX40L-Fc fusion proteins, transfected DCs with OX40L mRNA, and tumor cells engineered to express OX40L on their surface, immune-activating recombinant modified vaccinia virus Ankara (rMVA, MVA[?]E5R-Flt3L-OX40L)), that activate OX40 have shown encouraging result [275, 294, 295, 296] These agents aim to amplify T cell responses within the TME, where immune responses are often suppressed. By enhancing T cell activation and function, OX40 agonists can potentially overcome immune evasion mechanisms employed by tumors and improve the efficacy of anti-cancer immune responses. Fully human IgG1 agonist mAb developed include INCAGN01949, IBI101, GSK3174998 and BMS-986178. [294, 297, 298, 299]. Fully human IgG2 agonist Ab developed include Ivuxolimab (PF-04518600) and utomilumab (PF-05082566) [300]. mRNA-2752 is a lipid nanoparticle encapsulating mRNAs encoding human OX40L, IL-36γ and IL-23 [301]. MEDI6383 is a human OX40L IgG4P Fc fusion protein. SL-279252 is a dual-sided Fc fusion protein PD1-Fc-OX40L [275]. In a study by Campos Carrascosa et al., treatment with an Fc-engineered αOX40 antibody (αOX40_v12), which has selectively enhanced FcγRIIB affinity, stimulated the

expansion of CD4+ and CD8+ TILs in vitro, as well as the secretion of cytokines and chemokines [302]. A study by Reuter et al. demonstrated that, OX40L transgenic Ewing sarcoma cells showed enhanced immune stimulation against Ewing sarcoma cells in combination with IL-2 and stimulation of CD137 [303].

Monotherapy and combination therapies involving OX40 agonists with other immunotherapies, such as ICIs (e.g., anti-PD-1, anti-CTLA-4 antibodies), are actively being explored. Phase I /II completed clinical trials include, [NCT02274155, MEDI6469] [NCT02219724, MOXR0916] [NCT01644968, 9B12] [NCT03894618, SL-279252] [NCT01303705, MEDI6469 in combination with Cyclophosphamide, radiation] [NCT03390296, PF-04518600 in combination with Azacitadine/ Avelumab/ Glasdegib/ Gemtuzumab/ Ozogamicin] [NCT02315066, PF-04518600 in combination with Utomilumab (4-1BB agonist mAb)] [NCT02410512, MOXR0916 in combination with anti-PD-L1]. Active clinical trials (currently recruiting/not recruiting) include [NCT03336606, MEDI0562] [NCT05105971, BAT6026] [NCT04714983, DNX-2440 (intra-tumoral injection)] [NCT05229601, HFB301001] [NCT04730843, ES102] [NCT04648202, FS120 (bispecific antibody, OX40/CD137)] [NCT05263180, EMB-09 (bispecific antibody, OX40 and PD-L1)] [NCT01862900, MEDI6469 in combination with stereotactic body radiation] [NCT03831295, BMS 986178 in combination with TLR9 agonist SD-101] [NCT03410901, BMS 986178 in combination with TLR9 agonist SD-101, radiation] [NCT03217747, PF-04518600 in combination with Avelumab, utomilumab, ivuxolimab, radiation] [NCT03971409, PF-04518600 in combination with Avelumab, binimetinib, utomilumab, liposomal doxorubicin, or sacituzumab govitecan] [NCT04198766, INBRX-106 in combination with Pembrolizumab] [NCT04991506, ES102 in combination with Toripalimab] [NCT04215978, BGB-A445 in combination with Tislelizumab] [NCT05109650, BAT6026 in combination with ati PD-1] For Recommended phase 2 dosing and complete response rate, also clinical trial is being done (NCT03636503)

3.4 GITR (Glucocorticoid-Induced TNF Receptor)

Glucocorticoid-Induced TNF Receptor (GITR, TNFRSF18, and CD357), is a co-stimulatory receptor expressed on various immune cells, including activated T cells and Tregs. Its expression can be upregulated upon T cell activation, and it plays a critical role in modulating immune responses [317]. In the context of Tregs, GITR seems to be a marker of active Tregs, indicated by its expression linked with other Treg activation markers or suppressive cytokines (e.g., TGF-β and IL-10), the existence of GITR+ cells in tissues with active Tregs (e.g., solid malignancies), or via. functional studies on Tregs [317].

GITR interacts with its ligand, GITR ligand (GITRL), which is expressed on APCs, endothelial cells, and other immune cells [318]. This interaction delivers co-stimulatory signals to T cells, promoting their activation, proliferation, and effector functions. GITR signaling enhances the production of cytokines such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), which are essential for promoting immune responses against pathogens and tumors [319]. One of the distinctive features of GITR is its expression on Tregs, a subset of T cells that play a crucial role in maintaining immune tolerance and preventing autoimmunity. Activation of GITR on Tregs can lead to their functional modulation, potentially reducing their suppressive activity and enhancing anti-tumor immunity mediated by effector T cells [320, 321]. According to Ronchetti et al., "GITR activation impacts Treg/effector cell interplay in four distinct ways: (1) temporary inhibition of Treg regulatory activity, (2) reduced sensitivity of effector T cells to Treg suppression, (3) killing of Tregs (particularly within solid tumors), and (4) enhanced proliferation and expansion of the Treg compartment" [317].

In the context of cancer immunotherapy, GITR has emerged as a promising target. Agonistic antibodies or other agents that activate GITR have been developed and are under investigation in preclinical and clinical studies. These GITR agonists aim to boost anti-tumor immune responses by overcoming immune suppression mediated by Tregs within the TME [322]. Also by stimulating GITR on activated T cells and modulating Tregs, GITR agonists can enhance T cell proliferation, cytokine secretion, and cytotoxic activity against cancer cells [322, 323]. A study by Amoozgar et al. concluded that, although immune checkpoint blockers (ICBs) have been unsuccessful in all Phase III glioblastoma (GBM) trials due to Treg activities, targeting GITR in Treg cells with an agonistic antibody (αGITR) promotes CD4 Treg cell differentiation into CD4 effector T cells, reduces Treg cell-mediated suppression of the anti-tumor immune response, and induces

potent anti-tumor effector cells in GBM [324]. A study by Schoenhals et al. revealed that GITR Therapy Overcomes Radiation-Induced Treg Immunosuppression and leads to enhanced effects of radiotherapy , in two tumor 344SQR murine models [325]. Clinical trials are evaluating GITR agonists as monotherapy and in combination with other immunotherapies, such as ICIs (e.g., anti-PD-1, anti-CTLA-4 antibodies). AMG 228 (NCT02437916), BMS-986156 (NCT02598960), MEDI1873 (NCT02583165), and GWN323 (NCT02740270) are various GITR mAbs currently in clinical trials [326]. The first-in-human Phase 1 trial (NCT01239134) of GITR agonism using the anti-GITR antibody TRX518 demonstrated that it is safe and produces significant immune effects in patients with incurable cancer. The trial team further indicated that there is mechanistic preclinical evidence supporting the rational combination of GITR agonism with checkpoint blockade [327].

3.6 CD27 (TNF Receptor Superfamily Member 7)

CD27, also known as TNF receptor superfamily member 7 (TNFRSF7), is a co-stimulatory receptor expressed on various immune cells, normally expressed on CD4+ and CD8+ T cells, natural killer (NK) cells and thymocytes, and on memory B cells (primed B cells) [337]. CD27 is expressed on naive CD4+ and CD8+ T cells, while most other co-stimulatory TNFRs are produced only after T cell activation [338]. Its ligand, CD70 (CD27-L, TNFSF7), is primarily expressed on activated NK cells, APCs such as dendritic cells, and on some subsets of activated T (conventional- and regulatory T cells) and B cells. The interaction between CD27 and CD70 plays a critical role in regulating immune responses, particularly in promoting T cell activation and memory formation [339, 340].

When CD27 on T cells engages with CD70, it initiates signaling pathways that enhance T cell activation, survival, and effector function. This includes promoting T cell proliferation and cytokine production, such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) [337, 341, 342]. These cytokines are crucial for orchestrating effective immune responses against infections and tumors. In addition to its role in T cell activation, CD27 signaling also contributes to the generation and maintenance of memory T cells. Memory T cells are essential for providing long-lasting immune protection against previously encountered pathogens and tumors [337, 341, 342].

Preclinical research has shown that CD27 agonists can enhance tumor-specific T cell responses, promote tumor regression, and improve survival in animal models. Agonistic anti-CD27 antibodies in a murine model of melanoma, led to reduction in growth of lung metastases and subcutaneous tumors, due to enhanced effector function and persistence, and reduced PD-1 expression of tumor infiltrating CD8(+) T cells [343]. In a study by Sakanishi et al. on mice with syngeneic T-cell lymphoma, a non-depleting agonistic mAb against CD27 demonstrated promise for cancer therapy by co-stimulating the induction of tumor-specific cytotoxic T lymphocytes (CTLs) [344]. A study by French et al. discovered that administering agonistic anti-CD27 mAbs without a DC maturation signal completely protected tumor-bearing mice, offering a highly potent method for enhancing antitumor T-cell immunity [345]. Yang et al. conducted a study showing that TanCAR-T cells, which target CD70 and B7-H3, displayed improved antitumor activity and addressed the issues of antigenic heterogeneity and variability across multiple tumor tissue samples [346].

The monoclonal antibody (mAb) targeting CD27, known as varlilumab (also referred to as CDX-1127 or 1F5), has progressed into clinical trials following promising results in preclinical studies [347, 348]. In transgenic mice expressing hCD27, the fully human IgG1 monoclonal antibody 1F5, which has agonist activity, effectively induced proliferation and cytokine production from hCD27-Tg-derived T cells when combined with TCR stimulation [348]. Early phase clinical trials have been done or are underway, for evaluating CD27 agonists either as monotherapy [NCT0146013440] [NCT0101591121] [NCT0221689044] [NCT0149782145] [NCT01813539+NCT0275925046] or in combination with other treatment modalities, including checkpoint inhibitors [NCT04081688] [NCT03038672], anti-CD20 monoclonal antibody, Rituximab [NCT03307746], and chemotherapy [NCT04023526/ NCT04150887]. Fourth-generation CAR-T cell targeting CD70 is also undergoing clinical trials [NCT03125577]. The combination of CD27 agonists with checkpoint inhibitors, for example, aims to enhance the efficacy of immune checkpoint blockade by augmenting T cell activation and overcoming immunosuppressive mechanisms within tumors. Preliminary data from these trials show promising results (well tolerated with promising biological and early clinical activity) [349, 350].

3.7 TNFRSF25 (Death Receptor 3, DR3)

TNFRSF25, or Death Receptor 3 (DR-3, also known as TRAMP, LARD and WSL-**1**), is a member of the tumor necrosis factor receptor superfamily expressed on various immune cells, including T cells and natural killer (NK) cells [351, 352]. Its ligand, TNF-like ligand 1A (TL1A or TNFSF15), is primarily expressed on antigen-presenting cells (APCs) and endothelial cells. The interaction between TNFRSF25 and TL1A plays a critical role in regulating immune responses, particularly in modulating T cell and NK cell functions [351, 352].

When TNFRSF25 engages with TL1A, it triggers intracellular signaling pathways that enhance immune cell activation and effector functions. This includes promoting T cell proliferation, survival, and cytokine production, such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α). These cytokines are essential for mounting effective immune responses against infections and tumors [353, 354].

In the context of cancer immunotherapy, TNFRSF25 has emerged as a potential therapeutic target [355]. Agonistic antibodies or other agents that activate TNFRSF25 are being investigated in preclinical studies [356]. These TNFRSF25 agonists aim to enhance anti-tumor immune responses by boosting the cytotoxic activity of T cells and NK cells against cancer cells. A study by et al. demonstrated that TNFRSF25 agonists (soluble TL1A) in mouse plasmacytomas lead to the elimination of tumor cells in a CD8(+) T-cell-dependent manner and render mice immune to subsequent tumor cell challenges. They proposed that TNFRSF25 agonists like soluble TL1A could potentially be used to enhance the immunogenicity of vaccines designed to elicit human anti-tumor CD8(+) T cells [357].

4. Targeting the Tumor Microenvironment

Targeting the tumor microenvironment (TME) has become a central focus in the search for new immune targets in cancer immunotherapy. The TME, which includes various non-cancerous cells, signaling molecules, and the extracellular matrix surrounding the tumor, plays a crucial role in helping tumors evade the immune system [358]. This approach not only weakens the tumor's defenses but also enhances the effectiveness of existing therapies. As we better understand the complex interactions within the TME, these new targets (Figure 3) offer hope for more effective and durable cancer treatments, potentially leading to improved patient outcomes.

4.1 CD73 and Adenosine Pathway

The adenosine pathway, involving the enzymes CD73 and CD39, plays a crucial role in shaping the immunosuppressive TME. These enzymes are highly expressed in various cell types within the TME, including tumor cells, endothelial cells, and infiltrating immune cells such as Tregs and stromal cells [359]. Notably, CD73 and CD39 are upregulated in response to adenosine signaling and the hypoxic conditions commonly found in tumors. The generation of adenosine through the CD39/CD73 pathway is a key mechanism underlying the immunosuppressive function of Tregs [359, 360].

The extracellular degradation of ATP by CD39 and CD73 contributes significantly to immunosuppression. This process reduces ATP-dependent immune activation and results in the production of adenosine (ADO) [359, 360]. CD73 activity on the cell surface is the rate-limiting step in the production of extracellular adenosine, a process that hinders antitumor immunity and supports tumor progression [361]. Adenosine, a nucleoside molecule, exerts its potent immunosuppressive effects by binding to specific receptors on immune cells, primarily the A2A and A2B adenosine receptors. This receptor engagement triggers a cascade of intracellular signaling events that inhibit immune cell activation and effector functions, thus enabling tumors to evade immune detection and destruction [359, 360, 362, 363].

CD73, also known as ecto-5'-nucleotidase , is an is a glycosyl-phosphatidylinositol-linked cell membrane-bound ecto-enzyme, encoded by the gene *NT5E [364].* Its primary function involves catalyzing the conversion of extracellular AMP (adenosine monophosphate) to adenosine. This enzymatic activity leads to the accumulation of adenosine in the tumor milieu, particularly heightened under conditions of

tissue hypoxia and inflammation typical of solid tumors [359]. Adenosine, upon binding to A2A and A2B receptors (A2AR and A2BR) expressed on T cells and natural killer T (NKT) cells, monocytes, macrophages, dendritic cells and NK cells, exerts potent immunosuppressive effects. These effects include the suppression of cytotoxic T cell responses, inhibition of dendritic cell maturation and antigen presentation, promotion of Treg cell differentiation and function, and reduction in pro-inflammatory cytokine production such as IFN-γ and TNF-α. [365]. A2AR is up-regulated in macrophages in response to NF-$\varkappa$B, STAT1 and PPARγ as well as adenosine signaling, and A2AR activation inhibits the secretion of neutrophil chemokines, thereby reducing the inflammatory response [359]. Thus, CD73-mediated adenosine production plays a critical role in fostering an immunosuppressive environment within tumors, contributing to immune evasion and supporting tumor progression. CD73 has been shown to play a role in various cancer processes, such as metastasis [366], tumor invasion [367], and increased cell proliferation [368].

CD39, also known as ectonucleoside triphosphate diphosphohydrolase-1 or NTPDase 1**,** is an ectoenzyme prominently expressed on immune cells, including Tregs and subsets of activated T cells [369, 370]. Its primary function involves the hydrolysis of ATP (adenosine triphosphate) and ADP (adenosine diphosphate) into AMP (adenosine monophosphate). This enzymatic activity serves as a critical step in the production of adenosine within the TME. By generating AMP, CD39 acts upstream of CD73, facilitating the subsequent conversion of AMP into adenosine [371].

A significant proportion of cancer patients fail to respond to immunotherapies such as PD-1/PD-L1 and CTLA-4 blockade, indicating that other immunosuppressive pathways may contribute to immune evasion in these non-responding tumors [372]. The adenosinergic pathway, presents a promising new therapeutic approach in cancer immunotherapy, though still in its early stages [370]. Preclinical studies and clinical trial data have shown that targeting this pathway is a viable therapeutic strategy for the future. Small-molecule inhibitors and monoclonal antibodies targeting CD39, CD73 and A2AR have been developed for cancer therapy [359, 373]. As small molecules could cross physiologic barriers in TME, they are better than monoclonal antibodies (mAb) which are macromolecules. Bastid et al. in their study showed that, administering a CD39 inhibitor or blocking antibody reduced the tumor-induced suppression of CD4 and CD8 T-cell proliferation and enhanced the cytotoxic activity of CTLs and NK cells [374]. In a lung cancer model study, an anti-CD39 monoclonal antibody, which inhibits the mouse ectoenzyme CD39, was found to increase CD107a expression in infiltrating NK cells and stimulate IFN-γ release, leading to enhanced cancer cell killing and anti-metastatic effects cells [375]. Simmilarly, in mouse model of melanoma, the administration of anti-CD39 monoclonal antibody (mAb) stimulated the release of IFN-γ , resulting in the eradication of cancer cells [375]. A study by Lu et al. demonstrated that the bifunctional antibody-ligand trap, ES014 (targeting CD39/TGF-β), effectively inhibited CD39, preventing the degradation of extracellular ATP, while also neutralizing autocrine/paracrine TGF-β near target cells leading to restoration of anti-tumor immunity [376]. Anti-CD73 monoclonal antibody (3F7), in a mouse model of TNBC, suppressed tumor growth and metastasis [376]. An experimental study by Jin et al. found that the combination of tumor CD73 knockdown with tumor-specific T-cell transfer successfully cured all tumor-bearing mice. Notably, adoptive T-cell immunotherapy alone provided no therapeutic benefit in mice with tumors that did not undergo CD73 knockdown [377]. Another study in tumor-bearing mouse models, showed that anti-CD73 antibodies can amplify the anticancer effects of both anti-CTLA-4 and anti-PD-1 immunotherapies in MC38-OVA (colon) and RM-1 (prostate) subcutaneous tumors and established metastatic 4T1.2 breast cancer. The activity of anti-PD-1 mAb was also enhanced by anti-CD73 mAb, against 3-methylcholanthrene (MCA)-induced fibrosarcomas [378]. In a study conducted by Perrot et al., it was observed that the antibodies IPH5201 and IPH5301, which target the human membrane-associated and soluble forms of CD39 and CD73 respectively, effectively inhibited the hydrolysis of immunogenic ATP into immunosuppressive adenosine. The mechanism of action involved stimulating dendritic cells and macrophages, as well as restoring the activation of T cells isolated from cancer patients [379]. Drugs that block the A2AR-mediated adenosinergic pathway could boost antitumor immunity by counteracting the effects of extracellular adenosine generated by both tissue cells and Tregs. Pharmacological treatment of mice with A2AR antagonists enhanced antitumor T-cell activity, leading to greater inhibition of tumor growth, destruction of metastases, and reduced neovascularization of

cancerous tissues [380].

Current clinical trials are evaluating adenosinergic pathway targets either as monotherapy or in combination therapy:

1. CD39 inhibitors like, **anti-CD39 monoclonal antibody** [NCT05508373, JS019] [NCT05234853, PUR001,], **CD39 antagonist** [NCT04261075, IPH5201] [NCT04336098, SRF617] [NCT05075564, ES002023], **αντι-ՇΔ39/ΤΓΦ-β βισπεςιφις αντιβοδψ** [NCT05381935, ES014], **CD39 antagonist with chemotherapy** [NCT04336098, Combination SRF617 with pembrolizumab, gemcitabine, albuminbound paclitaxel], **Anti-CD39 antibody with immunotherapy** [NCT04306900, Combination TTX-030 with immunotherapy and/or chemotherapy]
2. CD373 inhibitors like, **Anti-CD73 monoclonal antibody** [NCT05431270, PT199] [NCT05174585, JAB-BX102]; **CD73 antagonist** [NCT04797468, HLX23] [NCT04104672, AB680] [NCT03736473, MEDI9447 (oleclumab)] [NCT04148937, LY3475070] [NCT03549000, NZV930] [NCT02754141, BMS-986179] [NCT05227144, ORIC-533]; **Anti-CD73 antibody with immunotherapy** [NCT05174585, JAB-BX102 with pembrolizumab] [NCT05431270, PT199 with an anti-PD-1 monoclonal antibody] [NCT03549000, NZV930 with PDR001] [NCT04672434, Sym024 with Sym021]; **Anti-CD73 antibody with chemotherapy** [NCT05143970, IPH5301 with chemotherapy and trastuzumab] [NCT04572152, AK119 with AK104] [NCT05119998, IBI325 with sintilimab] [NCT04940286, oleclumab with gemcitabine, nab-paclitaxel, durvalumab]; **Αντι-ՇΔ73-ΤΓΦβ-Τραπ αντιβοδψ ωιτη ςηεμοτηεραπψ** [NCT03954704, dalutrafusp (GS-1423) with mFOLFOX6 regimen]; **CD73 antagonist with immunotherapy** [NCT04148937, LY3475070 with pembrolizumab] [NCT02754141, BMS-986179 with nivolumab (BMS-936558)] [NCT04989387, INCA00186 with INCB106385 and/or retifanlimab]
3. **A2AR antagonist** [NCT05501054, Ciforadenant (CPI-444)] [NCT04969315, TT-10] [NCT03207867, Taminadenant (NIR178)] [NCT02403193, PBF-509] [NCT05117177, Inupadenant (EOS100850)] [NCT04580485, INCB106385] [NCT04478513, AZD4635]; **A2AR and A2BR antagonist** [NCT04262856, Etrumadenant (AB928)];**Anti-CD39 antibody with A2AR and A2BR** [NCT05177770, SRF617 with AB928 (Etrumadenent) and AB122 (zimberelimab)];**Anti-CD73 antibody with A2AR antagonist** [NCT04089553, AZD4635 with durvalumab or oleclumab (MEDI9447)] [NCT03454451, CPI-006 with ciforadenant or pembrolizumab] [NCT03381274, oleclumab (MEDI9447) with AZD4635]; **A2AR antagonist with chemotherapy** [NCT05403385, inupadenant (EOS100850) with Chemotherapy]; **A2AR antagonist with immunotherapy** [NCT04580485, INCB106385 with immunotherapy] [NCT05501054, lpilimumab, nivolumab with ciforadenant (CPI-444)] [NCT03549000, NZV930 with PDR001 and /or NIR178] [NCT02403193, taminadenant with PDR001] NCT03207867, NIR178 with PDR001] [NCT04895748, DFF332, spartalizumab with taminadenant].

4.2 TAM Receptors (Tyro3, Axl, and Mer)

TAM receptors, comprising **Tyro3** (also called Brt, Dtk, Etk-2, Rek, Rse, Sky, and Tif), **Axl** (also called Ark, Tyro7, and Ufo), and **Mer** (also called c-Eyk, Mertk, Nyk, and Tyro12), are a family of receptor tyrosine kinases (RTK) expressed on diverse immune cells and tumor cells. It is composed of an extracellular domain, a transmembrane domain, and a conserved intracellular kinase domain [381].

The TAM receptors and their ligands, vitamin K-dependent proteins Gas6 and Protein S, play crucial roles in facilitating the effective phagocytosis of apoptotic cells and membranes within tissues. Additionally, within the immune system, they serve as versatile inhibitors that modulate the innate inflammatory response to pathogens. They also play pivotal roles in regulating processes critical to cancer progression [382]. These receptors are involved in mediating signals that promote tumor growth, survival, invasion, and metastasis, while also contributing significantly to immune evasion mechanisms within the tumor microenvironment. Among the TAM receptors, Axl has emerged as particularly significant due to its association with aggressive tumor phenotypes and resistance to therapies, making it a prime target for therapeutic intervention [383].

In preclinical models, inhibitors specifically targeting Axl have demonstrated efficacy in inhibiting tumor

growth and metastasis, as well as in enhancing anti-tumor immune responses by reprogramming the tumor microenvironment towards a more immune-supportive state. In research conducted by Lin et al., both genetic and pharmacological inhibition of AXL in resistant models led to a reduction in cell proliferation, migration, invasion, and tumor growth. These effects were notably enhanced when AXL inhibition was paired with docetaxel treatment [384]. In a study by Taniguchi et al., AXL inhibition decreased the viability of EGFR-mutated lung cancer cells overexpressing AXL treated with osimertinib (EGFR-tyrosine kinase inhibitor), resulting in reduced tumor size and delayed tumor regrowth compared to treatment with osimertinib alone [385]. In a preclinical study, glioblastoma cell lines U118MG and SF126, were treated with temozolomide (TMZ) and radiation, with and without AXL tyrosine kinase inhibitor (TKI). In the group treated with TZM and radiotherapy alongwith AXL tyrosine kinase inhibitor (R428) showed significantly increased therapeutic effects [386].

Promising preclinical findings have prompted the initiation of clinical trials aimed at evaluating the safety, efficacy, and therapeutic potential of Axl inhibitors, both as monotherapy[NCT03990454, AXL inhibitor SCL-391] [NCT02988817, AXL Antibody–drug conjugates Enapotamab vedotin] [NCT04893551, AXL monoclonal antibodies Tilvestamab (BGB149)] [NCT02729298, AXL inhibitor Dubermatinib (TP-0903)] , and in combination with other treatment modalities [NCT02424617, AXL inhibitor Bemcentinib (BGB324) + Erlotinib] [NCT02922777, Bemcentinib + Docetaxel] [NCT03649321, Bemcentinib + + Nab-paclitaxel, gemcitabine, cisplatin] [NCT03184571, Bemcentinib + Pembrolizumab] [NCT02488408, Bemcentinib ± Cytarabine or decitabine] [NCT03255083 , AXL inhibitor DS-1205 + Osimertinib] [NCT03599518 , AXL inhibitor DS-1205 + Gefitinib] , to validate the preclinical results and to determine whether targeting TAM receptors, especially Axl, can overcome resistance mechanisms and improve outcomes for cancer patients, particularly those with advanced or refractory disease.

Conclusion

The identification of new immune targets stands as a pivotal frontier in advancing cancer immunotherapy, offering substantial promise in overcoming current treatment limitations and improving outcomes for patients. Emerging immune checkpoints such as TIGIT, LAG-3, and VISTA, which regulate immune responses and are often upregulated in tumors to evade immune surveillance, present exciting opportunities for therapeutic intervention. Strategies aimed at blocking these checkpoints can potentially enhance anti-tumor immunity by unleashing the full power of the immune system against cancer cells.

Additionally, novel co-stimulatory molecules like ICOS, OX40, and CD137 provide further avenues for augmenting immune responses against tumors. These molecules, when engaged with agonistic antibodies or through other therapeutic approaches, stimulate T cell activation, proliferation, and effector functions, thereby bolstering the immune system's ability to recognize and eliminate cancer cells.

Targeting the TME represents another critical aspect of advancing cancer immunotherapy. Pathways such as CD73 and TAM receptors (Tyro3, Axl, and MerTK), which contribute to immunosuppression and tumor progression, are being actively explored as therapeutic targets. Inhibiting CD73 or TAM receptors can potentially disrupt immunosuppressive mechanisms within the TME, allowing for enhanced anti-tumor immune responses.

Moreover, personalized immunotherapy approaches centered on neoantigens offer tailored treatments that exploit the unique genetic signatures of individual tumors. By identifying and targeting neoantigens—tumor-specific antigens derived from somatic mutations—researchers can develop personalized cancer vaccines and adoptive T cell therapies that specifically target and eliminate cancer cells while sparing healthy tissues.

Continued research and clinical development in these areas are crucial for realizing the full potential of these innovative strategies in cancer therapy. Advances in understanding immune checkpoints, co-stimulatory molecules, TME interactions, and personalized neoantigen-based therapies hold promise for transforming cancer treatment paradigms. Ultimately, these efforts aim to improve patient outcomes, enhance treatment efficacy, and pave the way for more personalized and effective cancer therapies in the future.

Declarations:

Conflict of Interests: None

Funding: None

Data availability statement: Data sharing is not applicable to this article as no new data were created or analysed in this study.

Ethics Statement: Not Applicable as this is a review article

Competing interests: The author(s) declared no potential conflicts of interest.

Disclaimer: Nothing to disclise

Acknowledgement: AI used to improve the readability and language of the paper

This paper has been prepared by the above mentioned authors and reviewed and agreed upon for submission. The requirements for authorship as stated above in this document have been met, and that each author believes that the manuscript represents honest work.

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Legends to Figures

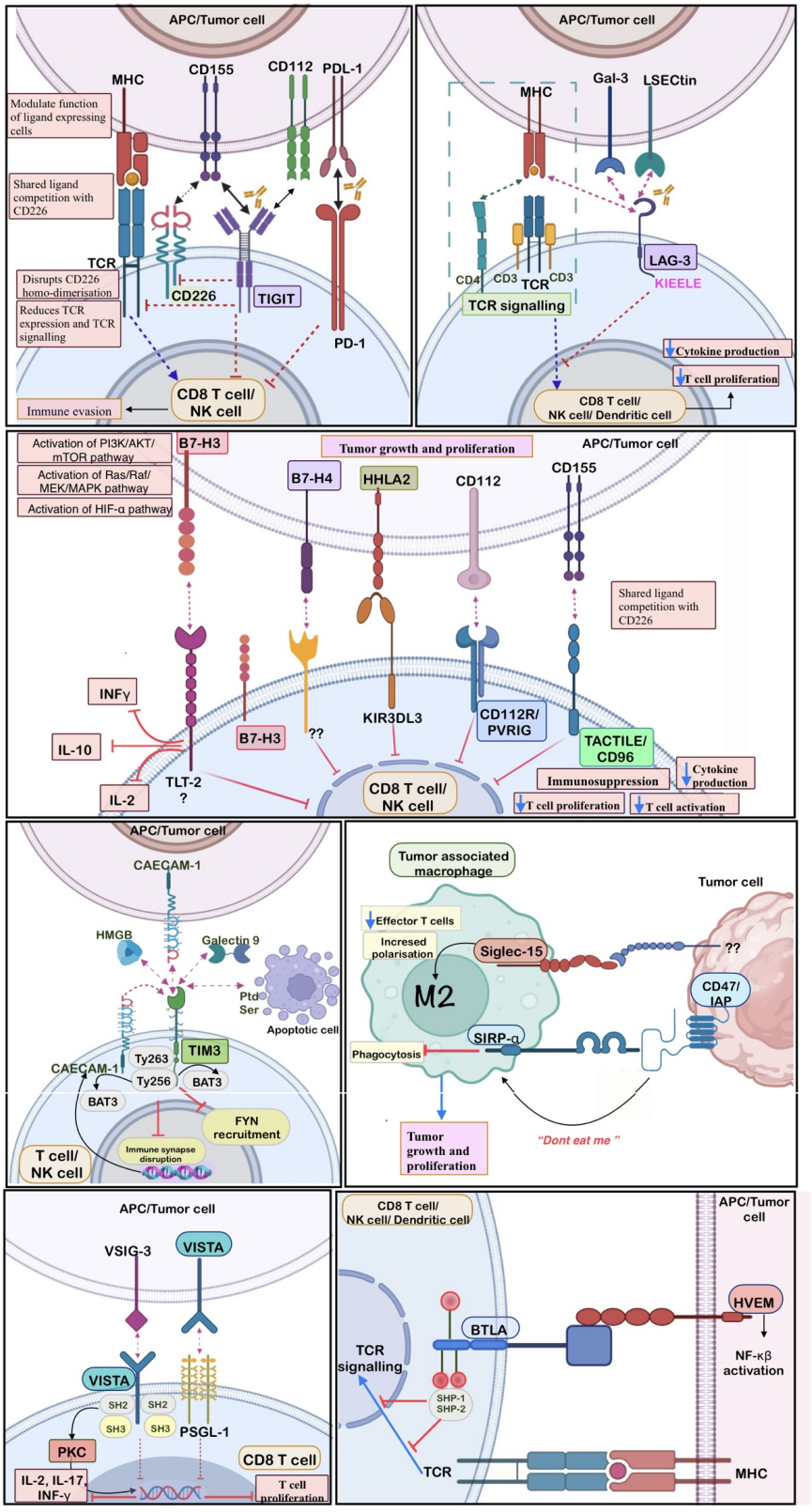
Figure 1: Emerging Immune Checkpoints in cancer immunotherapy: Interaction of emerging immune checkpoint receptors and their respective ligands. Various immune checkpoint molecules expressed on T cells are shown with their ligands on Antigen presenting cells or tumor cells. **A.** TIGIT and CD226 bind to the same ligands, CD112 and CD155. CD226 is a co-stimulatory receptor whereas TIGIT is a co-inhibitory receptor. TIGIT binds with CD112/CD155 with higher affinity than CD226 leading to the suppression of T cell and natural killer (NK) cell activity, thereby contributing to immune evasion by tumors. **B.** LAG3 binds to MHC-II to inhibit CD4-dependent T cell function with its cytoplasmic domain. TME-derived Galectin3 and LSECtin bind with LAG3 to inhibit T cell function, which requires the KIEELE motif in the LAG3 cytoplasmic domain. **C.** B7 family receptors (B7-H3, B7- H4, HHLA2) and their known and unknown ligands are inhibitory molecules which mediate various mechanisms to evade tumour-antigen-specific T-cell immunity, including T-cell apoptosis, anergy and exhaustion. **D.** TIM-3 is expressed in both T cells and innate immune cells, with four known ligands including Ceacam1, Galectin-9, HMBG1, and PS. In the absence of ligands, Bat3 binds to unphosphorylated TY256/263 in TIM3 cytoplasmic domain and recruits active Lck to deliver stimulatory signal in T cells. Interaction with Galectin9/Ceacam1 leads to phosphorylation of TIM3 TY256/263 and the subsequent abolishment of Bat3 binding. Thus, functioning as an inhibitory receptor and contributing to immune tolerance and anti-tumor immunity suppression. **E.** CD47 interacts with SIRPα, acting as a "don't eat me" signal to prevent macrophages and phagocytes from engulfing cancer cells. Siglec-15 interacts with sialylated ligands, modulating immune responses in the tumor microenvironment and contributing to immune evasion. F. VISTA serves dual immunosuppressive roles as both a ligand on tumor cells/APCs with PSGL-1 being its receptor on T cells and a receptor on T cells with VSIG-3 as its ligand. G. BTLA interacts with HVEM on APC/tumor cells causing NF-kb activation. ITIM and ITSM in BTLA recruit SHP1/SHP2 to inhibit both TCR and CD28 signaling.

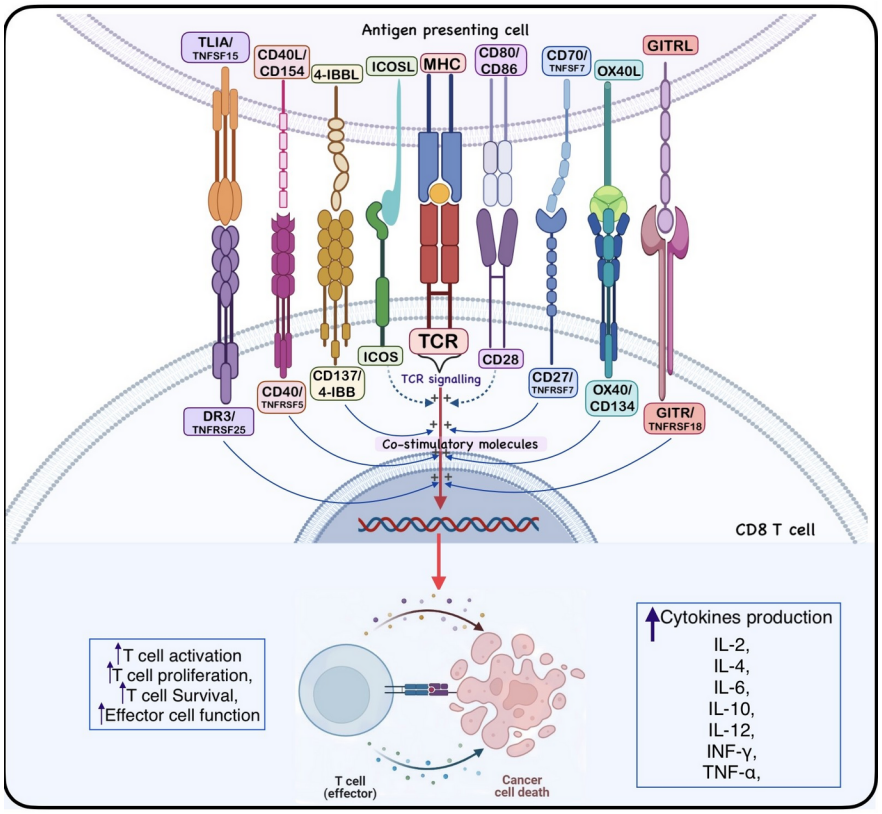
BTLA (B- and T-lymphocyte attenuator); HMGB1 (High mobility group box 1); ITIM (immunoreceptor tyrosine-based inhibitory motif); LAG3 (Lymphocyte Activation Gene 3); ITSM (immunoreceptor tyrosine-

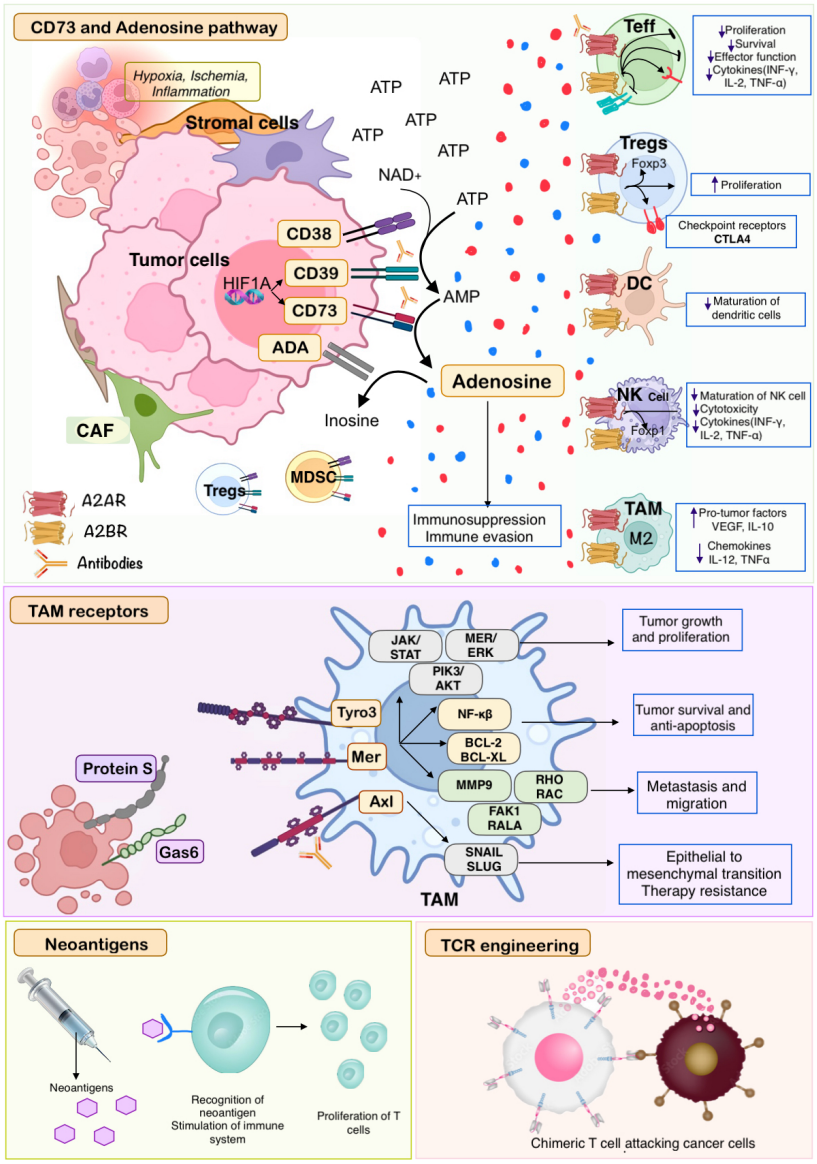
based switch motif); PSGL-1 (P-selectin glycoprotein ligand-1); SIRPα (Signal regulatory protein ALPHA); TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domain); SHP2 (Src-homology-2-containing Protein tyrosine phosphatases-2); Tim-3 (T-cell immunoglobulin and mucin domain 3); TME (tumor microenvironment); VISTA (V-domain immunoglobulin suppressor of T-cell activation)

Figure 2: Novel Co-stimulatory molecules: This diagram illustrates the interaction of various novel costimulatory molecules on T cells with their corresponding ligands on antigen-presenting cells (APCs), highlighting their roles in T cell activation and immune response modulation. GITR (Glucocorticoid-Induced TNFR-related protein), ICOS (Inducible T cell Co-Stimulator), DR3 (Death Receptor 3), TCR (T Cell Receptor), MHC (Major Histocompatibility Complex).

Figure 3: Targeting the Tumor Microenvironment: This diagram illustrates key pathways and targets within the tumor microenvironment. The adenosine pathway includes CD39 and CD73, which convert ATP to adenosine, leading to immunosuppression. TAM receptors (Tyro3, Axl, Mer) are shown, which mediate immune evasion and tumor progression. Neoantigens and TCR engineering are highlighted, representing the identification of tumor-specific antigens and the modification of T cells to enhance anti-tumor immune responses.







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