VISTA in Cancer Immunotherapy: A Survey

www.surveyx.cn

Abstract

V-domain Ig suppressor of T cell activation (VISTA) has emerged as a crucial immune checkpoint regulator in cancer immunotherapy, offering potential avenues to overcome the limitations of current immune checkpoint inhibitors. This survey paper provides a comprehensive exploration of VISTA's role in modulating immune responses within the tumor microenvironment (TME), highlighting its dual function as both a ligand and receptor. VISTA's significant expression across various cancers, including ovarian, endometrial, and oral squamous cell carcinoma, underscores its contribution to immune suppression and its correlation with poor prognosis. The paper delves into the mechanisms by which VISTA facilitates immune evasion, focusing on its interactions with myeloid-derived suppressor cells and tumor-associated macrophages, and its regulation under hypoxic conditions. Therapeutic strategies targeting VISTA, such as monoclonal antibodies, are discussed, emphasizing their potential to enhance anti-tumor immunity and their integration with other immune checkpoint therapies. Despite promising preclinical and clinical outcomes, challenges remain in fully understanding VISTA's complex regulatory mechanisms. The development of robust biomarkers for VISTA is essential for patient stratification and optimizing treatment strategies. Future research directions include exploring VISTA's integration with other checkpoints and leveraging advanced imaging technologies to unravel TME dynamics. This survey concludes that VISTA holds promise as a transformative target in cancer immunotherapy, with the potential to improve treatment outcomes and address therapeutic resistance. Continued research into VISTA's biological roles and therapeutic applications will be pivotal in advancing the field of cancer immunotherapy.

1 Introduction

1.1 Significance of VISTA in Cancer Immunotherapy

V-domain Ig suppressor of T cell activation (VISTA) has emerged as a crucial immune checkpoint regulator in cancer immunotherapy, particularly in light of the limited efficacy of existing immune checkpoint inhibitors, which benefit only a minority of patients [1]. VISTA's expression and function within the tumor microenvironment (TME) highlight its potential as a therapeutic target, offering new strategies for addressing both cancer and autoimmune diseases [2].

The role of VISTA as a negative checkpoint regulator (NCR) extends to the central nervous system (CNS), with ongoing investigations into its immune modulation implications in cancer and autoimmune conditions [3]. Notably, VISTA contributes to the immune suppression seen in tumors, particularly in ovarian and endometrial cancers, presenting significant challenges to effective immunotherapy [4].

Tumor-infiltrating immune cells, including VISTA-expressing populations, have critical implications for therapeutic strategies in cancer [5]. Addressing the complexities of the immunosuppressive TME, where VISTA is a key player, is essential for improving cancer treatment efficacy [6]. The stagnant survival rates in malignancies like oral squamous cell carcinoma (OSCC) further underscore the need for enhanced immunotherapeutic strategies [7].

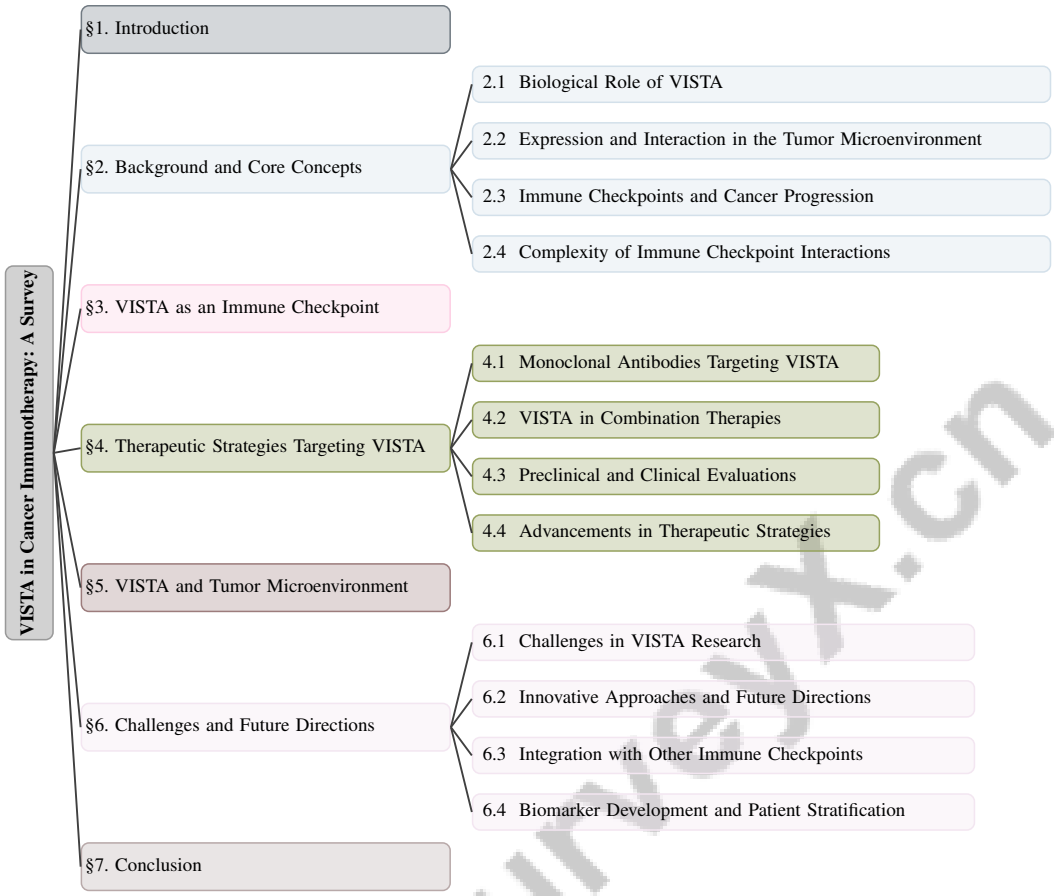

Figure 1: chapter structure

Resistance to immune checkpoint blockade (ICB) remains a significant hurdle in clinical oncology. Elucidating the mechanisms of resistance, including those associated with VISTA, is vital for developing effective combination therapies that can improve patient outcomes [8]. As research evolves, integrating VISTA-targeted therapies with existing modalities shows promise for enhancing immunotherapy efficacy and overcoming current limitations.

1.2 Structure of the Survey

This survey presents a detailed examination of VISTA's role in cancer immunotherapy, focusing on its immunoregulatory functions and therapeutic potential [9]. The introduction establishes the significance of VISTA in cancer treatment, providing a foundation for understanding its impact on clinical outcomes. The subsequent background and core concepts section explores VISTA's biological role, its expression within the TME, and its interactions with immune cells, emphasizing the importance of immune checkpoints in cancer progression and therapy.

The survey provides an in-depth analysis of VISTA (V-domain immunoglobulin suppressor of T cell activation) as a pivotal immune checkpoint, elucidating its complex mechanisms in modulating T cell activation and promoting immune tolerance. It examines VISTA's role in cancer immune evasion across various cancer types, detailing its influence on myeloid cell-mediated inflammation and immunosuppression, as well as its potential as a therapeutic target in immunotherapy [9, 10, 11, 12]. The discussion includes therapeutic strategies targeting VISTA, encompassing the development and application of monoclonal antibodies, potential combination therapies, and insights from preclinical and clinical evaluations, alongside recent advancements in these strategies.

Furthermore, the survey analyzes VISTA's influence on the TME, particularly its interactions with myeloid-derived suppressor cells and tumor-associated macrophages, as well as the resistance mechanisms associated with it. The concluding sections address the challenges and future directions

in targeting VISTA for cancer therapy, proposing innovative approaches and exploring integration with other immune checkpoint therapies. The development of biomarkers for VISTA and strategies for patient stratification are also discussed to enhance therapeutic efficacy. The survey concludes by summarizing key findings and emphasizing the necessity for further research to fully elucidate VISTA's role and therapeutic potential.The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Biological Role of VISTA

The V-domain Ig suppressor of T cell activation (VISTA) is a critical immune checkpoint molecule that modulates immune responses, particularly within the tumor microenvironment (TME). Functioning as both a ligand and receptor, VISTA is essential for maintaining immune homeostasis and preventing excessive immune activation [9]. Its role as a negative regulator is central to promoting tolerance and anti-inflammatory responses in macrophages [13]. Elevated VISTA expression in cancers such as ovarian, endometrial, and oral squamous cell carcinoma (OSCC) is linked to immune suppression and poor prognosis.

VISTA's presence on tumor-infiltrating immune cells underscores its role in modulating immune responses and facilitating tumor immune evasion [5]. The competition for resources between tumor and immune cells, both relying on glycolysis, exacerbates immune suppression, hindering effective responses. VISTA's interactions with TME components, like cancer-associated fibroblasts and tumor-associated macrophages, highlight its involvement in tumor progression and therapeutic resistance [14]. Advanced visualization and analytical methods are required to understand these interactions and spatial dynamics within the TME [15].

In the central nervous system (CNS), VISTA regulates microglia, impacting immune responses in CNS diseases and extending its immunoregulatory functions [3]. The immune system's role in managing pathogen load aligns with VISTA's functions, as illustrated by mathematical control theory [16]. VISTA's potential as a therapeutic target in cancer immunotherapy offers avenues to enhance anti-tumor immunity and address therapeutic challenges.

2.2 Expression and Interaction in the Tumor Microenvironment

VISTA's expression in the TME is crucial for modulating immune responses and enabling tumor immune evasion. As both a ligand and receptor, VISTA engages in unique interactions with immune cells, contributing to its complex regulatory functions [17]. Its expression on tumor-infiltrating inflammatory cells correlates with poor disease-specific survival in cancers, such as primary cutaneous melanoma [18], underscoring its prognostic significance as a marker of immune suppression and tumor progression.

Hypoxic conditions in the TME induce VISTA expression, enhancing immune suppression [19]. This adaptive strategy illustrates tumor evasion of immune detection. VISTA interacts with ligands like VSIG-3 and PSGL-1, critical for modulating immune responses. Targeting these pathways has shown promise in preclinical and clinical settings, suggesting potential strategies to disrupt VISTA-mediated immune suppression [20].

In gliomas, VISTA expression varies with tumor grade and correlates with other immune checkpoints, reinforcing its potential as a therapeutic target [21]. The TME's complexity, comprising diverse cellular components, complicates VISTA's interactions with the immune system [22]. A comprehensive framework is necessary to systematically investigate how distinct tumor regions influence immune responses [23].

Spatial heterogeneity within the TME, assessed through gene expression data, illuminates the dynamic interactions between VISTA and its microenvironment [24]. In the CNS, VISTA's expression in microglia affects neuroinflammation and neurodegeneration, illustrating its regulatory functions beyond the TME [3]. These multifaceted interactions emphasize VISTA's significance as a cancer immunotherapy target, necessitating further research to elucidate its role in immune modulation and therapeutic resistance.

2.3 Immune Checkpoints and Cancer Progression

Immune checkpoints, including VISTA, are integral to modulating immune responses within the TME, significantly influencing cancer progression and therapeutic outcomes. Frequently upregulated in tumors, these checkpoints facilitate immune evasion and resistance to anti-tumor responses [1]. As a negative checkpoint regulator, VISTA modulates immune responses in both cancer and autoimmune conditions [2]. Its expression in hepatocellular carcinoma (HCC) correlates with clinicopathological features and survival outcomes, underscoring its critical role in cancer progression [25].

The TME's complexity, characterized by heterogeneity and pro-tumor activities of certain cell types, complicates the differentiation between beneficial and harmful elements [14]. This complexity is exacerbated by the spatial heterogeneity of tumor regions, posing significant challenges for methodologies that capture tumor-immune interactions accurately [24]. The dynamics of immune responses, correlated with varying pathogen loads, highlight the role of immune checkpoints like VISTA in cancer progression [16].

Resistance to immune checkpoint inhibitors (ICIs), whether intrinsic or acquired, poses a significant challenge in cancer immunotherapy, hindering treatment efficacy [26]. Resistance mechanisms are categorized into tumor-intrinsic and tumor-extrinsic factors, emphasizing the complexity of tumor-immune interactions [8]. Understanding the role of tumor-infiltrating immune cells in therapy response is crucial, particularly in immunologically-cold tumors with low T-cell infiltration, which presents obstacles to immunotherapy success [27].

VISTA's role in OSCC exemplifies the challenges in cancer treatment, where its impact on immunosuppression and patient survival is significant [7]. Current strategies to regulate macrophage responses to inflammatory stimuli are inadequate, leading to uncontrolled inflammation and potential septic shock [13]. Additionally, the contribution of nonmalignant cells in the TME to cancer progression complicates targeting these interactions therapeutically [22].

The adaptive resistance of tumors to therapies, facilitated by the TME, necessitates innovative approaches to enhance treatment efficacy [5]. A nuanced understanding of immune checkpoints, including VISTA, is vital for developing more effective therapeutic strategies and improving cancer treatment outcomes.

2.4 Complexity of Immune Checkpoint Interactions

The intricate network of immune checkpoint interactions, particularly involving VISTA, is crucial for modulating immune responses within the TME. VISTA's dual role as both a ligand and receptor enables it to regulate T cell activation through both extrinsic and intrinsic mechanisms, distinguishing it from other immune checkpoints [12]. This unique characteristic underscores the complexity of immune regulation and poses challenges in developing effective VISTA-targeted therapies, especially given its variable role across different cancer types [10].

The TME is characterized by heterogeneity, immune cell plasticity, and the presence of immunosuppressive factors that inhibit effective anti-tumor immunity [28]. These elements contribute to dynamic interactions within the TME, where metabolic exchanges and signaling pathways facilitate immune evasion and treatment resistance [29]. The acidic, hypoxic, and nutrient-depleted conditions of the TME further impede immune cell function, complicating immune checkpoint interactions [30].

Innovations in understanding VISTA's role in modulating TLR-mediated signaling in myeloid cells add complexity, highlighting its involvement beyond traditional T cell checkpoints [11]. Variability in tissue samples can obscure the effectiveness of ICIs and hinder the development of consistent prognostic markers. Stromal cells within the TME play significant roles in tumor metabolism, growth, immune evasion, and treatment resistance, illustrating the multifaceted nature of immune checkpoint interactions [31].

The tumor's ability to evade treatment is significantly influenced by its microenvironment, promoting drug resistance and complicating therapeutic responses [32]. Resistance mechanisms are categorized into innate and acquired types, providing insight into how tumors evade immune responses facilitated by ICIs [26]. Researchers face challenges in fully understanding the dynamic interactions within the TME that contribute to therapeutic resistance, necessitating innovative approaches to unravel these complexities [33].

The SpatialVisVR platform, utilizing virtual reality for enhanced visualization and analysis of multiplexed pathology images, offers a novel approach to addressing these challenges by enabling real-time comparisons and contextual searches, thereby advancing our understanding of immune checkpoint interactions [15]. Ongoing exploration of VISTA's interactions with other immune checkpoints is crucial for developing more effective cancer immunotherapies and overcoming challenges posed by the TME and its intricate immune regulatory networks.

In recent years, the role of immune checkpoints in cancer therapy has garnered significant attention, particularly with the identification of novel targets such as VISTA. This immune checkpoint is characterized by a complex hierarchical structure that is crucial for understanding its mechanisms of action and implications in cancer immune evasion. As illustrated in Figure 2, the figure provides a comprehensive overview of VISTA's dual role in immune modulation. It delineates the interactions between VISTA and other immune checkpoints, thereby underscoring its potential as a therapeutic target. Furthermore, the figure highlights the significance of VISTA across various cancers, elucidating its mechanisms of immune evasion and presenting therapeutic strategies aimed at enhancing the efficacy of immunotherapy. Importantly, the influence of the tumor microenvironment on VISTA expression and regulation is also depicted, which has profound implications for therapeutic resistance and clinical outcomes. This multifaceted depiction not only enriches our understanding of VISTA but also frames it within the broader context of cancer immunotherapy, paving the way for future research and clinical applications.

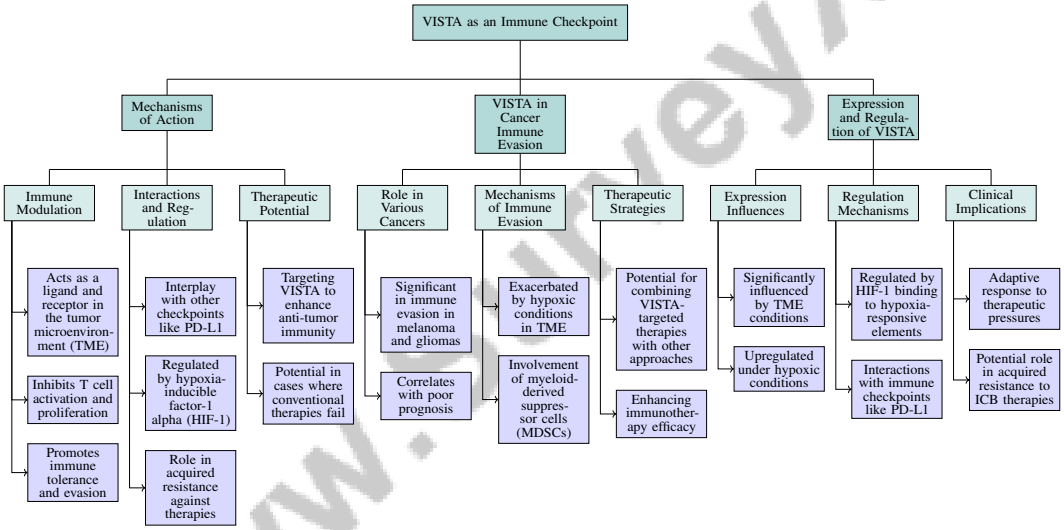

Figure 2: This figure illustrates the hierarchical structure of VISTA as an immune checkpoint, detailing its mechanisms of action, role in cancer immune evasion, and expression and regulation. It highlights VISTA's dual role in immune modulation, its interactions with other checkpoints, and its potential as a therapeutic target. Additionally, it outlines the significance of VISTA in various cancers, its mechanisms of immune evasion, and therapeutic strategies to enhance immunotherapy efficacy. Finally, the figure emphasizes the influence of the tumor microenvironment on VISTA expression and regulation, with implications for therapeutic resistance and clinical outcomes.

3 VISTA as an Immune Checkpoint

3.1 Mechanisms of Action

V-domain Ig suppressor of T cell activation (VISTA) acts as a pivotal immune checkpoint by modulating immune responses within the tumor microenvironment (TME) through its dual role as a ligand and receptor. By inhibiting T cell activation and proliferation, VISTA fosters immune tolerance and facilitates immune evasion, thereby promoting an immunosuppressive environment conducive to tumor progression [13]. VISTA's modulation of myeloid cell activation enhances T cell responses against tumors, indicating that VISTA blockade could counteract the immunosuppressive milieu and

bolster anti-tumor immunity [11]. In hypoxic conditions typical of the TME, VISTA expression is regulated by hypoxia-inducible factor-1 alpha (HIF-1), which exacerbates immune suppression [19].

The interplay between VISTA and other checkpoints, such as PD-L1, is critical in various cancers, including prostate cancer, where their combined roles in immune suppression post-immunotherapy are being studied [34]. This suggests that targeting VISTA could enhance anti-tumor immunity, especially in cases where conventional therapies have failed. In melanoma, for instance, VISTA's negative regulation of immune checkpoints contributes to acquired resistance against anti-PD-1 therapy [35]. Overexpression of VISTA in cancers like oral squamous cell carcinoma (OSCC) correlates with poor prognosis, highlighting its role in disease progression and patient outcomes [7]. The variability in patient responses to immune checkpoint blockade (ICB) therapies, with some failing to achieve durable responses, underscores the need for a comprehensive understanding of VISTA's regulatory mechanisms [8].

Research into VISTA extends to the central nervous system (CNS), where its role in modulating immune responses during CNS diseases is under investigation [3]. These insights into VISTA's mechanisms as an immune checkpoint emphasize its potential as a therapeutic target, paving the way for enhanced efficacy in cancer immunotherapies.

As illustrated in Figure 3, the hierarchical structure of VISTA's mechanisms of action is categorized into immune modulation, checkpoint interactions, and therapeutic potential. This figure highlights VISTA's influence on T cell inhibition, myeloid cell activation, and hypoxia regulation, as well as its interactions with PD-L1 and resistance in melanoma, alongside its potential in CNS diseases and combination therapies. The first image emphasizes the interplay between fibroblasts and immune cells, showing how oncogenic reciprocity and nutrient competition drive fibroblast recruitment and activation, thus modulating the immune landscape of tumors. The second image provides a schematic overview of therapeutic avenues targeting the TME, highlighting strategic interventions that can alter cellular interactions to combat cancer. These depictions encapsulate the intricate biological processes and potential therapeutic targets within the TME, underscoring VISTA's significance as a checkpoint in cancer treatment strategies [29, 33].

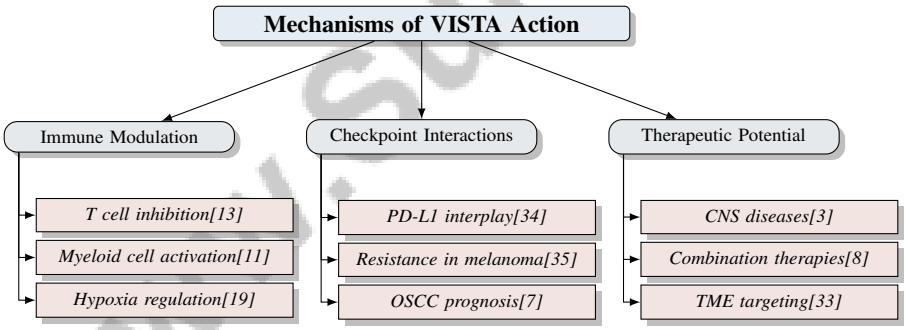

Figure 3: This figure illustrates the hierarchical structure of VISTA's mechanisms of action, categorizing its roles into immune modulation, checkpoint interactions, and therapeutic potential. It highlights VISTA's influence on T cell inhibition, myeloid cell activation, and hypoxia regulation, its interactions with PD-L1 and resistance in melanoma, and its potential in CNS diseases and combination therapies.

3.2 VISTA in Cancer Immune Evasion

VISTA is a key player in immune evasion across various cancers by modulating immune responses within the TME. In melanoma, elevated VISTA expression is a significant negative prognostic factor, correlating with immune evasion mechanisms that contribute to poor disease-specific survival [18]. This highlights VISTA's potential as a therapeutic target to disrupt immune evasion pathways and improve patient outcomes.

In gliomas, VISTA's role in immune evasion is evidenced by its correlation with other immune checkpoints, reinforcing its role in fostering an immunosuppressive environment [21]. Targeting VISTA, alongside other checkpoints, could enhance immunotherapy efficacy by counteracting immune evasion strategies. Hypoxic conditions in the TME exacerbate VISTA-mediated immune suppression through myeloid-derived suppressor cells (MDSCs), where VISTA expression is up-

regulated, intensifying immune system suppression and facilitating tumor growth [19]. Targeting VISTA may mitigate MDSC influence, enhancing anti-tumor immunity and reducing immune evasion potential.

VISTA's involvement in diverse cancer contexts underscores its significance as a key player in immune evasion, necessitating further research to elucidate its mechanisms and develop effective therapeutic strategies. Incorporating VISTA-targeted therapies with established immunotherapeutic approaches holds substantial promise for addressing current treatment limitations, especially for patients with immune-resistant tumors. As a novel negative checkpoint regulator, VISTA modulates both innate and adaptive immune responses, which can be leveraged to enhance existing therapies, potentially improving clinical outcomes and offering insights into the interactions between VISTA and its ligands for more effective treatment modalities [34, 10, 2, 20].

3.3 Expression and Regulation of VISTA

Understanding VISTA's expression and regulation is crucial for elucidating its role in cancer progression and therapeutic resistance. VISTA expression is significantly influenced by the TME, where hypoxic conditions can upregulate its expression, enhancing its immunosuppressive effects [19]. This regulation occurs through hypoxia-inducible factor-1 alpha (HIF-1), which binds to hypoxia-responsive elements in the VISTA promoter, leading to increased expression under low oxygen conditions [19].

Immunohistochemical analyses demonstrate significant changes in VISTA expression dynamics, revealing alterations in immune marker expression in biopsies taken before and after disease progression [35]. These findings highlight VISTA's adaptive response to therapeutic pressures and its potential role in acquired resistance to ICB therapies. VISTA regulation is also linked to its interactions with other immune checkpoints, such as PD-L1, which collectively contribute to tumor immune evasion strategies [34]. In prostate cancer, co-expression of VISTA and PD-L1 is associated with enhanced immune suppression, suggesting that targeting both checkpoints may be a viable strategy to overcome resistance [34].

Beyond tumor-infiltrating immune cells, VISTA is expressed on various cell types within the TME, including MDSCs and tumor-associated macrophages (TAMs), where it significantly modulates immune responses [11]. The upregulation of VISTA in these cells contributes to the establishment of an immunosuppressive TME, presenting challenges for effective cancer therapy. A comprehensive understanding of VISTA expression regulation and its complex interactions within the TME is essential for developing targeted therapeutic strategies, particularly given its role as a significant negative regulator of T-cell function and associations with poor prognostic outcomes in various cancers, such as melanoma and OSCC [7, 12, 18]. Inhibiting VISTA may enhance the efficacy of existing immunotherapies, improving clinical outcomes for patients with resistant tumors. Further research into the molecular mechanisms governing VISTA expression will be critical for advancing cancer immunotherapy and overcoming therapeutic resistance.

4 Therapeutic Strategies Targeting VISTA

4.1 Monoclonal Antibodies Targeting VISTA

Monoclonal antibodies targeting VISTA have emerged as a promising cancer immunotherapy strategy, aiming to disrupt its inhibitory effects within the TME. These antibodies target VISTA's function on myeloid cells, alleviating their suppressive influence to enhance anti-tumor immune responses [11]. This approach is crucial given VISTA's role in sustaining an immunosuppressive TME, a significant barrier to effective cancer treatment. Agonistic antibodies modulating macrophage activity could induce immune tolerance and reduce inflammatory responses [13], potentially shifting the TME to a more immune-active state and enhancing existing immunotherapies.

Future research should focus on combination therapies integrating VISTA-targeting antibodies with other checkpoint inhibitors like anti-PD-1 therapies to overcome resistance [35]. Identifying biomarkers predictive of response could refine patient selection and improve therapeutic outcomes. Platforms such as SpatialVisVR and DreameSpase offer advanced diagnostic capabilities by visualizing immune cell spatial distribution and assessing spatial heterogeneity, respectively, aiding the development of VISTA-targeting therapies [15, 24].

The ongoing development of monoclonal antibodies targeting VISTA aims to enhance cancer immunotherapy outcomes by addressing challenges posed by the immunosuppressive TME. Understanding VISTA and its ligands, such as VSIG-3 and PSGL-1, could unveil new therapeutic avenues to minimize side effects while maximizing anti-tumor responses, thus improving patient survival and treatment success [34, 7, 20].

4.2 VISTA in Combination Therapies

Integrating VISTA-targeting therapies with other treatment modalities promises enhanced cancer immunotherapy efficacy. Combination therapies targeting multiple immune checkpoints or pairing immune checkpoint blockers (ICBs) with conventional treatments have shown improved outcomes over monotherapies [8]. This strategy leverages the synergistic effects of different agents to overcome single-agent treatment limitations, especially in tumors resistant to standard ICBs.

VISTA maintains immune suppression within the tumor microenvironment (TME), contributing to resistance in various cancers. Combining VISTA-targeting agents with other ICBs, such as PD-1 or CTLA-4 inhibitors, could address diverse immune evasion mechanisms [1, 8, 30, 11]. This approach targets multiple suppression pathways, enhancing immune activation and potentially overcoming metabolic challenges posed by the TME.

As illustrated in Figure 4, the integration of VISTA-targeting therapies with other treatment modalities highlights various therapeutic strategies, conventional treatments, and research technologies aimed at enhancing cancer immunotherapy efficacy. Combining VISTA-targeting therapies with conventional treatments like chemotherapy or radiation could improve efficacy. Conventional therapies reshape the TME by inducing immunogenic cell death and modifying immune cell infiltrate composition, particularly enhancing cytotoxic T cell presence, which is crucial for predicting patient outcomes [36, 28]. Concurrent VISTA targeting may enhance these effects by reducing immune suppression and promoting robust anti-tumor responses.

Active research in combination therapies involving VISTA-targeting agents explores various combinations and treatment regimens, focusing on maximizing efficacy while minimizing adverse effects through advanced technologies like multiplexed tissue imaging and machine learning frameworks [14, 6, 37]. As research progresses, integrating VISTA-targeting therapies with other treatments holds promise for overcoming immunotherapy resistance challenges and improving patient outcomes.

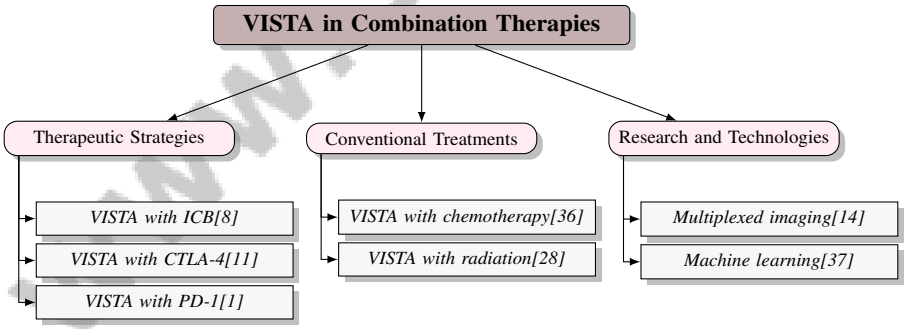

Figure 4: This figure illustrates the integration of VISTA-targeting therapies with other treatment modalities, highlighting therapeutic strategies, conventional treatments, and research technologies to enhance cancer immunotherapy efficacy.

4.3 Preclinical and Clinical Evaluations

Preclinical and clinical evaluations underscore the potential of VISTA-targeting therapies in enhancing cancer immunotherapy. Anti-VISTA antibodies have shown significant therapeutic efficacy in preclinical models, prolonging survival in mice with high VISTA expression [4]. Clinical trials with agents like CI-8993 and CA-170 focus on their effectiveness in advanced solid tumors, aiming to elucidate immune checkpoint regulation and optimize interventions [3]. VISTA's role extends beyond cancer, with implications for enhancing anti-tumor immunity and mitigating autoimmune responses, particularly in CNS diseases [3].

Benchmark	Size	Domain	Task Format	Metric
VISTA-HCC[25]	555	Oncology	Survival Analysis	Kaplan-Meier analysis, Cox regression
VISTA-OSCC[7]	256	Oral Squamous Cell Carcinoma	Immunohistochemistry Analysis	Histoscore, Pearson's correlation coefficient
RNMT-BM[38]	1,000,000	Oncology	Survival Analysis	Cox Regression; Kaplan-Meier

Table 1: Table illustrating key benchmarks utilized in VISTA-targeting therapy research, detailing their size, domain, task format, and evaluation metrics. These benchmarks provide foundational data for survival analysis and immunohistochemistry analysis in oncology, emphasizing the significance of VISTA in cancer prognosis and therapeutic interventions.

VISTA expression on MDSCs under hypoxic conditions contributes to their suppressive function, highlighting the potential of VISTA-targeting therapies to bolster antitumor immunity in hypoxic TME [13]. This approach could enhance existing ICIs by alleviating MDSC suppressive influences. VISTA is also proposed as a prognostic biomarker, with studies linking high expression to poor survival in glioma patients [21], though some evidence suggests VISTA-positive staining correlates with prolonged survival [25].

Integrating VISTA-targeting therapies with other modalities, such as combining with other immune checkpoints, holds promise for overcoming resistance and improving efficacy [7]. Advanced visualization tools like SpatialVisVR enhance multiplexed pathology image analysis, contributing to improved diagnostic accuracy in immuno-oncology [15]. Spatially structured regression models provide insights into complex TME interactions, supporting more effective VISTA-targeting strategies [24]. A comprehensive understanding of VISTA's role across cancers is crucial for optimizing therapeutic strategies and advancing cancer immunotherapy. Table 1 presents a detailed overview of representative benchmarks used in the evaluation of VISTA-targeting therapies, highlighting their relevance in oncology and immunohistochemistry analysis.

4.4 Advancements in Therapeutic Strategies

Recent advancements in therapeutic strategies targeting VISTA underscore its potential as a pivotal target in cancer immunotherapy, particularly in melanoma. VISTA's role in melanoma links its expression to immune evasion mechanisms contributing to poor survival [18]. Monoclonal antibodies and small molecule inhibitors targeting VISTA have shown promise in preclinical models, demonstrating efficacy by modulating immune responses and prolonging survival. These strategies aim to inhibit VISTA-mediated immunosuppressive pathways, compensatory mechanisms following checkpoint blockade therapies like ipilimumab, to enhance existing inhibitor efficacy [34, 2, 11].

Exploring VISTA-targeting therapies in combination with established strategies, such as PD-1 and CTLA-4 inhibitors, aims to enhance efficacy by addressing compensatory inhibitory pathways during treatment, particularly in challenging cancers like prostate cancer [2, 17, 34, 12, 20]. This combinatorial approach leverages synergistic effects of targeting multiple checkpoints, addressing diverse immune evasion mechanisms. Concurrent VISTA targeting may enhance overall immune activation against tumor cells, improving patient outcomes.

Advancements in diagnostic tools, including imaging platforms and spatially structured regression models, facilitate VISTA expression analysis and interactions within the TME. These innovations enhance understanding of immune cell spatial distribution and dynamics, critical for optimizing VISTA-targeting strategies in immunotherapy. By elucidating VISTA's roles in immune regulation, particularly interactions with myeloid cells and influence on inflammation and immunosuppression, these insights pave the way for effective interventions to improve outcomes in cancer and autoimmune diseases [2, 10, 11, 12, 20].

As research progresses, continued exploration of VISTA's role across cancers and its integration with other modalities is crucial for optimizing strategies and advancing immunotherapy. VISTA-targeting therapies have the potential to reshape cancer treatment paradigms by addressing immunotherapy resistance and enhancing clinical outcomes. As a novel checkpoint regulator, VISTA modulates innate and adaptive responses, making it a compelling target for intervention. Understanding interactions with ligands and mechanisms underlying its effects could lead to strategies that improve existing treatment efficacy and broaden options for resistant tumors [2, 34, 12, 20].

5 VISTA and Tumor Microenvironment

The interaction between VISTA and the tumor microenvironment (TME) is pivotal in understanding immune suppression and tumor progression. This section delves into VISTA's specific interactions with myeloid-derived suppressor cells (MDSCs), highlighting its contribution to the immunosuppressive milieu that impedes effective anti-tumor immunity and fosters tumor growth.

5.1 VISTA Interactions with Myeloid-Derived Suppressor Cells

VISTA's engagement with MDSCs is critical in elucidating immune suppression mechanisms and tumor advancement. VISTA expression on MDSCs augments their immunosuppressive functions, posing a significant barrier to anti-tumor immunity [7]. Within the TME, MDSCs inhibit T cell activation, promoting an environment conducive to tumor growth.

Cytokines such as IL-4 and IFN- play crucial roles in macrophage polarization, influencing MDSC interactions [36]. These cytokines modulate VISTA expression and activity on MDSCs, enhancing their suppressive capabilities. This cytokine-mediated regulation underscores the complexity of immune interactions and the therapeutic challenges in targeting these pathways.

Hypoxic conditions in the TME further upregulate VISTA on MDSCs, amplifying their immunosuppressive abilities and contributing to immune evasion and therapeutic resistance [19, 7, 11]. High VISTA levels correlate with poor survival, emphasizing its role in immune escape [11]. Targeting VISTA may disrupt MDSC-mediated suppression, enhancing anti-tumor immunity and improving immunotherapy efficacy. Combining VISTA targeting with other checkpoint inhibitors could offer novel strategies to overcome the immunosuppressive barriers posed by MDSCs.

5.2 VISTA and Tumor-Associated Macrophages

VISTA's modulation of tumor-associated macrophages (TAMs) is a key aspect of the TME's immunosuppressive landscape. VISTA, highly expressed on TAMs, promotes their polarization toward an immunosuppressive phenotype, facilitating tumor progression and immune evasion [13]. This underscores VISTA's role in maintaining an environment that suppresses effective anti-tumor responses.

TAMs exhibit plasticity, often adopting a pro-tumorigenic M2-like phenotype characterized by anti-inflammatory cytokine production [22]. VISTA enhances TAMs' immunosuppressive activities, inhibiting T cell activation crucial for anti-tumor responses [11]. This modulation by VISTA is central to establishing an immunosuppressive TME.

Hypoxia further regulates VISTA expression on TAMs, exacerbating their suppressive effects and enhancing immune evasion [19]. Targeting VISTA on TAMs could potentially reverse their phenotype, promoting a shift to a pro-inflammatory state and enhancing immunotherapy efficacy by reducing TAMs' suppressive influence.

Strategically targeting VISTA on TAMs, alongside other checkpoint inhibitors, may offer a novel approach to overcoming TME immunosuppression and improving cancer immunotherapy [11]. Understanding VISTA-TAM interactions is essential for developing therapies that modulate the TME and improve clinical outcomes.

5.3 Resistance Mechanisms in the Tumor Microenvironment

The TME presents significant challenges to cancer therapy due to its immunosuppressive nature, which inhibits immune cell activity and facilitates tumor progression [36]. VISTA plays a crucial role by modulating immune responses and contributing to therapeutic resistance. Its expression on MDSCs and TAMs enhances their suppressive functions, promoting immune evasion and resistance to immune checkpoint blockade (ICB) therapies.

The TME's spatial and functional heterogeneity complicates immune resistance. Distinct tumor regions exert differential influences on immune responses, necessitating a nuanced understanding to optimize therapies [23]. This heterogeneity complicates VISTA targeting and other checkpoints due to variability in immune cell distribution and activity.

Hypoxic conditions significantly enhance VISTA-mediated immune suppression by increasing its expression on MDSCs and TAMs, correlating with poorer survival in various cancers [13, 11, 18, 19, 7]. Hypoxia-induced VISTA expression reinforces the immunosuppressive environment, hindering T cell activation essential for anti-tumor immunity. Targeting VISTA may alleviate these suppressive influences, enhancing immunotherapies and overcoming resistance.

Improving cancer treatment outcomes requires strategies that modulate VISTA within the TME, as elevated VISTA levels correlate with poor survival and immune evasion [13, 18, 12, 4, 7]. Exploring combination therapies integrating VISTA-targeting agents with other inhibitors or conventional treatments is crucial to address immune resistance's multifaceted nature. Comprehensive understanding of VISTA's role in resistance mechanisms is pivotal for advancing cancer immunotherapy and improving patient outcomes.

6 Challenges and Future Directions

The exploration of V-domain Ig suppressor of T cell activation (VISTA) as a therapeutic target in cancer immunotherapy presents multifaceted challenges that hinder progress in this field. Addressing these challenges is essential for identifying innovative solutions and guiding future research directions. The following subsections will discuss specific challenges in VISTA research, emphasizing its dual role, expression variability, and the complex dynamics of the tumor microenvironment (TME), thereby highlighting the necessity for targeted strategies to navigate these obstacles effectively.

6.1 Challenges in VISTA Research

VISTA research is complicated by its dual role as a receptor and ligand, with variable expression across cell types [3]. The complexities of VISTA's signaling within the TME and CNS complicate targeted therapy development [13]. A limited understanding of VISTA's ligands and their immune modulation roles further impedes effective therapeutic strategy creation [8]. This is compounded by diverse immune suppression mechanisms and incomplete tumor-immune interaction models [16]. Patient immune response heterogeneity complicates VISTA-targeted therapy development due to a lack of robust predictive biomarkers [8].

The TME's intricate nature and dynamic interactions pose significant therapy development challenges [22]. Tumor spatial heterogeneity and expert annotation reliance can bias spatial analyses, hindering accurate tumor-immune interaction characterization [15]. High computational demands and discomfort with advanced visualization technologies complicate their deployment in resource-limited settings [15].

In cancers such as oral squamous cell carcinoma, findings may not be generalizable across all populations, necessitating broader validation [7]. Potential side effects and long-term implications of anti-VISTA therapy require further investigation to ensure treatment safety and efficacy [4]. Understanding VISTA's role as a negative checkpoint regulator in immune responses and its influence on tumor progression and immune tolerance is crucial for developing targeted therapies that enhance cancer immunotherapy effectiveness [34, 18, 12, 20].

6.2 Innovative Approaches and Future Directions

Advancing VISTA-targeting strategies requires innovative approaches and focused research. Integrating VISTA blockade with other immune checkpoint inhibitors, such as PD-L1, could enhance therapeutic efficacy and overcome resistance, particularly in hypoxic TMEs where VISTA expression is upregulated [19]. Future research should prioritize identifying patient subsets most likely to benefit from VISTA-targeted therapies, necessitating robust predictive biomarkers [13].

Elucidating metabolic reprogramming mechanisms within the TME is critical, as these interactions significantly influence immune responses and therapeutic resistance [29]. Investigating tumor-associated stromal cells (TASCs) and developing targeted therapies to modulate their functions could enhance VISTA-targeting efficacy [22]. Exploring VISTA's functions in microglia and its potential as a therapeutic target in CNS pathology offers promising research avenues with implications for broader VISTA modulation in inflammatory diseases [3].

Technological advancements, such as improving multiplexed slide resolution and integrating rapid diagnostic features, will be crucial for expanding VISTA-targeting therapy clinical applications [15]. Extending DreameSpase to multi-omic data and enhancing random effects selection processes could improve model performance and deepen insights into complex TME interactions [24]. Addressing these research directions can advance cancer immunotherapy, improving patient outcomes and overcoming current treatment limitations.

6.3 Integration with Other Immune Checkpoints

Integrating VISTA with other immune checkpoint therapies offers a promising strategy to enhance cancer immunotherapy efficacy. VISTA plays a significant role in maintaining immune suppression within the TME, posing a major cancer treatment challenge [17]. Combining VISTA-targeting agents with other immune checkpoint inhibitors, such as PD-1 and CTLA-4 inhibitors, can address diverse immune evasion mechanisms employed by tumors. This integration is particularly relevant for tumors exhibiting resistance to standard immune checkpoint blockades, leveraging synergistic effects to enhance overall immune activation against tumor cells. Combination therapies have shown improved outcomes compared to monotherapies, offering a more comprehensive approach to overcoming single-agent treatment limitations [8].

The co-expression of VISTA with other immune checkpoints, such as PD-L1, in various cancer types suggests that targeting these checkpoints together could provide a more effective therapeutic strategy [34]. This co-expression reflects the complexity of immune regulation within the TME and highlights the potential benefits of integrating VISTA with other checkpoint inhibitors to enhance anti-tumor immunity. The development of combination therapies involving VISTA-targeting agents is an active research area, with ongoing clinical trials exploring various combinations and treatment regimens. These studies aim to identify optimal strategies that enhance patient outcomes by leveraging insights from the TME and employing advanced technologies, such as highly multiplexed tissue imaging and machine learning frameworks, to minimize adverse effects and tailor treatments to individual responses. By understanding complex interactions within the immune tumor microenvironment and utilizing mathematical modeling to address challenges in cancer immunotherapy, researchers strive to develop more effective, personalized treatment approaches that balance efficacy with safety [14, 6, 37]. As research progresses, integrating VISTA-targeting therapies with other treatments holds promise for overcoming immunotherapy resistance challenges and improving cancer patient outcomes.

6.4 Biomarker Development and Patient Stratification

Developing biomarkers for VISTA is essential for enhancing cancer immunotherapy precision and efficacy. Biomarkers can provide critical insights into VISTA expression levels and functional status within the TME, enabling more accurate patient stratification and personalized treatment approaches [3]. Identifying reliable biomarkers for VISTA is particularly important given its role in immune suppression and tumor progression, which varies significantly across cancer types and patient populations [13].

One promising approach involves using immunohistochemical analyses to assess VISTA expression in tumor biopsies, serving as a predictive marker for patient response to VISTA-targeting therapies [35]. This method allows quantifying VISTA expression levels and correlating them with clinical outcomes, providing valuable information for tailoring treatment strategies [25]. Additionally, integrating genomic and transcriptomic data can enhance biomarker discovery, offering a comprehensive view of the molecular landscape associated with VISTA expression and its regulatory pathways [24].

Patient stratification based on VISTA biomarker profiles can facilitate identifying subsets most likely to benefit from VISTA-targeted therapies, optimizing therapeutic efficacy and minimizing adverse effects [4]. This process can also aid in selecting appropriate combination therapies, such as those involving other immune checkpoint inhibitors, to address diverse immune evasion mechanisms within the TME [8]. Continued development of VISTA biomarkers and stratification strategies will be crucial for advancing cancer immunotherapy and improving clinical outcomes for patients with resistant tumors.

7 Conclusion

The survey of V-domain Ig suppressor of T cell activation (VISTA) highlights its critical function as an immune checkpoint in cancer immunotherapy. VISTA operates as both a ligand and receptor, intricately modulating immune responses and significantly contributing to tumor immune evasion and therapeutic resistance. Its expression and regulation within the tumor microenvironment (TME) are influenced by factors such as hypoxia, which intensify its immunosuppressive effects, revealing the complexity of its interactions with other immune checkpoints [16].

Therapeutic strategies targeting VISTA, including monoclonal antibodies and small molecule inhibitors, have demonstrated promising preclinical and clinical results in enhancing anti-tumor immunity and overcoming resistance mechanisms. The combination of VISTA-targeting therapies with other immune checkpoint inhibitors, such as PD-1 and CTLA-4, presents a synergistic approach to modulating immune responses and improving therapeutic efficacy.

Despite these advancements, the intricate mechanisms of VISTA within the TME and its interactions with various immune cells require further investigation to fully understand its role and therapeutic potential. The identification and development of robust biomarkers for VISTA are essential for patient stratification and optimizing treatment strategies. Future research should also consider integrating control theory concepts to deepen insights into immune system dynamics and cancer risk assessment [16].

References

[1] Julian A Marin-Acevedo, Bhagirathbhai Dholaria, Aixa E Soyano, Keith L Knutson, Saranya Chumsri, and Yanyan Lou. Next generation of immune checkpoint therapy in cancer: new developments and challenges. *Journal of hematology & oncology*, 11:1–20, 2018.

[2] Mohamed A ElTanbouly, Walburga Croteau, Randolph J Noelle, and J Louise Lines. Vista: a novel immunotherapy target for normalizing innate and adaptive immunity. In *Seminars in immunology*, volume 42, page 101308. Elsevier, 2019.

[3] Malte Borggrewe, Susanne M Kooistra, Randolph J Noelle, Bart JL Eggen, and Jon D Laman. Exploring the vista of microglia: immune checkpoints in cns inflammation. *Journal of Molecular Medicine*, 98(10):1415–1430, 2020.

[4] Kumuluzi Mulati, Junzo Hamanishi, Noriomi Matsumura, Kenji Chamoto, Nathan Mise, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Naoki Horikawa, Ryusuke Murakami, et al. Vista expressed in tumour cells regulates t cell function. *British journal of cancer*, 120(1):115–127, 2019.

[5] Yuanyuan Zhang and Zemin Zhang. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cellular & molecular immunology*, 17(8):807–821, 2020.

[6] Anna Konstorum, Anthony T. Vella, Adam J. Adler, and Reinhard Laubenbacher. Addressing current challenges in cancer immunotherapy with mathematical and computational modeling, 2017.

[7] Lei Wu, Wei-Wei Deng, Cong-Fa Huang, Lin-Lin Bu, Guang-Tao Yu, Liang Mao, Wen-Feng Zhang, Bing Liu, and Zhi-Jun Sun. Expression of vista correlated with immunosuppression and synergized with cd8 to predict survival in human oral squamous cell carcinoma. *Cancer Immunology, Immunotherapy*, 66:627–636, 2017.

[8] Xiaolei Li, Changshun Shao, Yufang Shi, and Weidong Han. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. *Journal of hematology & oncology*, 11:1–26, 2018.

[9] Elizabeth C Nowak, J Louise Lines, Frederick S Varn, Jie Deng, Aurelien Sarde, Rodwell Mabaera, Anna Kuta, Isabelle Le Mercier, Chao Cheng, and Randolph J Noelle. Immunoregulatory functions of vista. *Immunological reviews*, 276(1):66–79, 2017.

[10] Xing Huang, Xiaozhen Zhang, Enliang Li, Gang Zhang, Xun Wang, Tianyu Tang, Xueli Bai, and Tingbo Liang. Vista: an immune regulatory protein checking tumor and immune cells in cancer immunotherapy. *Journal of Hematology & Oncology*, 13:1–13, 2020.

[11] Wenwen Xu, Juan Dong, Yongwei Zheng, Juan Zhou, Ying Yuan, Hieu Minh Ta, Halli E Miller, Michael Olson, Kamalakannan Rajasekaran, Marc S Ernstoff, et al. Immune-checkpoint protein vista regulates antitumor immunity by controlling myeloid cell–mediated inflammation and immunosuppression. *Cancer immunology research*, 7(9):1497–1510, 2019.

[12] Wenwen Xu, TMinh Hiu, Subramaniam Malarkannan, and Li Wang. The structure, expression, and multifaceted role of immune-checkpoint protein vista as a critical regulator of anti-tumor immunity, autoimmunity, and inflammation. *Cellular & molecular immunology*, 15(5):438–446, 2018.

[13] Mohamed A ElTanbouly, Evelien Schaafsma, Nicole C Smits, Parth Shah, Chao Cheng, Christopher Burns, Bruce R Blazar, Randolph J Noelle, and Rodwell Mabaera. Vista re-programs macrophage biology through the combined regulation of tolerance and anti-inflammatory pathways. *Frontiers in immunology*, 11:580187, 2020.

[14] Yi Xiao and Dihua Yu. Tumor microenvironment as a therapeutic target in cancer. *Pharmacology & therapeutics*, 221:107753, 2021.

[15] Jai Prakash Veerla, Partha Sai Guttikonda, Amir Hajighasemi, Jillur Rahman Saurav, Aarti Darji, Cody T. Reynolds, Mohamed Mohamed, Mohammad S. Nasr, Helen H. Shang, and Jacob M. Luber. Spatialvisvr: An immersive, multiplexed medical image viewer with contextual similar-patient search, 2024.

[16] Augusto Gonzalez. Mathematical control theory, the immune system, and cancer, 2016.

[17] Ji-Eun Irene Yum and Young-Kwon Hong. Terminating cancer by blocking vista as a novel immunotherapy: Hasta la vista, baby. *Frontiers in Oncology*, 11:658488, 2021.

[18] Lawrence F Kuklinski, Shaofeng Yan, Zhongze Li, Jan L Fisher, Chao Cheng, Randolph J Noelle, Christina V Angeles, Mary Jo Turk, and Marc S Ernstoff. Vista expression on tumor-infiltrating inflammatory cells in primary cutaneous melanoma correlates with poor disease-specific survival. *Cancer Immunology, Immunotherapy*, 67:1113–1121, 2018.

[19] Jie Deng, Jiannan Li, Aurelien Sarde, J Louise Lines, Yu-Chi Lee, David C Qian, Dov A Pechenick, Richard Manivanh, Isabelle Le Mercier, Christopher H Lowrey, et al. Hypoxia-induced vista promotes the suppressive function of myeloid-derived suppressor cells in the tumor microenvironment. *Cancer immunology research*, 7(7):1079–1090, 2019.

[20] Najibeh Shekari, Dariush Shanehbandi, Tohid Kazemi, Habib Zarredar, Behzad Baradaran, and Seyed Amir Jalali. Vista and its ligands: the next generation of promising therapeutic targets in immunotherapy. *Cancer Cell International*, 23(1):265, 2023.

[21] Amina Ghouzlani, Abdelhakim Lakhdar, Soumaya Rafii, Mehdi Karkouri, and Abdallah Badou. The immune checkpoint vista exhibits high expression levels in human gliomas and associates with a poor prognosis. *Scientific reports*, 11(1):21504, 2021.

[22] Borros Arneth. Tumor microenvironment. *Medicina*, 56(1):15, 2019.

[23] Mahmudul Hasan, Jakub R. Kaczmarzyk, David Paredes, Lyanne Oblein, Jaymie Oentoro, Shahira Abousamra, Michael Horowitz, Dimitris Samaras, Chao Chen, Tahsin Kurc, Kenneth R. Shroyer, and Joel Saltz. A novel framework for characterization of tumor-immune spatial relationships in tumor microenvironment, 2022.

[24] Nathaniel Osher, Jian Kang, Arvind Rao, and Veerabhadran Baladandayuthapani. Spatially structured regression for non-conformable spaces: Integrating pathology imaging and genomics data in cancer, 2024.

[25] Ming Zhang, Hua-Jin Pang, Wei Zhao, Yu-Fa Li, Li-Xu Yan, Zhong-Yi Dong, and Xiao-Feng He. Vista expression associated with cd8 confers a favorable immune microenvironment and better overall survival in hepatocellular carcinoma. *BMC cancer*, 18:1–8, 2018.

[26] Russell W Jenkins, David A Barbie, and Keith T Flaherty. Mechanisms of resistance to immune checkpoint inhibitors. *British journal of cancer*, 118(1):9–16, 2018.

[27] Zitong Jerry Wang, Alexander M. Xu, Aman Bhargava, and Matt W. Thomson. Generating counterfactual explanations of tumor spatial proteomes to discover effective strategies for enhancing immune infiltration, 2023.

[28] Nicolas A Giraldo, Rafael Sanchez-Salas, J David Peske, Yann Vano, Etienne Becht, Florent Petitprez, Pierre Validire, Alexandre Ingels, Xavier Cathelineau, Wolf Herman Fridman, et al. The clinical role of the tme in solid cancer. *British journal of cancer*, 120(1):45–53, 2019.

[29] Miguel Reina-Campos, Jorge Moscat, and Maria Diaz-Meco. Metabolism shapes the tumor microenvironment. *Current opinion in cell biology*, 48:47–53, 2017.

[30] Robert D Leone and Jonathan D Powell. Metabolism of immune cells in cancer. *Nature reviews cancer*, 20(9):516–531, 2020.

[31] Yan Zhao, Meili Shen, Liangqiang Wu, Haiqin Yang, Yixuan Yao, Qingbiao Yang, Jianshi Du, Linlin Liu, Yapeng Li, and Yuansong Bai. Stromal cells in the tumor microenvironment: accomplices of tumor progression? *Cell death & disease*, 14(9):587, 2023.

[32] J-J Wang, K-F Lei, and FJERMPS Han. Tumor microenvironment: recent advances in various cancer treatments. *European Review for Medical & Pharmacological Sciences*, 22(12), 2018.

[33] Peijie Wu, Wei Gao, Miao Su, Edouard C Nice, Wenhui Zhang, Jie Lin, and Na Xie. Adaptive mechanisms of tumor therapy resistance driven by tumor microenvironment. *Frontiers in cell and developmental biology*, 9:641469, 2021.

[34] Jianjun Gao, John F Ward, Curtis A Pettaway, Lewis Z Shi, Sumit K Subudhi, Luis M Vence, Hao Zhao, Jianfeng Chen, Hong Chen, Eleni Efstathiou, et al. Vista is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. *Nature medicine*, 23(5):551–555, 2017.

[35] Hojabr Kakavand, Louise A Jackett, Alexander M Menzies, Tuba N Gide, Matteo S Carlino, Robyn PM Saw, John F Thompson, James S Wilmott, Georgina V Long, and Richard A Scolyer. Negative immune checkpoint regulation by vista: a mechanism of acquired resistance to anti-pd-1 therapy in metastatic melanoma patients. *Modern Pathology*, 30(12):1666–1676, 2017.

[36] Mobina Tousian, Christian Solis Calero, and Julio Cesar Perez Sansalvador. Immune cells interactions in the tumor microenvironment, 2024.

[37] Martin Paulikat, Christian M. Schürch, and Christian F. Baumgartner. Studying therapy effects and disease outcomes in silico using artificial counterfactual tissue samples, 2023.

[38] Shuqiang Huang, Cuiyu Tan, Jinzhen Zheng, Zhugu Huang, Zhihong Li, Ziyin Lv, and Wanru Chen. Integrative pan-cancer analysis of rnmt: a potential prognostic and immunological biomarker, 2024.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.