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Tumor-Intrinsic Immune Checkpoints: Emerging Implications for Cancer Progression and Immunotherapy

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Abstract

Immune checkpoint pathways have revolutionized cancer therapy, with agents targeting PD-1, CTLA-4, and related molecules achieving durable clinical responses across multiple malignancies. Traditionally, these pathways have been viewed as regulators of immune cell activity, particularly in controlling T-cell activation and exhaustion. However, emerging evidence supports a paradigm shift in which tumor cells themselves express functional immune checkpoint molecules, including both canonical and noncanonical forms. This tumor-intrinsic checkpoint expression extends beyond passive immune evasion and represents an active component of cancer biology. Tumor-expressed checkpoints can promote proliferation, survival, and metastasis through oncogenic signaling pathways, while also shaping the tumor microenvironment via autocrine and paracrine interactions that reinforce immunosuppression. Notably, the functional consequences of these pathways are highly context-dependent, with divergent roles observed across tumor types and molecular backgrounds. These findings have significant clinical implications, including their impact on response heterogeneity to immune checkpoint blockade and their potential as novel therapeutic targets and biomarkers. In this perspective, we discuss the biological and translational relevance of tumor-intrinsic checkpoint signaling, highlight current challenges, and propose future directions for integrating this emerging dimension into precision immuno-oncology.

Keywords

Tumor-Intrinsic Checkpoint Signaling, Immune Checkpoint Blockade, Tumor Microenvironment, Immune Evasion, Cancer Immunotherapy

1. Introduction: Reframing the Checkpoint Paradigm

Over the last two decades, immune checkpoint signaling has transformed the therapeutic landscape of cancer treatment. Immune regulatory molecules such as programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene 3 (LAG-3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), T-cell immunoglobulin and mucin domain-3 (TIM-3), and V-domain Ig suppressor of T-cell activation (VISTA) have traditionally been recognized as central modulators of adaptive immune responses, particularly in the regulation of T-cell activation, tolerance, and exhaustion [1] [2]. The development of immune checkpoint blockade (ICB) therapies targeting these pathways has produced remarkable clinical benefits across several malignancies, establishing checkpoint inhibition as a major pillar of contemporary cancer immunotherapy. Recently, however, accumulating evidence has challenged the exclusively immune-centered interpretation of checkpoint biology. Studies have demonstrated that tumor cells themselves may express both canonical and noncanonical immune checkpoint molecules, including PD-L1 and PD-1 [3] [4]. This tumor-intrinsic expression broadens the current understanding of checkpoint signaling, indicating that these molecules may exert functions beyond immune modulation. In this context, checkpoint proteins can participate in autocrine and paracrine signaling networks that influence tumor cell behavior, remodel the tumor microenvironment (TME), and promote cellular survival and proliferation. Such tumor-associated checkpoint expression has been described in multiple cancer types, including melanoma, pancreatic ductal adenocarcinoma, triple-negative breast cancer, glioblastoma, colorectal cancer, and non-small cell lung cancer.

For the purpose of this Perspective, tumor-intrinsic immune checkpoint signaling refers to the functional expression and biological activity of immune checkpoint receptors or ligands within malignant cells themselves, independent of their canonical immunoregulatory roles on immune cells. Evidence supporting a tumor-intrinsic mechanism should ideally include tumor-cell-specific expression confirmed by immunohistochemistry, flow cytometry, or single-cell approaches, together with functional validation demonstrating direct effects on tumor cell proliferation, survival, invasion, metabolism, or intracellular signaling following genetic or pharmacological manipulation. In contrast, observations derived solely from bulk tumor transcriptomic datasets or mixed tissue specimens should be interpreted cautiously, as these analyses cannot unequivocally distinguish tumor-cell expression from signals originating from infiltrating immune or stromal populations.

Collectively, these findings indicate that checkpoint molecule expression by

malignant cells represents more than a secondary consequence of tumor progression. Instead, it appears to constitute an adaptive mechanism that enhances immune escape, sustains tumor development, and contributes to resistance to therapy [4]-[10]. This evolving perspective expands the current model of tumor–immune interactions and carries important implications for the design and optimization of checkpoint-targeted therapeutic strategies. Furthermore, tumor-intrinsic checkpoint signaling may actively support tumor plasticity, cellular fitness, and resistance phenotypes, rather than simply reflecting a passive imitation of physiological immune regulatory pathways.

2. Functional Spectrum of Tumor-Intrinsic Checkpoint Expression

Tumor cells are not passive recipients of immune surveillance but active participants in immunoregulatory networks. The expression of immune checkpoint molecules on tumor cells introduces new signaling axes that operate independently or synergistically with immune cell pathways. Mechanistically, these tumor-intrinsic checkpoint programs can be broadly categorized into four overlapping functional domains: 1) Promotion of tumor growth and survival; 2) Facilitation of immune escape through local crosstalk; 3) Context-dependent regulation of tumor behavior, and 4) Emerging Checkpoints Beyond PD-1.

2.1. Promotion of Tumor Growth and Survival

Accumulating evidence, derived predominantly from in vitro cancer cell models, xenograft experiments, and a limited number of translational clinical studies, suggests that tumor-expressed checkpoint molecules can directly influence oncogenic behavior. Although these findings consistently support biologically relevant tumor-intrinsic functions, the strength and direction of these effects may vary among tumor types and therefore warrant further validation in large prospective clinical cohorts. PD-1 is a central example: tumor-intrinsic PD-1 expression has been reported in its expression on melanoma, pancreatic ductal adenocarcinoma, and TNBC, where it has been associated with enhanced proliferation, survival and metastatic potential through pathways including mTOR and Hippo-YAP/TAZ-CYR61/CTGF signaling [4]-[7]. Similar protumorigenic effects have been observed with TIM-3 in glioblastoma, where it increases invasion and neurosphere formation and induces IL-6 secretion, leading to activation of protumor macrophages [11] [12]. In breast cancer, CTLA-4 expression supports colony formation and migration, while VISTA co-expression with CTLA-4 has been associated with increased clonogenicity and reduced apoptosis [13]-[15]. These findings reveal that checkpoint molecules can act as bona fide tumor growth regulators, challenging the traditional notion that they function only in immune cells.

2.2. Facilitation of Immune Escape through Crosstalk

A second major functional axis involves tumor-tumor and tumor-immune cell

interactions mediated by checkpoint signaling. Tumor cells may co-express receptors and ligands (e.g., PD-1 and PD-L1), enhancing potential autocrine or paracrine signaling loops, that reinforce immune evasion and local immunosuppression [7]. In this context, checkpoint signaling contributes to the exclusion or functional impairment of cytotoxic T lymphocytes, shaping an immunologically "cold" tumor microenvironment. VISTA expression in ovarian and endometrial cancers, for instance, has been shown to suppress T-cell proliferation and cytokine production, resulting in reduced CD8+ infiltration *in vivo* [16]. Additionally, CD4+ T cells can induce PD-1 expression on mesenchymal stem-like tumor cells, further amplifying immunomodulatory feedback loops [8]. This bidirectional communication creates a self-protective niche in which tumor cells actively manipulate immune tone. It should be noted that most mechanistic evidence supporting these tumor-intrinsic interactions has been generated using experimental systems, including cultured cancer cell lines and animal models. Although these studies provide compelling biological insights, confirmation in well-characterized human clinical specimens using spatially resolved technologies remains an important priority for future investigation.

2.3. Context-Dependent Regulation of Tumor Behavior

Perhaps the most intriguing aspect of tumor-intrinsic checkpoint expression is its functional heterogeneity. In some context PD-1 expression correlate with enhanced tumor growth (e.g., melanoma, TNBC, pancreatic), whereas in others, such as colorectal and lung cancer, it is associated with tumor suppression [9] [10]. Similarly, TIM-3 positivity in renal cell carcinoma has been associated with favorable progression-free and overall survival in some studies, while others report the opposite [17]. These opposing effects suggest that tumor-intrinsic checkpoint signaling does not follow a uniform pattern but is highly dependent on cellular context, including the tumor's genetic background, oncogenic signaling landscape, differentiation state, and microenvironmental composition. Several non-mutually exclusive mechanisms may explain these context-dependent effects. First, distinct oncogenic drivers can rewire downstream checkpoint-associated signaling pathways, resulting in divergent biological outcomes despite expression of the same checkpoint molecule. Second, the differentiation state and cellular plasticity of malignant cells may influence receptor availability and signaling competence. Third, ligand abundance within the tumor microenvironment, together with cytokine composition and stromal interactions, may modify checkpoint activity through autocrine and paracrine mechanisms. Finally, immune contexture including the density, phenotype, and spatial organization of infiltrating immune cells may determine whether tumor-intrinsic checkpoint signaling primarily promotes immune evasion, tumor suppression, or adaptive therapeutic resistance. Together, these variables provide a conceptual framework explaining why identical checkpoint molecules may exert opposite biological effects across different malignancies. This context dependency carries profound therapeutic implications.

Unlike classical checkpoint blockade, which presumes an inhibitory effect on immune cells, tumor-intrinsic checkpoint signaling may produce divergent or even opposing outcomes following ICB therapy. For example, anti-PD-1 therapy may interfere with tumor signaling in ways that either enhance or blunt clinical benefit, depending on tumor type and signaling dependencies [4]-[10].

2.4. Emerging Checkpoints beyond PD-1

While PD-1 remains the most extensively studied, other tumor-intrinsic checkpoints are gaining attention. TIGIT expression in colorectal and breast cancer cell lines has been linked to migratory and clonogenic capabilities [18] [19]. LAG-3 expression has been detected in some non-small cell lung cancers and may correlate with advanced disease stage [20]. Although mechanistic studies on BTLA and LAG-3 remain limited, their emerging roles in tumor cell signaling warrant deeper investigation, particularly in the context of resistance to ICB. In summary, tumor-intrinsic checkpoint signaling spans multiple biological layers: enhancing tumor survival, enabling immune evasion, and shaping disease trajectories in a context-dependent manner. These diverse functions are not merely extensions of immune signaling but constitute independent oncogenic programs that can profoundly influence therapeutic response. Understanding these pathways mechanistically is essential to unlocking the full potential of checkpoint-based cancer therapy.

3. Clinical Implications and Translational Opportunities

The recognition that tumor cells themselves can express immune checkpoint molecules introduces a critical new dimension to immuno-oncology and has profound clinical implications. Classical checkpoint blockade therapies such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies were designed to reinvigorate T-cell responses by interrupting inhibitory signaling between immune and tumor cells. However, when the tumor is also an active checkpoint-expressing entity, the biological and therapeutic consequences become more complex. Tumor intrinsic checkpoint signaling may act independently of immune modulation, influencing tumor proliferation, survival and metastasis, thereby influencing both treatment response and disease trajectory [4]-[10].

One major clinical implication lies in heterogeneous treatment responses to immune checkpoint blockade (ICB). Patients with tumors harboring high levels of intrinsic PD-1 or other checkpoint molecules may experience paradoxical or attenuated benefits from standard checkpoint inhibitors. For example, PD-1 expression by melanoma, pancreatic ductal adenocarcinoma, and triple-negative breast cancer cells has been reported to enhance tumor growth and metastatic capacity [5] [7]. In these contexts, blocking PD-1 may not only modulate T-cell activity but could also directly affect tumor signaling pathways such as Hippo, NF-κB, or mTOR, resulting in unpredictable clinical outcomes. Conversely, in colorectal and some lung cancers, tumor-intrinsic PD-1 expression correlates with growth inhibition, underscoring the context-dependent biology of checkpoint signaling [9]

[10]. Such variability highlights the need for molecular stratification of patients receiving ICB. Second, intrinsic checkpoint expression represents an emerging therapeutic target in its own right. Strategies that selectively or dually inhibit both immune cell mediated and tumor intrinsic checkpoint signaling could improve efficacy, particularly in tumors with strong autocrine checkpoint loops. This might involve novel antibody formats, bispecific molecules, or small-molecule inhibitors targeting downstream signaling cascades (e.g., PD-1-Hippo-CYR61/CTGF axis in pancreatic cancer, TIM-3-IL-6-macrophage axis in glioblastoma) [4] [6] [11] [12]. Tumor checkpoint expression could potentially modulate responses to adoptive cell therapies such as CAR-T cells, by shaping the immune microenvironment and creating resistance niches.

Third, tumor-intrinsic checkpoint expression has diagnostic and prognostic value. Importantly, tumor-intrinsic checkpoint profiling is not intended to replace current biomarker strategies but rather to complement them. Existing clinical assays evaluate checkpoint expression within tumor cells, immune cells, or both depending on the cancer type and the validated scoring system. However, these assessments generally do not distinguish between checkpoint molecules functioning as markers of immune interaction and those actively participating in tumor-cell-intrinsic signaling. Integrating spatial transcriptomics, multiplex immunohistochemistry, and single-cell profiling into future biomarker platforms may enable more precise characterization of tumor-specific checkpoint biology, thereby improving patient stratification and informing rational combination immunotherapy strategies.

The presence and level of checkpoint molecules on tumor cells may serve as potential biomarkers, metastatic potential, and patient survival outcomes. For instance, high tumor-intrinsic PD-1 correlates with poorer overall survival in pancreatic and triple-negative breast cancers, whereas TIM-3 positivity has shown both pro- and anti-tumor associations depending on the cancer type [6] [7] [11]. Integrating these biomarkers into patient selection algorithms could enhance predictive precision and guide therapeutic decision-making. Finally, these findings urge a paradigm shift in clinical trial design. Current ICB trials often classify patients based on immune infiltrate or PD-L1 expression on immune cells, overlooking tumor-intrinsic checkpoint status. Incorporating this dimension through tumor molecular profiling and functional assays could refine eligibility criteria, explain non-responders, and identify patients who might benefit from combination therapies targeting both immune and tumor components. Moreover, checkpoint expression by tumor cells may necessitate new dosing or scheduling strategies to optimize therapeutic windows and minimize compensatory signaling. In sum, tumor-intrinsic checkpoint expression is more than a molecular curiosity, it is a clinically actionable feature of cancer biology. Its integration into precision oncology frameworks has the potential to improve response prediction, expand therapeutic targets, and reshape the next generation of immunotherapy strategies.

4. Challenges and Open Questions

Despite rapid progress in identifying tumor-intrinsic immune checkpoint expression, several fundamental questions remain unanswered. These challenges represent not only conceptual gaps but also critical barriers to clinical translation. First, the determinants of functional heterogeneity in tumor checkpoint signaling remain unclear. The same checkpoint molecule can have opposing effects depending on the tumor context. For instance, intrinsic PD-1 signaling promotes proliferation and metastasis in melanoma, pancreatic cancer, and TNBC, yet correlates with growth suppression in colorectal and certain lung cancers [5] [10]. The molecular basis for this context-dependent duality is poorly understood. It likely reflects differences in downstream signaling networks, oncogenic mutations, epigenetic states, and microenvironmental cues. Second, there is currently no standardized framework to assess and classify tumor intrinsic checkpoint expression. Clinical pathology routinely evaluates PD-L1 expression on immune cells, but analogous assays for PD-1, CTLA-4, TIGIT, VISTA, or TIM-3 on tumor cells are not validated or widely implemented. This diagnostic gap prevents robust integration of tumor checkpoint expression into therapeutic decision-making. Advanced multiplex immunohistochemistry, spatial transcriptomics, and single-cell profiling may be essential to capture the spatial and functional complexity of these pathways. Third, it remains uncertain how tumor-intrinsic checkpoint expression interacts with standard immunotherapies. Antibodies designed to block immune checkpoint interactions were not developed with tumor-intrinsic signaling in mind. Their impact on tumor cells may differ dramatically from their effects on T cells, potentially contributing to variable clinical outcomes and resistance to therapy [5] [10] [11]. Finally, preclinical models are still limited in their ability to isolate and interrogate tumor-intrinsic checkpoint effects independently of immune components. Most existing studies rely on immune-competent or xenograft models, making it difficult to dissect the relative contributions of tumor and immune compartments. Developing refined models, including CRISPR-engineered tumor lines, organoids, and humanized systems, will be essential to untangle these interactions [14].

5. Conclusion and Future Outlook

The discovery that tumor cells can intrinsically express immune checkpoint molecules represents a paradigm shift in our understanding of cancer immune dynamics. No longer confined to immune regulation, checkpoint pathways are now recognized as active tumor-intrinsic signaling axes, shaping proliferation, survival, plasticity, and therapeutic resistance [20]. This expanded biological framework compels us to rethink how we design, interpret, and optimize immunotherapy and addressing these challenges will be central to translating tumor-intrinsic checkpoint biology into clinically actionable strategies.

Clinically, tumor-intrinsic checkpoint expression holds the potential to serve as both a therapeutic target and a predictive biomarker, guiding patient selection and improving treatment precision. However, realizing this promise will require over-

coming key challenges, including the establishment of standardized detection methods, the mechanistic dissection of context-dependent signaling, and the development of tailored therapeutic strategies that target both immune and tumor compartments. Looking forward, integrating tumor checkpoint profiling into clinical trial design, alongside immune profiling, could redefine how we approach combination immunotherapies and resistance mechanisms immune checkpoint interactions between tumor and immune cells represent a critical therapeutic axis in cancer immunotherapy (Figure 1). As the field advances, dual targeting of immune and tumor-intrinsic checkpoints could emerge as a promising strategy in next-generation cancer immunotherapy. By unmasking the tumor as an active participant in checkpoint signaling, we open new frontiers for precision oncology and reshape the therapeutic horizon for patients with advanced cancers.

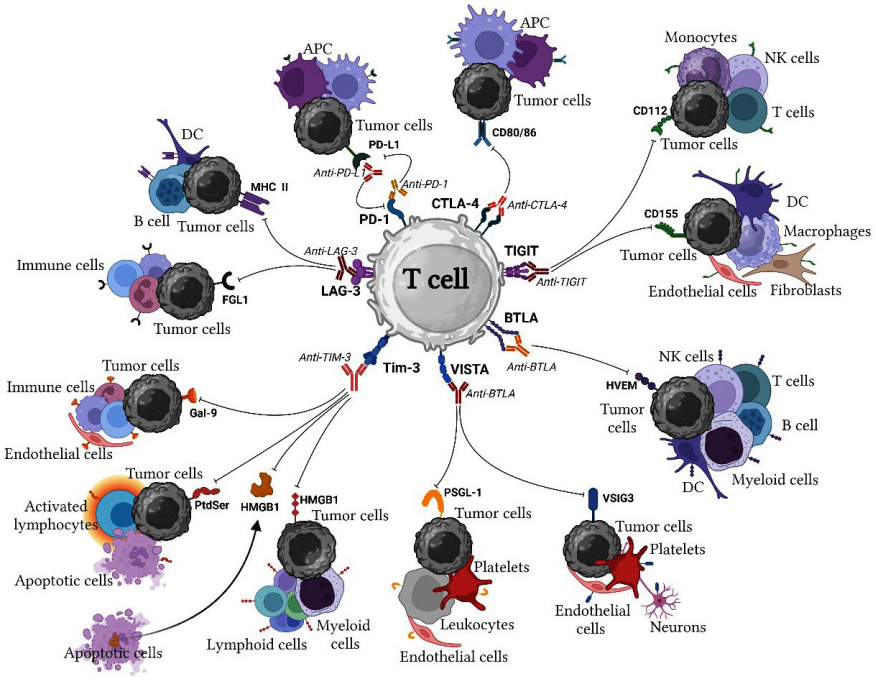

Figure 1. Immune checkpoint interactions in the tumor microenvironment and their therapeutic blockade. This schematic illustrates the major inhibitory immune checkpoint pathways engaged between tumor cells and various immune and stromal populations within the tumor microenvironment. Tumor cells can express both classical and emerging checkpoint molecules, including PD-1, CTLA-4, TIGIT, LAG-3, TIM-3, VISTA, VSIG3 and BTLA, enabling autocrine and paracrine signaling that shapes immune responses. These interactions suppress effector T-cell activation and promote immune evasion through crosstalk with antigen-presenting cells (APCs), dendritic cells (DCs), NK cells, macrophages, fibroblasts, platelets and endothelial cells. Key inhibitory axes include PD-1/PD-L1, CTLA-4/CD80-CD86, LAG-3/MHC-II-FGL1, TIM-3/Gal-9-HMGB1-PtdSer, TIGIT/CD112-CD155, BTLA/HVEM, VISTA/PSGL-1 and VSIG3-mediated signaling. Therapeutic monoclonal antibodies (shown in red) block these pathways, aiming to restore antitumor immunity. Highlighting tumor-intrinsic checkpoint expression underscores their dual role as immune regulators and direct drivers of tumor behavior, offering novel opportunities for therapeutic targeting and biomarker development. Figure created with BioRender.com.

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Authors' Contributions

VV concepted and drafted the manuscript. JAMN, PAS, KCL and RCC reviewed the manuscript and provided substantial intellectual input. VV supervised and final scientific reviewed. All authors read and approved the final version of the manuscript.

Data and Materials Availability

This manuscript is a "Perspective article" that presents the authors' interpretation and conceptual analysis of previously published studies concerning the expression of immune checkpoint molecules on tumor cells and their relevance to cancer therapy. No new experimental data, patient materials, or datasets were generated or analyzed in this work. All information discussed herein is derived from peer-reviewed publications cited in the reference list. These cited sources are publicly available through PubMed and other academic databases. The authors affirm that all statements and interpretations are based on the cited literature and that no proprietary data or unpublished results were used. As such, no additional data or materials are associated with this article.

Use of Artificial Intelligence Tools

The authors declare that AI tools, including Grammarly and ChatGPT, were used responsibly to assist with editing, summarizing source articles, and improving the clarity and flow of the text. All referenced materials were manually reviewed to ensure accuracy, reliability, and academic integrity.

Conflicts of Interest

The authors declare that they have no competing interests.

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