Roles of V-domain Ig suppressor of T-cell activation-mediated immunoregulation in tumor immune escape (Review)

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Abstract. V-domain Ig suppressor of T-cell activation (VISTA), a key member of the B7 family of immune checkpoint molecules, exerts regulatory effects on T-cell function both directly and indirectly, thus serving a notable role in tumor immune evasion. VISTA directly inhibits the phosphorylation of key molecules in the T-cell receptor signaling pathway, leading to a reduction in the expression levels of pro-inflammatory factors within the tumor microenvironment (TME) and the establishment of an immunosuppressive TME. Furthermore, VISTA can indirectly modulate T-cell function by regulating various immune cells, including dendritic cells, macrophages and myeloid-derived suppressor cells. Targeting VISTA can effectively restore T-cell metabolic function, with monoclonal antibodies against VISTA exhibiting notable potential in the treatment of patients with PD-1 resistance. Several inhibitors (e.g., CI-8993 and SNS-101) targeting VISTA have already entered phase I/II clinical trials. Through its dual mechanisms of directly inhibiting T-cell activation and indirectly modulating the TME, VISTA constitutes a key component of tumor immune evasion, offering a vital target for cancer immunotherapy.

Contents

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1. Introduction

Immune homeostasis relies on coordinated activities of diverse immune cells and regulatory molecules that exert precise control over nearly all immune responses (1). Disruption of this balance contributes to immunodeficiency disorders [e.g., autoimmune lymphoproliferative syndrome (2), acquired immunodeficiency syndrome (3)], tumorigenesis and infectious diseases [e.g., immune checkpoint inhibitor-associated pneumonia (4), reactivation of tuberculosis following ICI therapy (5)]. Immune checkpoints (ICs), such as programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors, have become the standard of care for multiple solid tumors (6-8). Based on the KEYNOTE-024 trial [first-line pembrolizumab for patients with advanced non-small cell lung cancer (NSCLC) with PD-L1 ≥50%; median progression-free survival (PFS) time of 10.3 vs. 6.0 months; median overall survival time of 26.3 vs. 13.4 months] (9) and CheckMate067 trial (nivolumab combined with ipilimumab for advanced melanoma; median PFS time of 11.5 vs. 2.9-6.9 months for monotherapy, with an 8-year overall survival time >72.1 months) (10,11), PD-1/PD-L1 inhibitors have markedly prolonged PFS and overall survival rates in advanced NSCLC and melanoma, establishing the central role of IC blockade in cancer treatment (12). However, the issues of primary resistance, where 30-40% of patients exhibit no initial response, and acquired resistance, where disease progresses after an initial remission, prevent PD-1/PD-L1 targeting from achieving long-term efficacy, prompting researchers to explore novel IC molecules (12,13). Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)/CD80/CD86, are key regulators that maintain self-tolerance and prevent excessive immune activation, primarily through receptor-ligand interactions (14). Although

previous studies on the blockade of the CTLA-4/CD80/CD86 pathway demonstrated a 5-year overall survival rate of 52% in the CheckMate067 trial (11,15,16), the incidence of grade 3 or higher treatment-related adverse events was 58% in the combination therapy group and 28% in the ipilimumab monotherapy group, with grade 3 or higher colitis occurring in 9.3% and colitis in 7.7% of patients and 0.5-2.1% of pituitary inflammation (15,16), all indicated a high incidence of immune-related adverse events, suggesting a need for more precise target selection and risk management in the future (17).

V-domain Ig suppressor of T-cell activation (VISTA), also known as PD-1 homolog, B7-H5, Dies1 and Gi24, is a negative IC protein that regulates T-cell responses and contribute to immune tolerance and tumor immune escape (Table SI). Structurally, VISTA belongs to the B7 family, containing an extracellular IgV-like domain that mediates its immunosuppressive function (18,19). Fig. 1 provides an overview of VISTA interactions within the immunosynapse. VISTA is expressed on antigen-presenting cells (APCs), tumor cells, and myeloid-derived suppressor cells (MDSCs) (top panel) and binds to PSGL-1 on the surface of cytotoxic T cells (bottom panel). However, it is noteworthy that although the evidence chain for VISTA functioning as a ligand to inhibit T cells is relatively complete, the absence of traditional immunoinhibitory receptor motifs such as immunoreceptor tyrosine-based inhibition motif (ITIM)/immunoreceptor tyrosine-based activation motif in its intracellular domain results in a signal transduction mechanism that differs from classical ICs, which remains incompletely elucidated to date (20,21). In tumors, VISTA upregulation is associated with immunosuppressive microenvironments and poor responses to PD-1/PD-L1 blockade. Preclinical studies reported that VISTA inhibition enhances antitumor immunity, while agonistic VISTA antibodies ameliorate autoimmune diseases (22,23). The unique expression pattern and bidirectional signaling distinguish VISTA from other checkpoints, highlighting its therapeutic potential in oncology and autoimmune diseases.

Previous reviews have systematically described the molecular characteristics and functional landscape of VISTA, exploring its expression patterns across various tumors, its bidirectional regulatory mechanisms as an IC in the B7 family and early clinical evidence for VISTA-targeted therapies. Building upon this foundation, the present review further expands and integrates the dual mechanisms of VISTA: Directly inhibiting T-cell signaling and indirectly remodeling the tumor microenvironment (TME) (13,14,17). The present review establishes a comprehensive knowledge chain spanning molecular, cellular and clinical levels, extending the understanding of the regulation of T-cell function by VISTA to the immunosuppressive network collaboratively constructed by MDSCs, macrophages and dendritic cells (DCs) (24,25). Furthermore, the present review comprehensively evaluates clinical development strategies targeting VISTA, with particular emphasis on combination therapies to overcome PD-1 resistance and the identification of predictive biomarkers (19,25,26). This integrated perspective advances fundamental understanding of bidirectional IC signaling regulation and metabolic programming, provides translational rationale for resistance reversal strategies and personalized treatment regimens, and potentially paves novel clinical pathways for patients with PD-1-resistant 'cold tumors', propelling the development of next-generation tumor immunotherapy.

2. Literature search strategy

The present review conducted as a narrative synthesis of the literature on the roles of VISTA-mediated immunoregulation in tumor immune escape A systematic literature search was performed in the following electronic databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/) and Scopus (https://www.scopus.com/), covering the period from January 2010 to March 2026. The search strategy combined key words associated with the topic using Boolean operators, including but not limited to: 'VISTA', 'immune checkpoint', 'tumor immunity', 'cancer immunotherapy', 'prognosis' and specific cancer types (for example, 'melanoma', 'pancreatic cancer' and 'NSCLC'). Additional relevant articles were identified by manually screening the reference lists of included studies. This review included a total of 135 publications, comprising 77 original studies, 34 reviews, 7 clinical trial reports, 14 conference abstracts and 3 other types of literature (website news, company press releases and clinical trial registration protocols).

Inclusion criteria were as follows: i) Original research articles, clinical trials and peer-reviewed reviews; ii) studies reporting on VISTA expression, function or therapeutic targeting; iii) articles published in English; and iv) case reports, editorials or conference abstracts

3. VISTA expression regulation and direct immunosuppressive functions

VISTA expression predicts immunotherapy resistance and clinical outcomes. During PD-1 therapy, the accumulation and functional activation of immunosuppressive cells within the tumor, including T-regulatory cells (Tregs), MDSCs and M2 macrophages, convert initially PD-1-sensitive lesions into resistant ones and ultimately lead to treatment failure (27,28). In this process, the role of VISTA has gained increasing attention. Several studies reported that high VISTA expression in tumors during PD-1 blockade is an independent risk factor for poor patient prognosis (29-31). Multiple clinical studies have demonstrated that VISTA is markedly upregulated following treatment with anti-PD-1 or -CTLA-4 agents. When the PD-1/PD-L1 pathway is blocked, VISTA acts as an independent IC to continuously suppress T-cell function and its activity is independent of the PD-1/PD-L1 or CTLA-4 signaling pathway (18,32,33). Clinical evidence revealed that in patients with a PD-1-resistant NSCLC, elevated VISTA levels were positively associated with Treg expansion, implicating them in the development of acquired resistance (34). In patients with metastatic castration-resistant prostate cancer, treatment with ipilimumab (anti-CTLA-4) was associated with a notable increase in tumor VISTA expression, which was associated with disease progression (33). Therefore, VISTA may serve as a predictive biomarker in predicting the efficacy of IC inhibitors (ICIs). An analysis of 514 solid tumor samples revealed that VISTA was the most highly expressed molecule among the nine ICs (32%) (31); in breast cancer, its expression levels were even higher compared with those of PD-1,

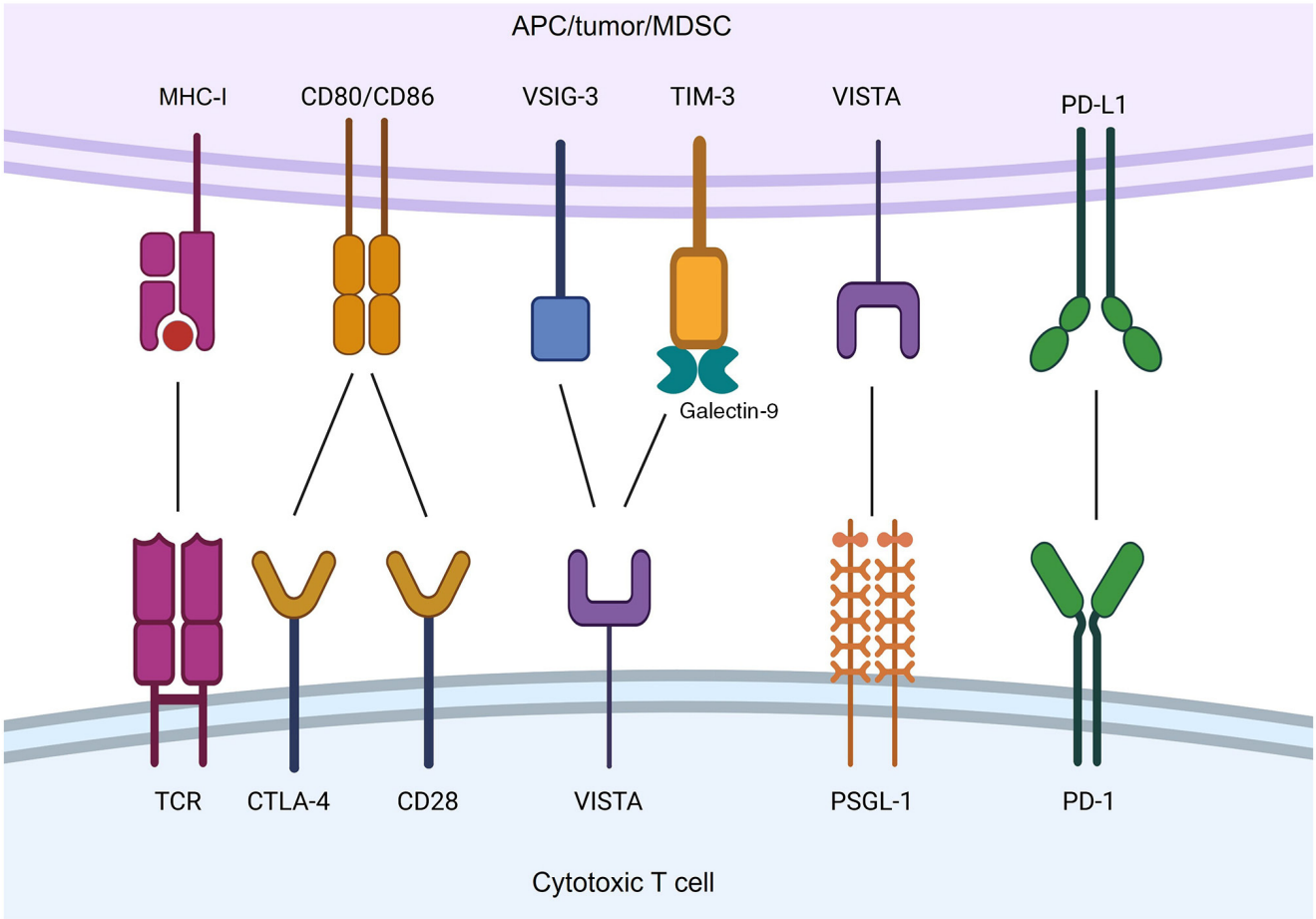

Figure 1. Interaction of VISTA with other immune checkpoints. VISTA interacts with classical antigen presentation pathways (MHC-I/TCR), multiple immune checkpoint axes (CD80/CD86-CD28/CTLA-4, PD-L1/PD-1), as well as TIM-3/galectin-9, VISTA/VSIG-3 pathway collectively constitute the multilayered inhibitory network that VISTA helps establish in the tumor microenvironment. VISTA, V-region immunoglobulin T-cell activation inhibitor; PD-1, programmed death protein-1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; APC, antigen-presenting cells; MHC-I, major histocompatibility complex class I; TCR, T-cell receptor; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; PD-L1, programmed cell death ligand 1; PSGL-1, P-selectin glycoprotein ligand 1; MDSC, myeloid-derived suppressor cells.

PD-L1, T-cell immunoreceptor with Ig and ITIM domains (TIGIT), T-cell immunoglobulin and mucin domain 3 (TIM-3) and lymphocyte-activation gene 3 (35). Le Mercier *et al* (36) further demonstrated that elevated VISTA expression on tumor-infiltrating lymphocytes were positively associated with the therapeutic benefit of VISTA-targeted therapy, underscoring its potential as a predictive biomarker (31,35,36).

However, it is worth noting that the clinical prognostic value of VISTA exhibits tumor-type-dependent variations; in malignant tumors such as primary cutaneous melanoma (37), gliomas (38) and oral squamous cell carcinoma (39), high VISTA expression is associated with poor prognosis. However, certain studies have reported that in colorectal cancer (40), esophageal adenocarcinoma (41) and hepatocellular carcinoma (42), high VISTA expression is associated with improved overall survival. In certain cancer types, such as gastric (43,44) and pancreatic cancer (45), the prognostic value of VISTA remains controversial and further research is needed to clarify whether blocking VISTA would benefit patients. The source of this debate may be influenced by the study design. In a previous study by Böger *et al* (43), traditional immunohistochemical analysis was performed on 464 tissue samples from a single center; this method is a bulk analysis, which evaluates the various immune cells in tumor tissue as a mixed whole. It cannot distinguish differences in VISTA expression across specific cell subsets and struggles to capture signals from rare but functionally key cell populations. By contrast, a previous study by Cao *et al* (44). conducted multidimensional analyses, including immunohistochemistry, flow cytometry, single-cell sequencing and multiplex immunofluorescence, on a total of 1,403 patients across eight independent cohorts (including data from public databases). This approach not only markedly expanded the sample size and population representativeness, but more notably, through single-cell technology, precisely localized the specific high expression level of VISTA on tumor-associated macrophages (TAMs). Combined with long-term follow-up data, this study revealed the true association between VISTA and poor prognosis as well as resistance to immunotherapy. Therefore, future research should increasingly adopt single-cell technologies to achieve a refined analysis of the tumor immune microenvironment.

The aforementioned studies indicated that when applying VISTA as a predictive biomarker, it should not only be evaluated in the context of specific cancer types and cell types, but also with full consideration of the technical resolution of the detection method, to avoid underestimating its clinical value

due to the limitations of bulk analysis. With the advancement of precision medicine, the integration of multi-omics technologies and validation in large-scale cohorts may become a key direction in IC biomarker research.

Multilayered molecular regulatory mechanisms of VISTA expression in the TME. VISTA expression is governed by multiple molecular mechanisms. At the transcriptional level, the IL-1 receptor-kinase 1-NF-κB axis activates VISTA transcription by promoting the phosphorylation and nuclear translocation of v-rel avian reticuloendotheliosis viral oncogene homolog A, enabling it to bind to specific response elements in the VISTA gene promoter region, thereby mediating the upregulation of VISTA in macrophages (46,47). Hypoxia-inducible factor (HIF)-1α markedly upregulates VISTA, most markedly on MDSCs within severely hypoxic tumor regions. Deng *et al* (48) demonstrated that direct binding of HIF-1α to a conserved hypoxia-response element in the VISTA promoter is a key driver of this induction in MDSCs. Previous research has demonstrated that yes-associated protein (YAP)/TEA domain transcriptional complex can directly bind to the VISTA promoter; YAP knockdown markedly reduces VISTA expression in tumor cells (49). The p53-related transcription factor forkhead box D3 (FOXD3) negatively regulates VISTA transcription; BRAF inhibitors can suppress VISTA levels by upregulating FOXD3 (50). Furthermore, certain signaling pathways exert bidirectional regulation on VISTA expression: In tumor cells, the TGF-β1-SMAD3 pathway suppresses VISTA expression; by contrast, in T cell subsets that do not express granzyme B, this pathway promotes VISTA expression. Furthermore, TGF-β released by apoptotic T cells can induce VISTA expression, thereby creating an immunosuppressive microenvironment that facilitates tumor immune evasion (51,52). Furthermore, the intracellular domain of the VISTA protein contains a protein kinase C-binding site and a proline-rich anchor site, and may undergo post-translational modifications such as glycosylation, phosphorylation and ubiquitination, which influence its stability, localization and signal transduction functions (24,53,54).

These regulatory mechanisms ensure that VISTA remains highly expressed in the TME, forming an immunosuppressive barrier that directly promotes tumor immune evasion and provides an alternative inhibitory pathway for PD-1/PD-L1 blockade therapy, leading to treatment resistance.

4. VISTA-mediated immunosuppressive network and tumor immune escape

VISTA-mediated inhibition of cytotoxic T-cell immunity. VISTA exerts its core inhibitory function by binding to receptors on T cells and directly blocking T-cell receptor (TCR) signaling, thereby suppressing T-cell activation and effector function (20,25). Fig. 2 depicts the dual immunosuppressive mechanism of VISTA in the tumor microenvironment. T cell-intrinsic VISTA engages its receptor leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1) in *cis* to directly inhibit proximal TCR signaling, thereby suppressing the phosphorylation of linker for activation of T cells, phospholipase C-γ and Src homology 2 domain-containing leukocyte protein of 76 kDa and subsequently dampening the activation of NF-κB, MAPK/ERK and AKT/mTOR cascades (20). In the acidic TME created by hypoxia, P-selectin glycoprotein ligand-1 (PSGL-1) serves as a confirmed ligand for VISTA. In melanoma, this interaction locks lymphocyte function-associated antigen 1 (αLβ2 integrin) into a low-affinity conformation, impairing T-cell adhesion to endothelium; interrupting the VISTA-PSGL-1 axis markedly increases $CD8^+$ T-cell tethering to tumor vessels (55,56).

VISTA also shapes an immunosuppressive milieu by promoting Treg cells while restraining effector T cells (Teffs). Tumor-infiltrating Tregs up-regulate VISTA, which-together with CTLA-4 and PD-1-drives naïve $CD4^+$ T cells toward forkhead box P3 $(FOXP3)^+$ Tregs and boosts IL-10/TGF-β secretion (18,36,57,58). In a melanoma model, VISTA blockade reduced induced Tregs by ~42% (from 61.5 to 35.8%), diminished Treg suppressive function and restored granzyme B positivity in $CD8^+$ T cells (36). Mechanistically, T cell-intrinsic VISTA engages LRIG1 to inhibit proximal TCR signaling and restricts mitochondrial metabolic fitness, thereby reducing $CD8^+$ T-cell expansion, survival and effector function including IFN-γ production (20).

Induction of T-cell exhaustion and apoptosis constitutes another key VISTA pathway. Co-expression with PD-1, TIM-3 and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains forms a multi-checkpoint brake that hinders antigen responsiveness, proliferation and survival (59,60); VISTA inhibition re-energizes metabolism and cell cycle progression, partially reversing exhaustion. In clear cell renal cell carcinoma, VISTA on tumor-associated immune cells were associated with the exhaustion driver thymocyte selection-associated high mobility group box (TOX), but only in venous tumor thrombi, highlighting context-dependent synergy that warrants further investigation (61,62).

Therefore, VISTA weakens the tumor-killing capacity of cytotoxic T cells through direct inhibitory effects, establishes an immunosuppressive microenvironment and drives tumor immune evasion. By depleting T-cell metabolic activity, blocking their cell cycle progression and inducing a state of functional exhaustion, VISTA ensures that tumor cells evade immune surveillance and maintain malignant proliferation.

VISTA orchestrates the functional maturation of MDSCs. Through a 'recruit-activate-cooperate' triad, VISTA positions MDSCs as central architects of TME immunosuppression. Hypoxia-driven and chemokine-mediated accumulation, metabolic exhaustion, contact-dependent inhibition and Treg cooperation collectively shape an immunosuppressive milieu (63). Targeting VISTA, for example, with anti-VISTA antibodies, reduces MDSC infiltration, reverses their suppressive phenotype and reinvigorates T-cell immunity, offering a promising strategy to convert 'cold' tumors into lesions responsive to immunotherapy (64).

In breast cancer models, tumor cell-derived C-X-C motif chemokine ligand 12 recruits $VISTA^+$ monocytic MDSCs from the bone marrow to the TME, where these cells establish a self-sustaining immunosuppressive network by further promoting the recruitment and differentiation of additional MDSCs (65). In the CT26 colon cancer mouse model, Under hypoxic conditions, $VISTA^+$ MDSCs exhibited ~60% reduction in their suppressive function on $CD8^+$ T cells and reduced the expression levels of T-cell activation markers

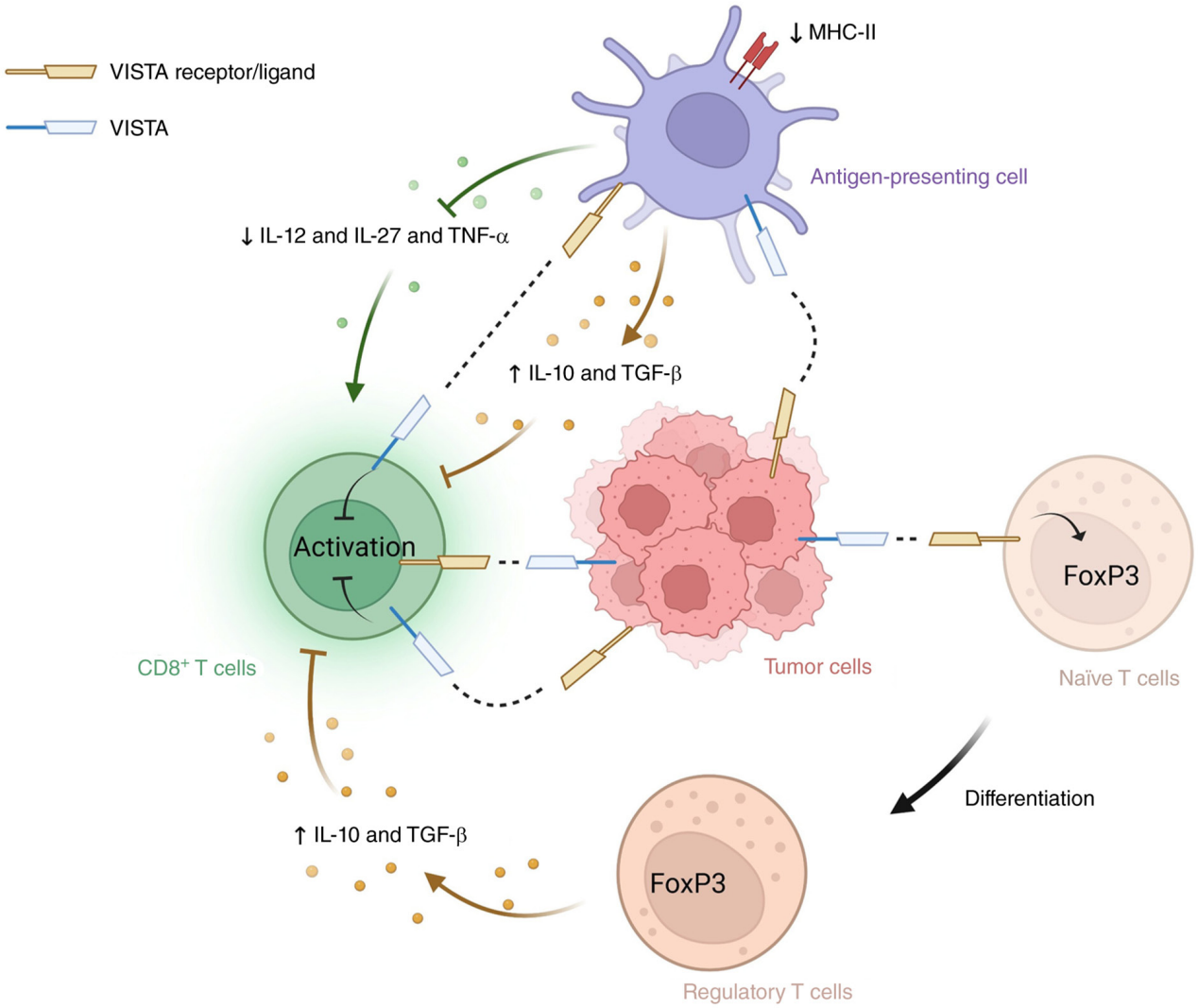

Figure 2. VISTA regulation of CD8⁺ T cells and tumor microenvironment. VISTA expression on antigen-presenting cells and tumor cells indirectly suppresses CD8⁺ T cell activation by downregulating MHC class II molecules (which affect CD4⁺ T cell helper function) and pro-inflammatory cytokines (IL-12, IL-27, TNF-α), while simultaneously promoting the secretion of IL-10 and TGF-β. Concurrently, VISTA signaling drives the differentiation of naive T cells into FoxP3⁺ Tregs. These cells further enhance immunosuppression through cytokine-mediated feedback loops, thereby establishing a self-sustaining tolerant environment that promotes tumor immune evasion. Green arrows, reduced release of pro-inflammatory cytokines leads to weakened activation of CD8+ T cells; brown arrows, increased release of anti-inflammatory cytokines leads to weakened activation of CD8+ T cells; black arrows, Treg differentiation; dotted lines, direct interaction with VISTA; VISTA, V-domain Ig suppressor of T-cell activation; MHC-II, major histocompatibility complex-II; Fox, forkhead box; Tregs, regulatory T cells.

CD25 and CD44, indicating impaired T-cell activation (48). VISTA⁺ MDSCs regulate the production of inflammatory chemokines, including C-C motif ligand (CCL)2, CCL3, CCL4 and CCL5, and modulate myeloid chemotaxis, which may impact T-cell trafficking within the TME (66). In an *in vitro* system using plate-bound VISTA-Ig fusion protein (soluble VISTA extracellular domain fused to human IgG_1 fragment crystallizable) to stimulate purified mouse CD8⁺ T cells in the presence of anti-CD3, VISTA engagement suppressed IFN-γ secretion by ~70%, demonstrating that VISTA can directly inhibit CD8⁺ T-cell effector function in a soluble-factor-dependent manner (67,68). VISTA further reinforces the suppressive phenotype of MDSCs through metabolic deprivation, contact-dependent inhibition and IC upregulation. VISTA activates arginase-1 and inducible nitric-oxide synthase in MDSCs, depleting arginine and oxygen required for T-cell proliferation (67). Nitric oxide (NO) produced by inducible NO synthase (iNOS) reacts with superoxide to form peroxynitrite, disrupting mitochondrial membrane potential and triggering caspase-3-dependent T-cell apoptosis (69,70). VISTA⁺ MDSCs secrete IL-10 and TGF-β to convert naïve T cells into FOXP3⁺ Tregs while stabilizing their suppressive phenotype (34,56). In the 4T1 murine triple-negative breast cancer model, combined blockade of VISTA and PD-1 with radiotherapy and low-dose cyclophosphamide reduces lung metastases from 13.1 to 1.7 (an 87% reduction) and extends median overall survival time from 42 to 48 days, demonstrating clear synergy (71).

Through these mechanisms, VISTA drives a self-amplifying cycle in MDSCs, multidimensionally suppressing T-cell function via metabolic deprivation, chemokine redirection and Treg conversion. VISTA also forms a dual inhibitory axis with PD-L1, jointly establishing an immunosuppressive microenvironment that promotes tumor immune evasion.

VISTA drives macrophages toward an M2 immunosuppressive fate. By suppressing the pro-inflammatory M1 program and fostering an immunosuppressive M2 state, VISTA directs macrophage polarization toward the M2 phenotype. In both the monocytic cell line THP-1 and $CD34^+$ cord blood stem cell-derived monocytes, ectopic VISTA expression drives macrophage differentiation toward the M2 phenotype (72). Clinically, gastric cancer specimens revealed that $VISTA^+$ TAMs exhibit canonical M2 markers, thereby imposing an immunosuppressive TME. By contrast, VISTA actively restrains M1 polarization: In lipopolysaccharide stimulated macrophage models, ligation of VISTA downregulates M1 cytokines such as IL-6 and TNF-α while upregulating immunoregulatory genes including TGF-β and IL-10, thereby blocking the M1 program. Since M1 macrophages possess antitumor activity by secreting pro-inflammatory mediators that potentiate T-cell responses, VISTA-mediated M1 suppression undermines this defense. For example, in classical Hodgkin lymphoma, $VISTA^+$ Hodgkin and Reed-Sternberg cells create a milieu in which M1 macrophages are scarce and M2 macrophages predominate, which are associated with T-cell exhaustion and tumor progression (30,73,74).

VISTA indirectly modulates T-cell immunity by regulating macrophage M1/M2 balance. M2 macrophages secrete IL-10 and TGF-β, which foster Treg differentiation and curb Teff (for example, $CD8^+$ T-cell) activation and proliferation (36,48,72). In extranodal natural killer (NK)/T-cell lymphoma, tumors with high VISTA expression exhibit a dense $FOXP3^+$ Treg infiltrate; although $CD8^+$ T cells are increased in number, they are functionally impaired, demonstrating reduced IFN-γ secretion, a phenotype tightly associated with VISTA-driven M2 polarization (72,75,76). Furthermore, M2 macrophages can express IC ligands such as PD-L1 and VISTA, which engage cognate receptors on T cells to extinguish cytotoxic function (33). In gastric cancer models, blockade of VISTA reprograms M2 TAMs toward a pro-inflammatory M1-like phenotype, accompanied by elevated IL-12 and TNF-α secretion; this phenotypic switch re-invigorates T-cell immunity, enhancing $CD8^+$ T-cell tumoricidal activity (44). These findings underscore the centrality of VISTA-mediated macrophage polarization in orchestrating T-cell responses within the tumor immune contexture.

VISTA-mediated M2 polarization disrupts the antitumor activity of M1-type defense, inhibits T-cell effector function through a dual mechanism involving soluble factors and checkpoint ligands, and promotes tumor immune evasion (72,77). Blocking VISTA can reprogram M2 TAMs to adopt a pro-inflammatory M1-like phenotype, thereby restoring T-cell immunity and potentially providing a strategy to overcome treatment resistance (78).

VISTA reprograms DCs to promote T-cell tolerance. VISTA indirectly suppresses T-cell immunity by modulating DC function. In murine tumor models, VISTA-expressing DCs exhibit reduced expression levels of the costimulatory molecules CD80 and CD86, which are associated with impaired T-cell activation. Blockade of VISTA elevates CD80 expression level and enhances T-cell stimulatory cytokine production, leading to improved antigen presentation and T-cell activation (36,72).

Subsequently, VISTA expressed on DCs suppresses their activation following toll-like receptor (TLR) stimulation and reduces the production of proinflammatory cytokines such as IL-12 and IL-23, thereby dampening antigen-specific T-cell responses (79). In a murine model of psoriasis induced by TLR7 agonist imiquimod, VISTA deficiency in DCs leads to exaggerated activation characterized by hyperactivation of ERK1/2 and JNK1/2 signaling, and augmented production of IL-23 (but not IL-12). This, in turn, promotes enhanced IL-17A expression in both $TCR\gamma\delta^+$ T cells and $CD4^+$ T helper (Th)17 cells, resulting in exacerbated psoriasiform inflammation (80). By contrast, VISTA-expressing MDSCs secrete IL-10 and TGF-β, contributing to immune suppression. VISTA blockade in tumor models enhances DC immunogenicity and promotes proinflammatory cytokine production, augmenting antitumor T-cell immunity, a mechanism distinct from classical tolerogenic DC programs (36,47).

Lastly, VISTA disrupts antigen presentation in the TME. In lung cancer models, tumor-educated DCs upregulate VISTA expression while downregulating major histocompatibility complex (MHC) class II and co-stimulatory molecules such as CD40 and CD80, thereby impairing their ability to activate $CD8^+$ T cells and recognize tumor antigens (81). By dismantling co-stimulation, imprinting a tolerogenic phenotype and disrupting antigen presentation, VISTA constructs a layered, DC-centric inhibitory network that effectively silences T-cell immunity (47,82).

Through co-stimulatory signals, the induction of a tolerant phenotype and the disruption of antigen presentation, VISTA is able to establish a DC-centered hierarchical suppression network that effectively suppresses T-cell immunity and promotes tumor immune evasion; functional defects in $VISTA^+$ DCs lead to insufficient T-cell activation and the induction of tolerance, representing a key mechanism underlying primary resistance to immunotherapy, whereas restoring DC function can enhance antitumor immune responses (47).

5. Antibodies and small-molecule drugs targeting VISTA in tumor treatment

VISTA serves a key role in tumor immune escape by regulating the function and fate of immune cells in TME (25). VISTA functions as a key IC that promotes tumor immune evasion by directly inhibiting T-cell activation and fostering an immunosuppressive TME (63). VISTA is also highly expressed on myeloid cells (for example, MDSCs and TAMs), further suppressing antitumor immunity by enhancing Treg activity and reducing Teff responses (25,83). Antibodies and small-molecule drugs targeting VISTA represent an emerging class of immunotherapies designed to counteract tumor immune evasion in solid malignancies, such as NSCLC (84), oral squamous cell carcinoma (85) and melanoma (86). Multiple therapeutic candidates, including small molecules (CA-170) and monoclonal antibodies (HMBD-002, JNJ-61610588 and CI-8993), are undergoing early-phase clinical trials (Phase I/II) in advanced solid tumors (19). While demonstrating acceptable safety profiles in initial studies, these antibodies and small-molecule drugs have exhibited limited objective responses as therapies, prompting a strategic shift toward combination approaches with established ICIs (for example,

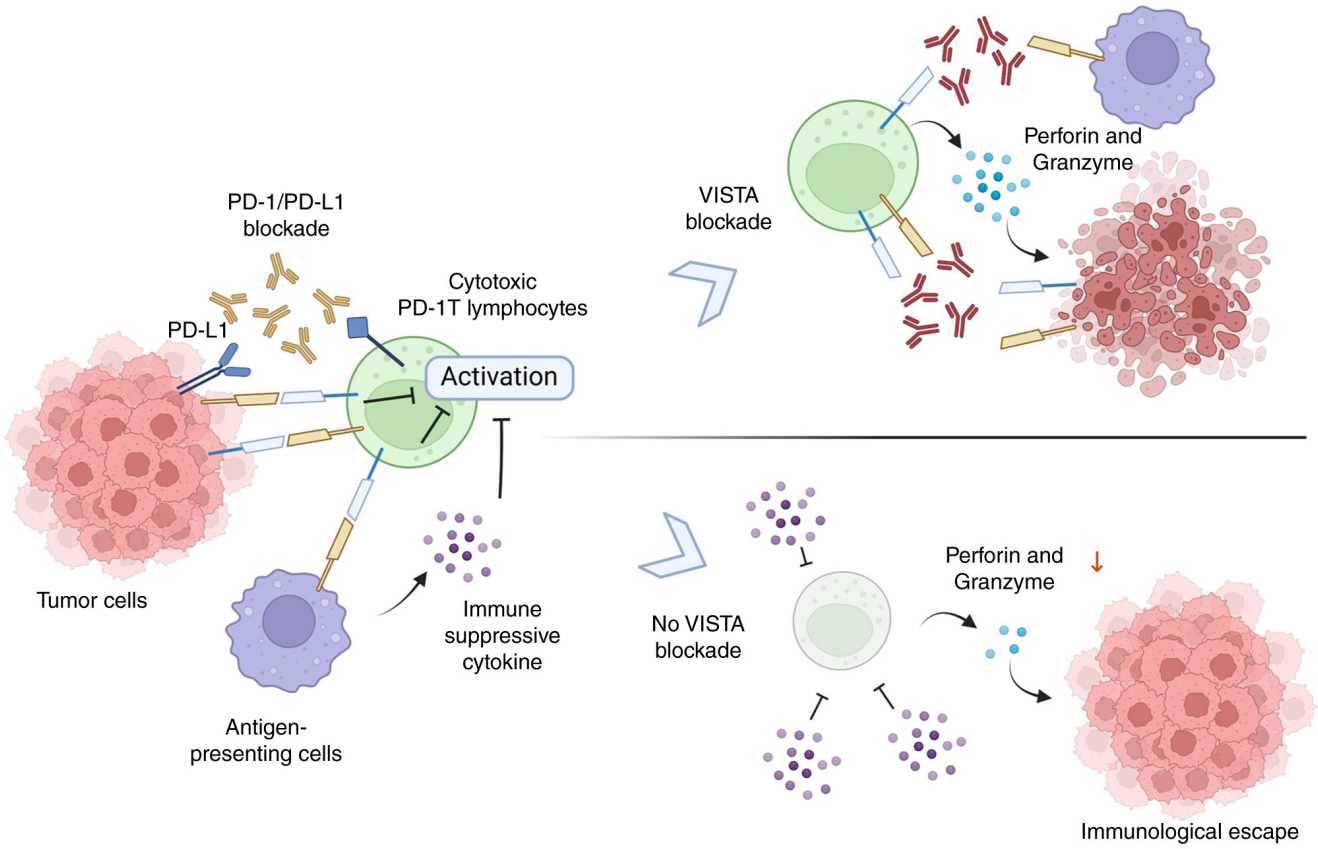

Figure 3. Role of VISTA in T-cell activation and immune escape. In the context of PD-1/PD-L1 pathway inhibition (left panel), when PD-L1 binding on tumor cells is blocked, PD-1-positive T lymphocytes receive activation signals; however, persistent VISTA signaling from antigen-presenting cells and tumor cells continues to suppress full T-cell activation by releasing immunosuppressive cytokines, thereby limiting the cytotoxic potential of effector T cells. In contrast, the addition of VISTA blockade (right panel) disrupts this residual inhibitory axis: Anti-VISTA antibodies can block VISTA-mediated inhibition, thereby enhancing the activation of PD-1-expressing T lymphocytes and promoting the secretion of perforin and granzyme-key effector molecules that mediate tumor cell lysis. This combination therapy strategy thus transforms an immunosuppressive microenvironment conducive to immune evasion into one that supports effective antitumor immunity, providing a molecular basis for the clinical development of combined VISTA inhibitors and PD-1/PD-L1 blockade. Blue arrows, VISTA-mediated inhibitory signals; black arrows, the direction of cytotoxic effects, i.e., activation of T cells to release perforin and granzyme to mediate tumor cell lysis; black T-shaped symbols, the inhibitory effect on T-cell activation exerted by VISTA signals originating from antigen-presenting cells and tumor cells; red arrows, secretion of perforin and granzyme is inhibited; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; VISTA, V-domain Ig suppressor of T-cell activation.

anti-PD-1/PD-L1 antibodies) (19). Current research focuses on identifying predictive biomarkers (for example, VISTA expression patterns on tumor-infiltrating myeloid cells) and optimizing combinatorial regimens to overcome primary resistance and enhance antitumor immunity (29,87) (Table SII). Fig. 3 illustrates the mechanistic basis for blocking VISTA as a therapeutic strategy to overcome tumor immune evasion.

Small-molecule drugs

CA-170. Currently, the application of VISTA in non-solid tumor settings remains in early-stage exploration. Several monoclonal antibodies that have already demonstrated efficacy in solid-tumor therapy are now undergoing clinical investigations at various stages in hematological malignancies such as lymphoma, aiming to explore novel combination immunotherapeutic strategies (88-90). CA-170, in particular, has accumulated notable evidence in solid tumors demonstrating its ability to counteract VISTA-mediated suppression of T-cell proliferation and effector function across multiple cancer types, including colon cancer and melanoma (91-94). In the non-solid tumor space, CA-170 is the most clinically advanced VISTA-targeting antibody. A multicenter, open-label phase I study (NCT02812875) sponsored by Curis, Inc. aims to enroll patients with lymphoma to evaluate the safety, pharmacokinetics and clinical efficacy of CA-170 (95). Preliminary data released from this trial indicated that CA-170 confers clinical benefit in patients with Hodgkin lymphoma, leading to the inclusion of non-solid tumor indications. The Phase II study of this drug was registered in India (CTRI/2017/12/011026) (93,96). Among patients with non-squamous NSCLC, the clinical benefit rate in the 400 mg group (75%) was notably increased compared with that in the 800 mg group (50%), with a corresponding median PFS of 19.5 and 7.9 weeks, respectively. This is consistent with the bell-shaped curve of immune activation observed in other preclinical studies (97), a phenomenon that may be associated with short half-life and pharmacodynamic characteristics of CA-170 (91).

Antibodies

JNJ-61610588. A phase I clinical trial targeting patients with colorectal and pancreatic cancer was initiated by ImmuNext, Inc. in 2016 (98,99). The study NCT02671955 primarily

enrolled patients with advanced or metastatic solid tumors who had progressed on or were intolerant to available standard therapies, without restriction to a specific line of prior treatment (96). The study comprised four main components: i) Determining the safe dose for patients with advanced solid tumor; ii) assessing biomarker changes in participants with metastatic NSCLC; iii) pharmacokinetic evaluation and iiii) conducting expanded experiments targeting different cancer types (lung, pancreatic, cervical, colorectal and head and neck cancer). The study primarily measured seven indicators, including the frequency of dose-limiting toxicity (DLT), the number of adverse and serious events, pharmacodynamic biomarker changes and VISTA expression. The last update was released in March 2018, after which the study was halted due to the economic decisions of the company. As of the last study record update, only 1 patient experienced a cytokine release syndrome (CRS) adverse event. Based on the available data, it can be concluded that the drug demonstrates clear safety when administered intravenously and certain patients have already benefited from this treatment regimen (98,100).

CI-8993. In June 2020, CI-8993, developed by Curis, Inc., initiated a Phase I clinical trial targeting patients with metastatic or unresectable solid tumors (non-lymphoma), aims to enroll 50 participants (NCT04475523) (101). The study was designed to investigate the DLT rate within 28 days of CI-8993 treatment to determine the maximum tolerated dose of CI-8993 and to establish the safe dose for the target population in the second phase of the study. The study was completed in 2023. According to the findings in this Phase I clinical trial, patients did not exhibit notable DLT at doses <0.6 mg/kg and patients treated with CI-8993 demonstrated increased NK cell maturation and reduced MDSC recruitment. Furthermore, patients treated with CI-8993 exhibited higher levels of T-cell activation factor release, suggesting that CI-8993 may activate anticancer mechanisms through multiple pathways. However, it is worth noting that in the currently disclosed study, cytokine levels in the high-dose group (0.6 mg/kg) were actually lower compared with those in the low-to-moderate-dose groups (0.15 or 0.3 mg/kg). The researchers attributed this finding to the immunomodulatory effects of the stepwise dosing design but did not discuss in depth whether this indicates insufficient immune activation or excessive immunosuppression. Furthermore, by the end of the study, only 26 patients had been enrolled, falling short of the target enrollment. These characteristics indicated that the clinical development of CI-8993 remains in its early stages and its precise biological effects and therapeutic window require further data to support.

HMBD-002. In the study by Thakkar *et al* (64), HMBD-002 was identified to block the binding of VISTA to its potential molecular partner. In various cell and animal models, including colorectal, breast and lung cancer, an inflammatory phenotype characterized by Th1/Th17 responses was observed, along with notable inhibition of tumor growth. Subsequently, Hummingbird Bioscience led a Phase I/II open-label, multicenter clinical trial to evaluate the safety, pharmacokinetics and antitumor activity of HMBD-002 (NCT05082610). In their 2023 presentation at the American Society of Clinical Oncology, Ahnert *et al* (102) reported that the study had completed a single-agent dose-escalation cohort (20-180 mg weekly), with no dose-limiting toxicities observed in the first four cohorts. This safety profile may be associated with the non-depleting IgG4 scaffold design used for HMBD-002; however, further data on cytokine release were not disclosed in this report. The latest data indicated that the study was completed in 2025. As of the completion of the study, a total of 48 patients had been enrolled. Data on pharmacokinetics, immunogenicity or preliminary antitumor activity, as well as results of biomarker analysis, are pending future publication.

SNS-101. Sensei Biotherapeutics, Inc. has developed SNS-101, a pH-selective anti-VISTA IgG1 antibody designed to overcome the safety and pharmacokinetic challenges of first-generation antibodies by binding to the active form of VISTA exclusively in the acidic TME (103). Preclinical studies indicated that SNS-101 exhibits 1,000-fold higher affinity for VISTA at pH 6.0 compared with physiological pH and exhibits linear pharmacokinetic characteristics in mouse models without evidence of CRS (103,104). Preliminary clinical data (as of February 2024, with 31 patients completing dose escalation) indicated that SNS-101 monotherapy (n=16; maximum dose, 15 mg/kg) and in combination with cemiplimab (n=15; maximum dose, 15 mg/kg + 350 mg cemiplimab) were well tolerated, with no dose-limiting toxicities (105). Only 1 patient receiving 15 mg/kg as monotherapy experienced grade 1 CRS (106), with no prophylactic medication administered. Furthermore, of note, based on the disclosed data, the response to SNS-101 monotherapy was modest: A patient in the highest dose group demonstrated a 17% tumor shrinkage (which did not meet the criteria for partial response) and among the 31 patients, only 1 patient confirmed partial response (in the combination therapy group) and 10 patients had stable disease. These preliminary efficacy data suggested that the antitumor activity of SNS-101 may be primarily limited to combination therapy; however, due to the small sample size and limited follow-up duration, its potential efficacy as a monotherapy cannot yet be determined.

Beyond oncology, although preclinical studies have suggested therapeutic potential for VISTA-targeted approaches in autoimmune diseases, organ-transplant rejection, chronic inflammatory disorders and fibrotic conditions, no clinical trials have yet been initiated in these non-oncological areas (107).

Clinical development and biomarker considerations. Currently, clinical drug development for VISTA primarily focuses on small-molecule drugs and monoclonal antibodies, majority of which are in Phase I/II clinical trials. A comprehensive analysis of publicly available safety data revealed that common drug-related toxicities include infusion-related reactions (chills, fever and fatigue), skin toxicity (acneiform dermatitis and maculopapular rash), mild gastrointestinal reactions (nausea) and CRS (106). Early-stage antibodies such as CI-8993 have been associated with grade 3 CRS and encephalopathy, which were major factors leading to the suspension of their studies (108). The new-generation pH-selective antibody SNS-101 and the engineered IgG1 antibody KVA12123 have markedly improved safety through molecular optimization. SNS-101 exhibited only one mild (grade 1) CRS event in the highest dose group (15 mg/kg) of monotherapy, with a safe dose range ~50 times higher compared with the dose level at which severe CRS occurred in the first-generation VISTA antibody. The engineered IgG1 antibody KVA12123 exhibited no DLT and no evidence of CRS within a dose range up to

1,000 mg every 2 weeks, demonstrating good tolerability. This finding confirmed the key value of engineered antibody design in eliminating severe immunotoxicity. Furthermore, the treatment response patterns of VISTA demonstrated clear advantages in combination therapy (105). Monotherapy primarily resulted in disease stabilization; for example, the best overall response in the KVA12123 monotherapy group was disease stabilization, whereas partial remission and further tumor regression were observed in the group treated in combination with the PD-1 inhibitor pembrolizumab (109). CA-170, an oral dual-target inhibitor (VISTA/PD-L1), demonstrated a 30% objective response rate in Hodgkin lymphoma and exhibited a 'bell-shaped curve' pattern of immune activation, suggesting the need to optimize the dosing regimen in the future (91).

Biomarker development has focused on VISTA expression on tumor-infiltrating myeloid cells. Preclinical evidence indicated that VISTA-high $CD33^+$ MDSCs are associated with poor prognosis in melanoma and VISTA can serve as a stratification marker for patients with high PD-1 expression (110). Cao *et al* (44) precisely localized high VISTA expression on TAMs using single-cell sequencing, revealing its association with immunotherapy resistance and poor prognosis. Several studies suggested that assessing VISTA expression levels, the activation status of circulating monocytes and changes in T-cell immunophenotypes as potential predictors of treatment efficacy may be a target for future research (111-113). Future studies will require the integration of single-cell sequencing and spatial multi-omics technologies to establish a VISTA-centric cellular interaction network to guide the design of precision combination therapies.

6. Discussion

As an emerging IC molecule within the B7 family, VISTA drives tumor immune escape by directly regulating T-cell function and indirectly reshaping the TME. The immunosuppressive function of VISTA forms a finely tuned synergistic network with molecules such as PD-1, TOX, TIM-3 and TIGIT. These 'multiple inhibitory circuits' suggest that single-target blockade may trigger compensatory pathway activation. However, combined VISTA and PD-1/PD-L1 blockade has demonstrated synergistic antitumor effects in preclinical models (25,103,114). Furthermore, VISTA interactions with myeloid cells amplify immunosuppression: i) VISTA on DC surfaces downregulates co-stimulatory molecules such as CD80/CD86 and MHC-I, blocking the first and second signals required for T-cell activation (47,75); and ii) VISTA-induced M2 macrophage polarization secretes IL-10 and TGF-β, suppressing Teffs and depleting key nutrients via metabolic enzymes such as arginase-1 (72). Notably, VISTA exhibits contradictory regulation of macrophage phagocytosis: VISTA enhances phagocytosis by downregulating signal regulatory protein α, yet impedes effective tumor antigen presentation due to reduced MHC-I and increased anti-inflammatory factors, creating a vicious cycle of 'enhanced phagocytosis-immune suppression' (72). The present review noted that VISTA serves distinct roles in different types of immune cells and its stimulatory or inhibitory effects depend on the cell type expressing it (25). In T cells, Johnston *et al* (55) demonstrated that under acidic TME conditions (pH, ~6.0), VISTA selectively binds to PSGL-1, thereby triggering NF-κB dephosphorylation and inhibiting T-cell proliferation and IFN-γ production. By contrast, in human monocytes, Rogers *et al* (115) revealed that VISTA acts as an activating receptor to promote the production of pro-inflammatory cytokines, whereas VISTA deficiency actually enhances the inflammatory phenotype. This functional duality extends to MDSCs; Zhang *et al* (116) demonstrated that VISTA drives the differentiation and metabolic reprogramming of MDSCs by maintaining STAT3 activation and polyamine biosynthesis. Although existing studies have elucidated the binding specificity of VISTA and associated signaling pathways across different cell types, the molecular mechanism by which VISTA switches between inhibitory and stimulatory signaling on different cell surfaces using the same extracellular domain structure remains to be elucidated (25,117).

VISTA-targeted immunotherapy is advancing from basic research to clinical validation. Multiple anti-VISTA monoclonal antibodies have entered Phase I/II trials. Notably, VISTA antibodies demonstrate unique advantages in PD-1-resistant models (61). In CT26 colorectal cancer models resistant to PD-1 blockade, combined VISTA inhibition reverses T-cell exhaustion, suggesting the potential of VISTA as a 'compensatory checkpoint'. Beyond monoclonal antibodies, gene editing (for example, CRISPR-CRISPR-associated protein 9 knockout of VISTA in chimeric antigen receptor-T-cells) and nanodelivery systems [pH-sensitive small-interfering RNA (siRNA) carriers] offer novel tools in precision targeting (118,119). In MCF7 breast cancer cells, VISTA silencing using siRNA resulted in a 1.5-1.8-fold reduction in cell migration and a 1.7-2.2-fold decrease in clonogenicity compared with control cells, while combined VISTA and CTLA-4 silencing further induced a 3-4-fold increase in apoptosis, confirming that dual targeting of tumor-intrinsic ICs can more effectively suppress tumor progression and enhance antitumor activity (120). Furthermore, targeting lactate metabolism with lactate dehydrogenase inhibitors such as FX-11 and exploiting acidic pH-selective VISTA antibodies represent promising strategies to potentially improve the TME for immunotherapy, offering novel insights in converting 'cold tumors' (103,121,122).

Despite notable advances in VISTA-targeting research, key scientific questions remain unresolved. First, the complete VISTA ligand landscape remains to be elucidated; only PSGL-1 has been confirmed as a functional ligand under acidic conditions, while potential interactions in neutral environments require further validation (55). Second, VISTA expression heterogeneity across different tumors and immune microenvironments may account for therapeutic variability, necessitating the development of precise biomarkers to identify responsive populations (95). Lastly, long-term VISTA inhibition may induce autoimmune toxicity, necessitating rigorous monitoring in clinical trials (123).

Therefore, elucidating the complex structures of VISTA with molecules such as PD-L1 to design bispecific antibodies that simultaneously block multiple inhibitory pathways, as well as investigating the role of VISTA in tumor vascular endothelial cells and its impact on T-cell migration, holds notable promise in expanding the application of VISTA in autoimmune

diseases (124). Furthermore, integrating single-cell sequencing with spatial multi-omics to map VISTA-related cell interactions within the TME could potentially provide a spatial foundation for combination therapies in the future (61). VISTA not only broadens the scope of IC research but also emerges as a highly promising tumor immunotherapy target due to its 'T-cell inhibition-myeloid cell synergistic inhibition' mechanism. Despite challenges in clinical translation due to complex mechanisms, VISTA demonstrates unique advantages in overcoming PD-1 resistance and reshaping the 'cold tumor' microenvironment (25). Therefore, VISTA-targeted therapy holds promise as a notable immunotherapy beyond PD-1/PD-L1, potentially offering novel hope for patients with cancer.

However, key questions remain to be addressed. First, the full ligand repertoire of VISTA has not yet been defined; PSGL-1 is the only functional ligand confirmed under acidic conditions, while putative interactions (for example, with V-set and immunoglobulin domain-containing 3) at neutral pH require validation. Second, heterogeneous VISTA expression across tumors and immune microenvironments may lead to variable responses, underscoring the need for predictive biomarkers, such as VISTA levels on tumor-infiltrating Tregs, to identify patients most likely to benefit from immunotherapy. Lastly, chronic VISTA inhibition could provoke autoimmune toxicity, warranting careful safety monitoring in clinical studies.

Future efforts should therefore focus on resolving the structure of VISTA in complex with PD-L1 to facilitate the design of bispecific antibodies that simultaneously block multiple suppressive pathways elucidating the role of VISTA in tumor-associated endothelial cells and its impact on T-cell trafficking; and leveraging single-cell sequencing and spatial multi-omics to map VISTA-centric cellular interactions within the TME, thereby providing a spatial framework for rational combination therapies. VISTA not only broadens the IC landscape but also exemplifies a 'T-cell suppression plus myeloid-cell cooperative suppression' paradigm, making it a highly promising therapeutic target. Despite the mechanistic complexity ahead, the unique potential of VISTA to overcome PD-1 resistance and remodel 'cold tumors' positions VISTA-targeted therapy as a next-generation immunotherapy that could offer novel hope for patients with cancer.

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Authors' contributions

YC, SW and GW contributed to the conception and design of the present review, and provided key insights into the intricacies of VISTA-mediated immunoregulation and related molecular pathways. BY and KY devised the literature search strategy, and performed the screening, data extraction and analysis of the cited studies. MQ revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and takes responsibility for the accuracy and integrity of the work. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools of Kimi K2.5 Thinking (Moonshot AI; v2.5; www.kimi.com) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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