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REVIEW

Tumor Immunotherapy Targeting B7-H3: From Mechanisms to Clinical Applications

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Abstract: B7-H3 (CD276) is an immune checkpoint from the B7 family of molecules and is abnormally expressed in tumor cells as a co-inhibitory molecule to promote tumor progression. Within the tumor microenvironment (TME), B7-H3 promotes tumor progression by impairing the T cell response, driving the polarization of tumor-associated macrophages (TAMs) to M2 phenotype, and inhibiting the function of other immune cells. In addition, B7-H3 promotes tumor cell proliferation, migration, invasion, metabolism disorder, angiogenesis, and resistance to treatment to promote tumor progression through its non-immunological functions. Immunotherapy targeting B7-H3, as well as combinations with other immune checkpoint therapies, have shown certain efficacy. In this review, we synthesizes the expression of B7-H3 and its mechanism to promote tumor progression through inducing immunomodulation and non-immunological functions, as well as its role of B7-H3 in tumor therapy, aiming to provide a reference for the clinical treatment of tumors.

Keywords: tumor, B7-H3 (CD276), immune checkpoint, tumor immunotherapy, tumor microenvironment

Introduction

The immune system has an intrinsic ability to recognize and eliminate spontaneous malignant tumors, a phenomenon that is significantly influenced by the tumor microenvironment (TME)[1]. T cells, as central executors of the immune system, are regulated by antigen-specific signals and also receive co-regulatory signals provided by B7 and other molecules.[2] The B7 family is recognized as a group of immunomodulatory ligands. Currently known members of the B7 family include B7-1 (CD80), B7-2 (CD86), B7-DC (PD-L2), B7-H1 (PD-L1), B7-H2 (CD275), B7-H3 (CD276), B7-H4, B7-H5, B7-H6, and B7-H7 (HHLA2).[3] Some B7 family members, like B7-1, B7-2, and B7-H2, bind to CD28 to provide co-stimulation, promoting T cell activation, proliferation, and differentiation.[4] Others, like B7-H4 and PD-L1, bind to inhibitory receptors such as CTLA-4 and PD-1, delivering co-inhibitory signals to suppress excessive T cell activation and maintain immune balance.[4] Most B7 family proteins are, widely expressed on immune cells and various cancer tissues, facilitate tumor immune evasion through their co-inhibitory effects.[5]

Among the B7 family members, B7-H3 has garnered significant attention due to its role in cancer progression. B7-H3, also known as CD276, was first identified as a member of the B7 family of immune checkpoint proteins in 2001.[6] B7-H3 is a type I transmembrane protein featuring extracellular Ig-like domains, a transmembrane region, and an intracellular domain.[7] In normal physiology, B7-H3 maintains immune balance by regulating the activity of immune cells.[8] B7-H3 can also act as a T cell co-stimulatory protein in vitro and in autoimmune disease models.[9] However, numerous scholars have found that B7-H3 is closely associated with many malignant tumors, and its overexpression correlates with poorer patient prognosis, such as pancreatic cancer, cutaneous melanoma, and breast cancer, among others.[10–20] In recent years, new insights into the functions of B7-H3 and its roles in cancer development have been gained. As a result, immunotherapy targeting B7-H3 has emerged as a promising strategy.

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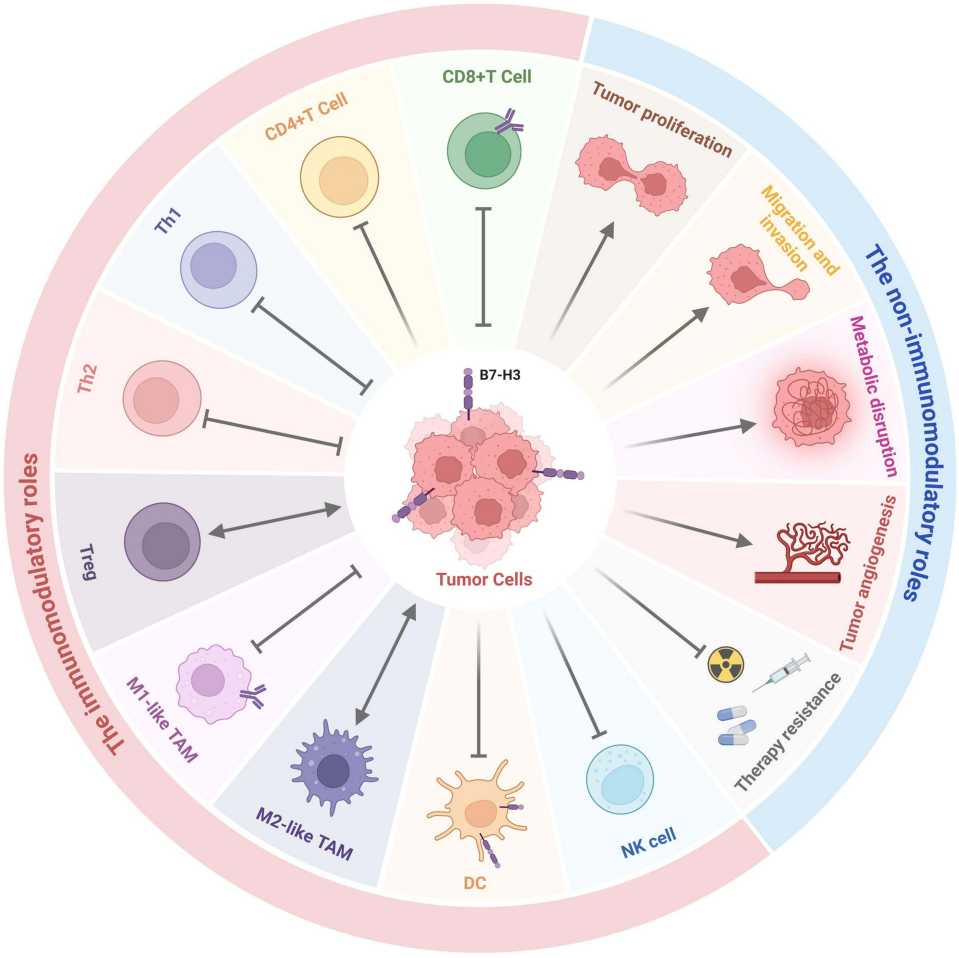
Graphical Abstract



In this review, we summarize the advances regarding the potentially key role of B7-H3 in tumor pathogenesis and progression. The findings from these studies may provide new insights and lead to breakthroughs for tumor immunotherapy.

B7-H3 Expression and Regulation in Tumors

B7-H3 mRNA is widely expressed in both lymphoid and non-lymphoid organs.[6] B7-H3 mRNA shows robust expression in many prevalent cancer types, including prostate, pancreatic, breast, colorectal, ovarian, and lung cancers.[20] However, at the protein level, B7-H3 is expressed at very low levels or is virtually non-existent in normal tissues, and is more restricted to the cell surface, for instance, on activated T cells, B cells, natural killer (NK) cells, and antigen-presenting cells (APCs).[8,21] B7-H3 is commonly overexpressed in human malignant tumors and is often associated with poor clinical outcomes in patients.[8,22–25] Notably, high levels of B7-H3 was detected in tumors with known driver mutations (eg EGFR, ESR1, KRAS, SPOP, ERG, AR, TP53, MYC, PTEN) or undruggable therapeutic targets (TP53, APC).[20,26]

Despite B7-H3 ubiquitous mRNA expression, protein levels are highly regulated, indicating strict post-transcriptional and post-translational control mechanisms (Figure 1). There exists a close and complex relationship between signaling pathways and protein transcription. Aberrant activation of mTOR pathway is one of the most common dysregulations in tumors, and it is closely related to the occurrence and progression of various cancers. ILT4 and BRD4 both upregulate

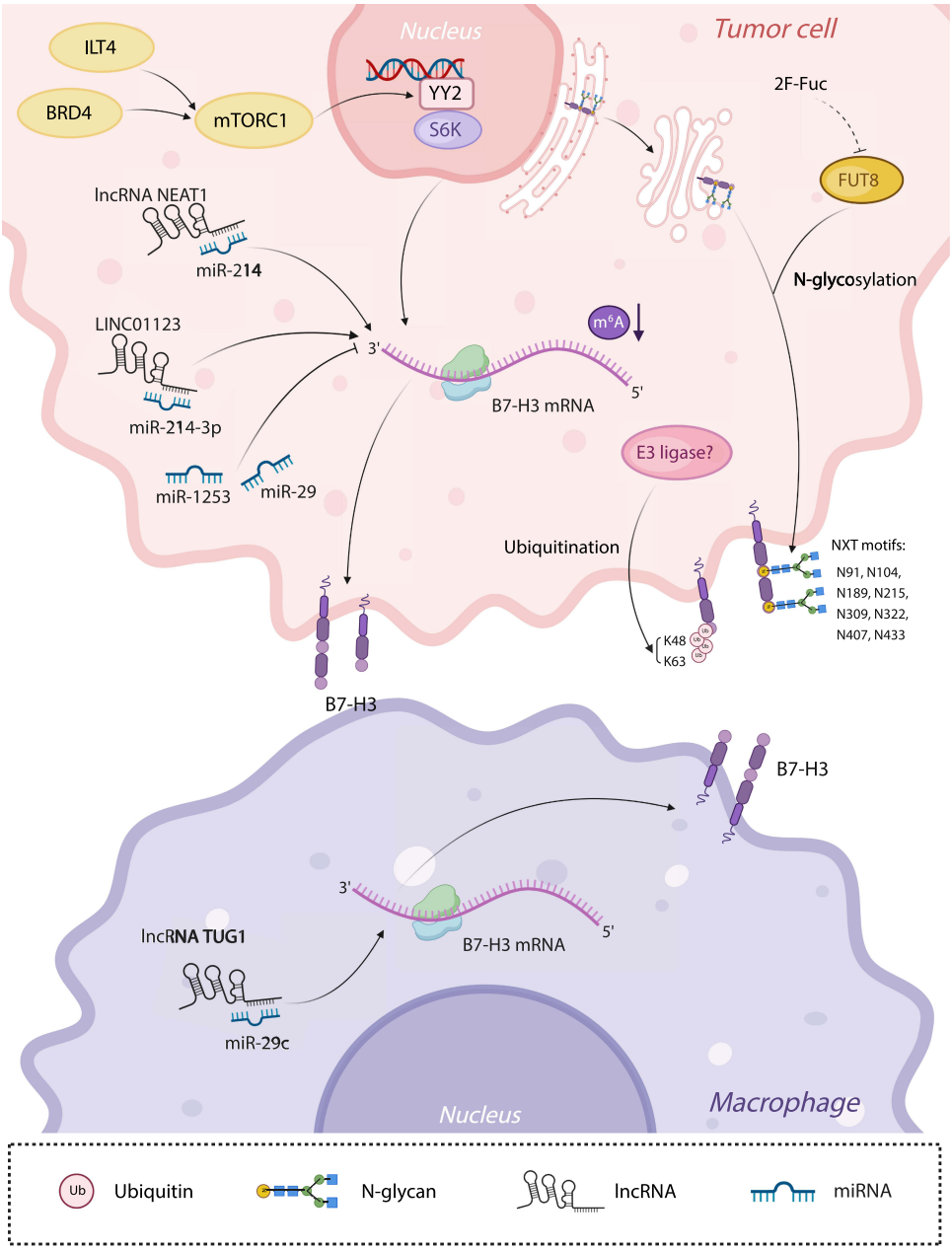


Figure 1 B7-H3 post-transcriptional and post-translational regulatory mechanisms. B7-H3 mRNA is regulated by the transcription factor YY2 and m6A modification, with various microRNAs and lncRNAs also impacting its expression. Glycosylation and ubiquitination of B7-H3 are also important for the stability of protein expression. Created in BioRender. Yining, G. (2025) https://BioRender.com/2cvopy1.

the expression of B7-H3 via the PI3K/AKT/mTOR signaling pathway.[27,28] Recent research have provided more detailed insights, that hyperactivated mTORC1 in tumors upregulates B7-H3 expression via direct phosphorylation of the transcription factor YY2 by p70 S6 kinase.[29] Non-coding RNAs also affect the transcription and expression regulation of proteins. The expression of B7-H3 protein was inversely correlated with microRNA 29 (miR-29) and miR-1253 levels in both cell lines and tumor tissues tested.[30–32] The long non-coding RNA (lncRNA) TUG1 Inhibits miR-29c, leading to upregulation of B7-H3 expression in macrophages.[33] In addition, the lncRNA NEAT1 sponged miR-214, thereby enhancing the expression of B7-H3 and promoting the polarization of M2 TAMs, which in turn accelerates the progression of multiple myeloma.[34] LINC01123 promotes immune escape by sponging miR-214-3p to regulate B7–H3 in head and neck squamous-cell carcinoma (HNSCC).[35] In addition, modifications of mRNA can affect the expression

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levels of proteins. In colorectal cancer, the downregulation of B7-H3 m6A modification affects its binding to specific RNA-binding proteins, stabilizes B7-H3 mRNA, and promotes its translation, ultimately facilitating immune evasion.[36] Together, these various post-transcriptional mechanisms reveal the different ways in which B7-H3 expression is regulated, affecting the occurrence and development of tumors. Furthermore, post-translational modifications of B7-H3 also play a crucial role. B7-H3 is a highly glycosylated protein.[37] Current evidence shows that the abnormal glycosylation of B7-H3 in tumors is of great significance for protein expression and ligand-receptor binding.[38] Aberrant glycosylation of B7-H3 stabilizes the protein itself, resulting in the accumulation of B7-H3 in tumors, which can be used as an important marker of oral cancer.[39] Aberrant B7-H3 glycosylation is highly expressed in triple negative breast cancer (TNBC), and N-glycosylation of B7-H3 at NXT motif sites is responsible for its protein stability and immunosuppression in TNBC tumors.[40] In addition, in vivo ubiquitination and TUBE assays have revealed that B7-H3 in non-small cell lung cancer (NSCLC) cells is regulated by the ubiquitin-proteasome system, with ubiquitination occurring at both K48 and K63 sites.[41] Moreover, B7-H3 protein may also be controlled by other post-translational regulatory mechanisms, which still need to be further explored, and may provide new insights for tumor immunotherapy.

The Role of B7-H3 in Tumors

The Immunomodulatory Function of B7-H3 in the TME

The TME includes a rich diversity of immune cells (such as APCs, T cells, NK cells, B cells, etc), tumor cells, the tumor stroma, and other cell types.[42] Given the current limited knowledge about the ligands of B7-H3, a comprehensive explanation of its immunomodulatory mechanisms is not yet feasible.[43] However, recent studies have indicated that the upregulation of B7-H3 in the TME is highly correlated with tumor immune evasion[44] (Figure 2).

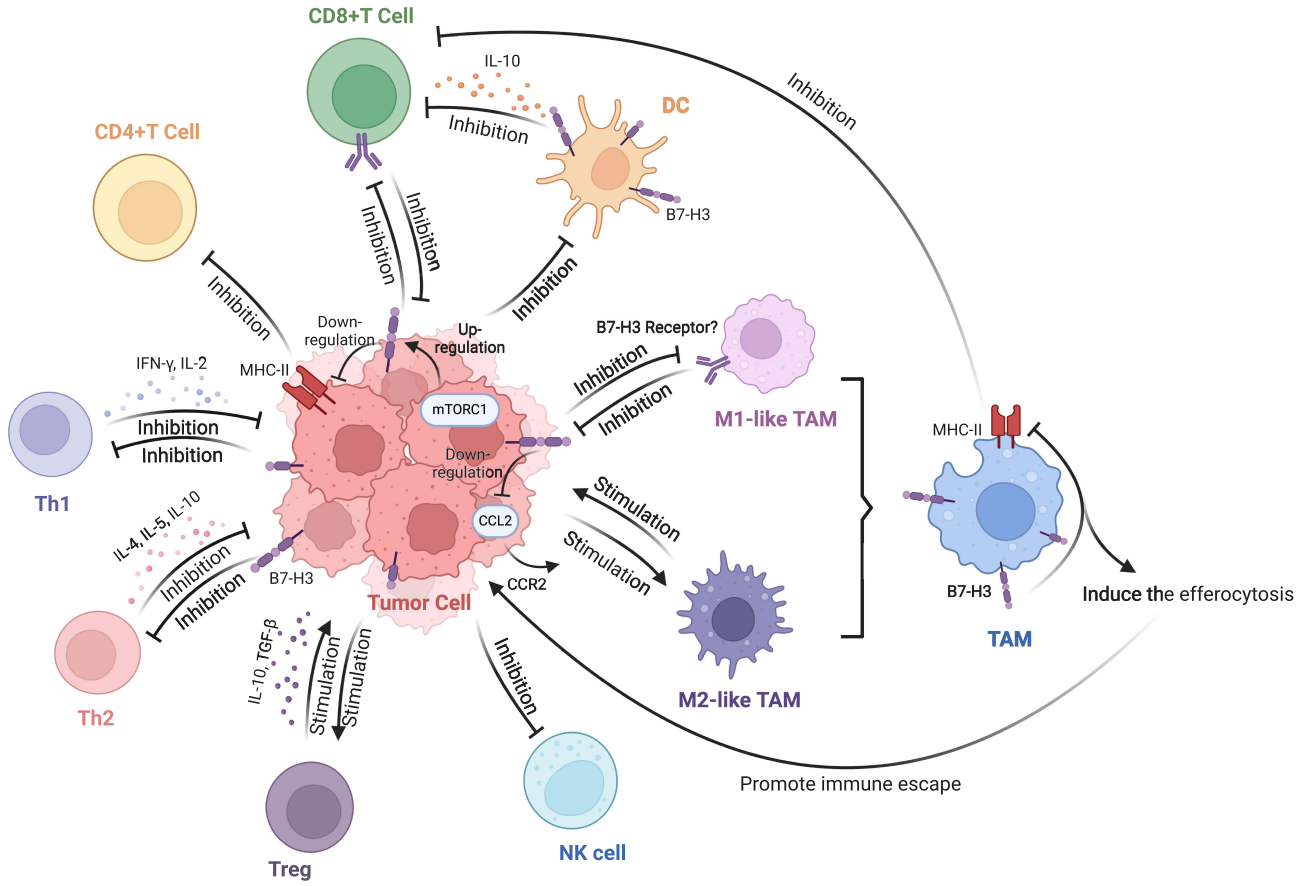

Figure 2 Immunomodulatory function B7-H3 in the TME. B7-H3 inhibits the proliferation and function of anti-tumor T cells, including CD8+ T cells, CD4+ T cells, Th1 cells, and Th2 cells. It also promotes the differentiation of T cells into tumor-promoting Tregs, thereby facilitating tumor progression. B7-H3 induces macrophages to shift from the anti-tumor M1 phenotype to the tumor-promoting M2 phenotype. Additionally, B7-H3 inhibits the activation of NK cells. TAMs and tumor-resident DCs also express B7-H3, contributing to their immunosuppressive functions. Created in BioRender. Yining, G. (2025) https://BioRender.com/0cj2xez.

B7-H3 Facilitates Multidimensional T Cells Suppression

The immune response mediated by T cells is of paramount importance in anti-tumor immunity.[45] A variety of co-stimulatory and co-inhibitory receptors are expressed to regulate and direct T cell function.[46] B7-H3 was initially characterized as a co-stimulatory molecule with antitumor capabilities. In a mouse lymphoma model, B7-H3 was shown to activate CD8+ T cells and NK cells, leading to tumor regression.[47]

However, accumulating evidence now highlights its predominant role as a co-inhibitory molecule in facilitating tumor progression. In melanoma, the requirement of NK and CD8+ T cells in B7-H3-mediated tumor immunity has been established. Inhibition of B7-H3 has been shown to potentially augment both the quantity and cytolytic function of tumor antigen-specific CD8+ T cells.[48] Similarly, intestinal epithelial B7-H3 deletion elevates tumor-infiltrating CD8+ T cells and their interferon-gamma (IFN-γ) production in colorectal cancer.[49] Furthermore, tumor-intrinsic B7-H3 suppresses CD8+ T cell proliferation and cytotoxicity within the TME, correlating inversely with CD8+ T cell infiltration and co-stimulatory molecule expression.[50,51] Recent research has indicated that B7-H3 is markedly overexpressed in the vasculature system associated with brain metastases (BrM) in both mice and humans. Therapeutic intervention using B7-H3 antibodies has led to a significant increase in CD8+ T cell infiltration in BrM, thereby demonstrating the potential of B7-H3 as a therapeutic target for BrM.[52] Therapeutically, tumor-expressed B7-H3 has been observed to inhibit the function of CD8+ T cells in ovarian cancer that is insensitive to PD-1 blockade therapy. This suggests that B7-H3 could represent a viable target for patients unresponsive to PD-L1/PD-1 inhibitory interventions.[50] Collectively, these findings suggest that B7-H3, as expressed by tumors, may suppress CD8+ T cell function. Additionally, studies have shown that tumor cells can inhibit the activity of CD4+ T cells, particularly cytotoxic CD4+ T cells (such as CD38+CD39+CD4+ T cells), by upregulating B7-H3 expression.[29] As such, B7-H3 is deemed to have considerable potential as a target for immunotherapy.

T helper (Th) cells play an important role in tumor immunity by secreting cytokines to activate and enhance the function of other immune cells. Th1 cells express IFN-γ and IL-2 as their effector cytokines to mediate cellular immunity, while Th2 cells express IL-4, IL-5, and IL-10 to mediate humoral immunity. Microarray analysis of B7-H3 peptide, B7-H3 negative and overexpressed tumor cells showed that B7-H3 inhibits the T cell proliferation, the Th1 cell response and the production of cytokines IL-2 and IFN-γ.[53] Similarly, B7-H3 on breast cancer cells binds to its receptor on T cells and inhibits the release of IFN-γ and the proliferation of Th1 cells by suppressing the activation of the PI3K/AKT/mTOR signaling pathway.[54] However, another study found that both Th1-type, IFN-γ and IL-2, and Th2-type, IL-4, cytokines were increased upon B7-H3 depletion.[55] At present, there are few studies on how B7-H3 acts on Th cells, and the mechanism remains unclear, so it is necessary to elucidate the mechanism of B7-H3 on Th cell polarization.

B7-H3 plays a critical role in immunosuppression via interactions with regulatory T cells (Tregs). Tumor cells may promote the differentiation of T cells into Tregs by increasing the expression of B7-H3.[56] There is the evidence that B7-H3 expression is positively associated with the density of tumor-infiltrating Foxp3+ Tregs, which assist tumor cells in evading immunosurveillance.[57] Likewise, in the intermediate-risk/high-risk subcohort of prostate cancer, there was a significant positive correlation between Tregs density and B7-H3 mRNA expression.[58] However, inhibiting B7-H3 alone caused compensatory immunosuppressive effects, including up-regulation of PD-L1 expression in myeloid cells and increased Treg infiltration into tumors.[55] It emphasizes the need for combinatorial strategies to overcome Treg-mediated suppression. These findings suggest that further investigation into the relationship between B7-H3 and Tregs could lay the groundwork for developing clinical treatment strategies in order to enhancing anti-tumor immunity.

In summary, B7-H3 orchestrates a complex immunosuppressive network through interactions with CD8+ T cells, CD4+ T cells, Th cells, and Tregs (Figure 2). Although existing research has given us a preliminary understanding of the potential functions of B7-H3, further up-to-date studies and in-depth exploration of its mechanisms are still needed to enhance our comprehension.

B7-H3 Modulates Tumor-Associated Macrophage (TAMs) Polarization and Function

Macrophages play a dominant role in the TME, where M1-type macrophages exhibit antitumor properties, while M2-type macrophages exert immunosuppressive effects and promote cancer cell growth.[59] In progressive tumors, M2 TAMs are a major component of the TME, and their presence within tumor tissues significantly contributes to the formation of an

immunosuppressive TME.[60] B7-H3 enhances the polarization of TAMs toward the pro-tumor M2 phenotype across multiple malignancies.[61] In HNSCC, B7-H3 is positively correlated with immature myeloid cells and the proportion of pro-M2 TAMs.[62] Studies have shown that B7-H3 induces the polarization of macrophages from the antitumor M1 phenotype to the pro-tumor M2 phenotype, leading to an increase in the proportion of pro-tumor macrophages.[63] Mechanistically, B7-H3 in tumor cells drives M2 polarization through pathways such as the CCL2-CCR2 axis in ovarian cancer,[64] while its genetic ablation reduces M2-TAM infiltration and enhances IFN-γ+ CD8+ T cell recruitment.[64] In addition, TAMs can also lead to increased expression of B7-H3 in tumors. Studies have shown that there is a subset of cells that express both macrophage and tumor signatures simultaneously in the tumor, and this group of double-positive TAMs is formed by phagocytosis of tumor cells and mediates immunosuppression through the transformation of M1 macrophages into M2 macrophages, as well as the up-regulation of the immune checkpoint protein B7-H3.[65] This suggests that high expression of B7-H3 influences the polarization of TAMs (Figure 2), but a detailed elucidation of the molecular mechanisms and signaling pathways involved still requires further investigation.

The immunomodulatory role of B7-H3 extends to TAMs functional reprogramming. Research has indicated that both human and murine tumor-associated macrophages in urothelial bladder cancer (BLCA) exhibit high B7-H3, which activates lysosomal signaling pathways and the transcription factor JUN, thereby affecting the efferocytosis of TAMs and promoting tumor immune escape.[66] Similarly, in pancreatic neuroendocrine tumors (PNEN), B7-H3-expressing TAMs suppress T cell proliferation and IFN-γ production, suggesting that B7-H3 could be a potential target for immunotherapy in PNEN.[67] These findings collectively position B7-H3 as a central regulator of TAM-mediated immunosuppression, though detailed molecular mechanisms warrant further elucidation.

B7-H3 Modulates Other Immune Cells

NK cells are able to recognize tumor cells through their surface receptors and directly kill them by releasing cytotoxins. B7-H3 inhibits the activation of both mouse and human NK cells[48] (Figure 2). In prostate cancer models, treatment with B7-H3 inhibitors restores NK cell cytolytic function and enhances tumor infiltration.[55] In like manner, the latest camelid B7-H3 tri-specific killer delivers an NK cell specific IL-15 signal to expand NK cells, facilitating the treatment of prostate cancer.[68] Dendritic cells (DCs) are pivotal antigen-presenting cells bridging innate and adaptive immunity. B7-H3 is significantly upregulated in tumor-residing DCs in NSCLC, causing DCs to have immunosuppressive effects. This results in increased levels of the inhibitory cytokine IL-10 and decreased secretion of the immunostimulating cytokine IL-12, ultimately weakening the ability of DCs to stimulate T cells.[69] This suggests that high expression of B7-H3 can significantly inhibit the immunostimulatory potential of DCs (Figure 2). However, the precise mechanisms through which B7-H3 exerts its effects on other immune cells remain to be fully elucidated.

The Non-Immunomodulatory Roles of B7-H3 in Tumors

Beyond its impact on the immune system, B7-H3 also exerts pro-tumorigenic effects through a variety of non-immunomodulatory mechanisms. It promotes tumor progression by stimulating tumor cell proliferation, disrupting metabolism, enhancing migration and invasion, facilitating angiogenesis, and conferring resistance to tumor treatments. B7-H3's immunosuppressive functions weaken anti-tumor immune responses, thereby creating favorable conditions for tumor cell proliferation and metastasis. Meanwhile, its non-immune regulatory functions enhance the biological properties of tumor cells, further shaping the TME that supports tumor progression. This dual mechanism makes B7-H3 a key driver of tumor immune evasion and progression. B7-H3's functional plasticity allows it to dynamically shift between immune regulation and tumor-intrinsic adaptation based on microenvironmental cues.

B7-H3 Drives Tumor Proliferation

Tumor cell proliferation drives tumor growth and spread, influenced by both the TME and the intrinsic properties of tumor cells. B7-H3 has been identified as a promoter of cell proliferation in various cancer types, including glioma,[70] breast cancer,[71] colorectal cancer,[72] and many others.[23] Functional studies demonstrate that silencing B7-H3 can significantly inhibit the proliferation, invasion, and migration of breast cancer, melanoma and the lung adenocarcinoma models.[71,73] Mechanistically, B7-H3 activates oncogenic signaling pathways within cancer cells, such as ERK, PI3K, and

STAT3, potentially driving accelerated proliferation and tumor growth.[74,75] Concurrently, B7-H3 leads to the suppression of apoptotic pathways, a significant reduction in cell cycle markers CDK4, CDK6, and cyclin-D1, and increased proliferation marker phosphorylated AKT, resulting in cell cycle arrest.[32] Notably, B7-H3 expression on circulating epithelial tumor cells (CETCs) is positively correlated with the expression of the proliferative marker Ki-67 in breast cancer.[13] Additionally, the stemness of tumor stem cells significantly drives their proliferation. Compared to regular cancer cells, B7-H3 is overexpressed in the stem cell population. B7-H3 enhances the interaction between B-RAF and MEK by increasing Major Vault Protein (MVP), thereby activating MEK and inducing stem cell proliferation.[76] These findings suggest that B7-H3 plays a multifaceted role in tumor progression, not only through its immunosuppressive functions but also by directly promoting tumor cell proliferation, highlighting its potential as a target for a broad range of cancer therapies (Figure 3A).

B7-H3 Promotes Tumor Cell Migration and Invasion

The migration and invasion of tumor cells are significant indicators of cancer progression, often associated with poor prognosis and high mortality rates. Clinically, B7-H3 has been confirmed to promote tumor cell migration and invasion across various cancer types, commonly linked to adverse outcomes.[72,77] Epithelial-mesenchymal transition (EMT) endows cells with the ability to invade and metastasize, representing a crucial step in tumor metastasis. In glioma cells with overexpression of B7-H3, the JAK2/STAT3 signaling pathway is activated, inducing glioma invasion and participating in EMT through the JAK2/STAT3/Slug/MMP-2/-9 pathway.[78] Similarly, in hepatocellular carcinoma, B7-H3 has been shown to promote EMT via the JAK2/STAT3/Slug signaling axis.[79] Evidence suggests that silencing B7-H3 can downregulate the expression of EMT marker proteins, such as MMP-2, vimentin, Snail, and N-cadherin, attenuating the migratory and invasive capabilities of lung adenocarcinoma cells.[73] Furthermore, B7-H3 can upregulate the expression of Sirtuins protein 3 (SIRT3) in NSCLC cell lines through the PI3K/AKT pathway, thereby enhancing the expression of E-cadherin and endowing tumor cells with stronger migratory and invasive abilities, thus facilitating EMT.[78] In clear cell renal cell carcinoma (CCRCC), B7-H3 promotes the EMT process by activating the fibronectin-mediated PI3K/AKT and p38/ERK mitogen-activated protein kinase (MAPK) signaling pathways.[80] Despite differences in the mechanisms, these studies collectively highlight the significant impact of B7-H3 on tumor invasion and metastasis, demonstrating its potential as a therapeutic target for disrupting these processes in cancer (Figure 3B). Additionally, a novel phenotype has been identified in the migration and invasion of tumor cells: the adherent-to-suspension transition (AST). This process involves the reprogramming of adherent cells into suspension cells by specific hematopoietic transcription factors, thereby endowing tumor cells with enhanced invasiveness and metastatic potential.[81] To date, research focusing on AST is quite limited, and studies exploring the relationship between B7-H3 and AST have not yet been reported. This represents a promising avenue for future investigation and may offer new perspectives for the treatment of metastatic tumors.

B7-H3 Causes Metabolic Disruption of Tumor Cells

Abnormal tumor metabolism, including aberrations in glycolysis and lipid metabolism, plays a critical role in tumor occurrence, development, and metastasis.[82] Both in vivo and in vitro studies have confirmed that overexpression of B7-H3 promote glucose intake and lactate production, driving aberrant glycolysis in tumors.[83] B7-H3 enhances the Warburg effect by upregulating the protein levels of hypoxia-inducible factor 1α (HIF-1α) and its downstream glycolytic enzymes, including lactate dehydrogenase (LDHA), phosphoglycerate kinase 1 (PGK1), and Pyruvate dehydrogenase kinase 1 (PDK1).[83,84] Mechanistically, B7-H3 promotes the reactive oxygen activity-dependent stability of HIF-1α by inhibiting the activity of stress-activated transcription factor Nrf2 and its target genes, including antioxidant enzymes such as SOD1, SOD2, and PRX3, further amplifying glycolysis and tumor progression.[83] In oral squamous carcinoma, B7-H3 activates the PI3K/AKT/mTOR to upregulate the expression of downstream HIF-1α, glucose transporter 3 (GLUT3), and phosphofructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3), allowing tumor cells to generate energy through glycolysis even in an oxygen-rich environment.[85] Additionally, hexokinase 2 (HK2) is a key mediator in the regulation of glucose metabolism. B7-H3 increases glucose consumption and lactate production by promoting HK2 expression in colorectal cancer cells, thereby enhancing cell migration, invasion, and apoptotic resistance.[86] HK2 inhibition reverses

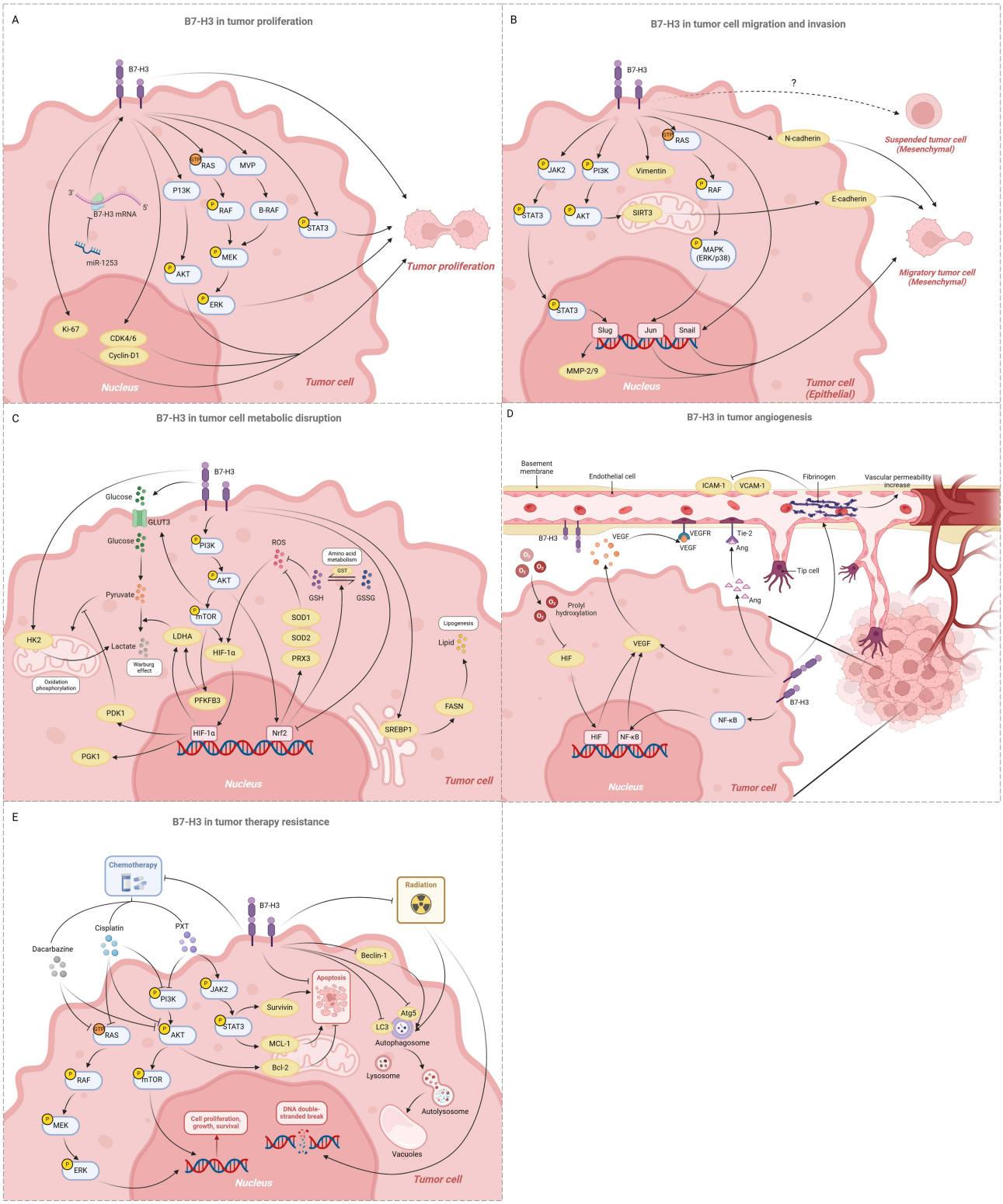

Figure 3 The non-immunomodulatory roles of B7-H3 in tumors. (**A**) B7-H3 drives tumor proliferation by activating oncogenic signaling pathways within tumor cells (eg, ERK, PI3K, and STAT3), inhibiting apoptosis pathways (eg, reducing cell cycle markers such as CDK4, CDK6, and cyclin-D1), and enhancing the stemness of tumor stem cells (B7-H3 upregulates MVP, activates MEK, and induces stem cell proliferation) Created in BioRender. Yining, G. (2025) https://BioRender.com/lps362n. (**B**) B7-H3 promotes epithelial-mesenchymal transition (EMT) by activating various signaling pathways (including JAK2/STAT3, PI3K/AKT, p38/ERK signaling pathways, and downstream EMT-related proteins), thereby facilitating tumor cell migration and invasion Created in BioRender. Yining, G. (2025) https://BioRender.com/ qqmks36. (**C**) B7-H3 causes metabolic disruption of tumor cells by driving aberrant glycolysis, lipid metabolism, and amino acid metabolismCreated in BioRender. Yining, G. (2025) https://BioRender.com/s9axlvi. (**D**) B7-H3 stimulates tumor angiogenesis by stimulating the secretion of VEGF, activating the Ang/Tie-2 pathway, and altering vascular structure at the molecular level Created in BioRender. Yining, G. (2025) https://BioRender.com/x16n3aq. (**E**) B7-H3 enhances tumor resistance to chemotherapy and radiotherapy by upregulating anti-apoptotic proteins, downregulating autophagy-related proteins, and inhibiting the repair of DNA double-strand breaks. Created in BioRender. Yining, G. (2025) https://BioRender.com/95tk9tm.

B7-H3-driven aerobic glycolysis, confirming its functional role.[87] Furthermore, B7-H3 regulates lipid metabolism in tumor cells, which is one of the key metabolic alterations in tumor progression. B7-H3 increases lipogenesis through the SREBP1/FASN signaling pathway, thereby promoting the occurrence and development of lung cancer.[88] Additionally, B7-H3 enhances the stemness of gastric cancer (GC) cells and promotes tumorigenesis and progression by activating the expression of Nrf2 through the AKT pathway, thereby modulating glutathione (GSH) metabolism in GC cells.[89] However, the relationship between B7-H3 and other amino acid metabolism disorders in tumors remains unexplored, highlighting a critical research gap. In summary, these studies consistently demonstrate that B7-H3 may favor tumor growth by manipulating tumor immunosurveillance through alterations in the metabolism of glucose, lipids, and amino acids in tumor and immune cells (Figure 3C). Further studies should explore its crosstalk with immunometabolic pathways.

B7-H3 Stimulates Tumor Angiogenesis

Angiogenesis, the process of generating new blood vessels from pre-existing ones, is one of the hallmarks of cancer and plays a complex role in the development of solid tumors.[90] Hypoxia in the TME triggers HIF activation, which drives angiogenesis through transcriptional upregulation of vascular endothelial growth factor (VEGF).[91,92] Studies have shown that B7-H3 can promote angiogenesis by stimulating the secretion of VEGF.[93] In colorectal cancer, B7-H3 upregulates VEGF expression through the activation of the NF-κB pathway, thereby promoting tumor angiogenesis; conversely, downregulation of B7-H3 significantly inhibits the in vitro tube formation of human umbilical vein endothelial cells (HUVECs).[92] Angiogenin (Ang)/Tie-2 (Tek) represents another pathway in tumor angiogenesis, and the expression levels of B7-H3 and Tie-2 are positively correlated, with immunofluorescence staining confirming the co-expression of B7-H3 and Tie-2 in the vascular endothelium of CCRCC.[94] Therefore, B7-H3 may promote the angiogenesis of CCRCC through the Tie-2 pathway, offering a potential therapeutic strategy for targeting angiogenesis in the context of cancer. Among various primary BrM, the expression of B7-H3 on tumor vasculature is significantly increased.[52] Blocking B7-H3 leads to a reduction in extravascular fibrinogen, thereby reducing the permeability of the blood-brain barrier, as well as an increase in cellular adhesion molecules ICAM-1 and VCAM-1, which alters the structure of the blood vessels at the molecular level, ultimately suppressing BrM growth.[52] Targeting of B7-H3 could inhibit neoangiogenesis and tumor growth[95] (Figure 3D). Furthermore, considering the complexity of angiogenesis, future research should take into account the interactions between B7-H3 and other angiogenic factors to gain a more comprehensive perspective.

B7-H3 Contributes to Tumor Therapy Resistance

Increased expression of B7-H3 in tumors is associated with the development of therapeutic resistance.[71] B7-H3 knockdown sensitizes melanoma cells to MAPK and AKT/mTOR pathways-targeted agents (dacarbazine, cisplatin), reversing chemoresistance.[96,97] Paclitaxel (PXT) is a commonly used chemotherapeutic drug in clinical practice. However, studies have found that in breast cancer, B7-H3 overexpression drives PXT resistance via Jak2/Stat3 signaling pathway activation, upregulating anti-apoptotic proteins.[98] Targeting B7-H3 can enhance the sensitivity of breast cancer to paclitaxel, a finding of significant importance for developing treatment strategies for paclitaxel-refractory cancers. Similarly, B7-H3 activates the PI3K/AKT signaling pathway and upregulates the protein levels of B-cell lymphoma 2 (BCL-2) in ovarian cancer cell lines, resulting in chemoresistance and sustained tumor growth.[99] Radiotherapy, which damages the DNA structure of cancer cells leading to apoptosis, is another standard treatment modality. B7-H3 downregulates the expression of autophagy-related proteins such as light chain 3 (LC3), autophagy-related protein 5 (Atg5), and Beclin-1, thereby enhancing the resistance of cancer cells to radiotherapy through the suppression of cellular autophagy.[100] Moreover, B7-H3 can also increase the resistance of gastric cancer cells to radiotherapy by inhibiting cellular apoptosis and DNA double-strand break repair.[100] However, no studies have yet elucidated the specific mechanisms by which B7-H3 affects these autophagy-related proteins. Targeted approaches, such as CRISPR screening or co-immunoprecipitation assays, are urgently needed to verify these potential interactions. Overall, these findings suggest that B7-H3 decreases the sensitivity of tumor cells to a range of chemotherapeutic drugs and radiotherapy, making it a novel target for enhancing the effectiveness of traditional cancer treatments (Figure 3E). To fully understand

the impact of B7-H3 and optimize its application in cancer treatment, it is necessary to further elucidate its mechanisms of action and expand research on the role of B7-H3 in different treatment modalities.

Current Status of Immunotherapy Strategies Targeting B7-H3

B7-H3's multifaceted role in tumor biology has propelled it as a prime therapeutic target. Current immunotherapeutic agents targeting B7-H3 encompass monoclonal antibodies (mAbs), bispecific antibodies (BsAbs), antibody-drug conjugates (ADCs), chimeric antigen receptor T cells (CAR-T), and other modalities. A number of anti-B7-H3 approaches have been studied in preclinical or clinical trials, with details of the clinical trials presented in Table 1.

Enoblituzumab (MGA271), a humanized mAb with engineered Fc domains to enhance its antitumor function by increasing binding to the activating receptor, CD16A, and reducing that to the inhibitory receptor, CD32B, was the first mAb tested against B7-H3-expressing tumors.[101] It is used to treat B7-H3-expressing refractory tumors, such as melanoma (NCT01391143), and other B7-H3-expressing tumors, including osteosarcoma and Ewing's sarcoma (NCT02982941).[102] In localized prostate cancer (NCT02923180), treatment with enoblituzumab was found to be relatively safe, exhibiting no off-target antibodies or antigen spread. Importantly, after treatment with enoblituzumab, significant activation of the immune system was observed in the TME, involving both T cells and myeloid cells.[103] Another study evaluated the preclinical in vitro efficacy of vobramitamab duocarmazine, an investigational ADC featuring a humanized B7-H3 mAb, demonstrating good in vitro activity in the treatment of acute myeloid leukemia.[19] A study on the Fc optimization (SDIE modification) of the mAb of B7-H3 for acute myeloid leukemia has shown it can significantly induce NK cell activation and effectively inhibit leukemia growth in vivo, without causing off-target immune activation.[104] Unfortunately, patient heterogeneity limits universal efficacy. A recent study found that ITGB6 is a key gene mediating differential response to anti-B7-H3 treatment and can be used as a predictive biomarker of anti-B7-H3 immunotherapy response.[105] The role of B7-H3 monoclonal antibodies in targeting advanced metastatic or recurrent diseases remains to be explored.

BsAbs, also known as bispecific T cell engagers (BiTEs), are artificially synthesized proteins that can recognize two different antigens, and simultaneously bind to antigens on tumour cells and the CD3 subunits on T cells.[106] Obrindatamab (MGD009) is generated by linking the anti-CD3 mAb scFv to the anti-B7-H3 mAb single-chain variable fragment (scFv), enabling dual binding to CD3 and B7-H3 and redirecting T cells to kill B7-H3-expressing tumor cells.[107] In preclinical models, obrindatamab enhances T cell cytotoxicity by promoting tumor-dependent secretion of IFN-γ, TNF-α, and IL-2; in immunodeficient mice, tumor growth is significantly reduced, and survival rates are increased.[108] These promising results have led to a Phase I open-label dose-escalation study for refractory B7-H3-expressing tumors (NCT03406949).[102] Studies have fabricated MMP-2-sensitive anti-B7-H3×CD3 bispecific antibody (biAb)/dEGCG-based nanoparticles to improve glioblastoma therapy by enhancing the ferroptotic effect and reversing immune inhibition.[109] Additionally, numerous clinical trials are currently evaluating the therapeutic efficacy of B7-H3 inhibitors in combination with other checkpoint inhibitors.[110,111]

ADCs combine the specificity of monoclonal antibodies with the potency of highly cytotoxic agents, selectively and stably delivering potent anticancer agents to tumor cells.[112,113] Duocarmazine (MGC018) is a duocarmycin-based ADC targeting B7-H3.[114] MGC018 specifically binds to B7-H3, delivering the potent DNA alkylating agent duocarmycin to tumor cells, inducing DNA damage and cell death, thereby providing a more potent antitumor effect than traditional mAbs.[114] Importantly, the "bystander effect"—whereby released payloads diffuse to neighboring B7-H3-negative cells—may enhance efficacy in heterogeneous tumors.[114] A Phase I dose expansion study is currently underway for NSCLC, triple-negative breast cancer (TNBC), and metastatic castration-resistant prostate cancer (mCRPC), as indicated by the clinical trial registration NCT03729596.[114] MGC018 has shown preliminary clinical activity in B7-H3-expressing preclinical models of neuroblastoma.[115] Moreover, the clinical trials of Ifinatamab deruxtecan (I-DXd, DS-7300a) have also had a broad impact. This ADC targets B7-H3 and is Non-coding RNAs also affect composed of a humanized anti-B7-H3 monoclonal antibody linked to a topoisomerase I inhibitor payload (DXd). The ADC has demonstrated significant antitumor activity and good safety in clinical trials[116] and has been granted orphan drug designation by the US FDA and the European Commission for the treatment of SCLC. The ongoing Phase III IDeate-Lung02 trial will further validate its potential in first-line treatment.

Table 1 Trials of Immunotherapeutic Agents Targeting B7-H3

Drug Type	Trail Number	Study Title	Intervention/Treatment	Trail Phage	Tumor Type	Actual Enrollment/ Estimated Enrollment	Status
Monoclonal Antibodies (mAbs)	NCT01391143	Safety Study of MGA271 in Refractory Cancer	Enoblituzumab (MGA271)	Phase I	Prostate Cancer Melanoma Renal Cell Carcinoma Triple-negative Breast Cancer Head and Neck Cancer Bladder Cancer Non-small Cell Lung Cancer	179	Completed
	NCT01918930	Tissue Procurement Substudy for Participants in Study CP-MGA271-01	Enoblituzumab (MGA271)	Phase I	Melanoma	6	Terminated
	NCT02982941	Enoblituzumab (MGA271) in Children With B7-H3-expressing Solid Tumors	Enoblituzumab (MGA271)	Phase I	Neuroblastoma Rhabdomyosarcoma Osteosarcoma Ewing Sarcoma Wilms Tumor Desmoplastic Small Round Cell Tumor	25	Completed
	NCT02923180	Neoadjuvant Enoblituzumab (MGA271) in Men With Localized Intermediate and High-Risk Prostate Cancer	Enoblituzumab (MGA271)	Phase II	Prostate Cancer	32	Active, not recruiting
	NCT06014255	Trial of Neoadjuvant Enoblituzumab vs SOC in Men With High-Risk Localized Prostate Cancer (HEAT)	Enoblituzumab (MGA271) +Standard of Care	Phase II	Prostate Cancer	219	Recruiting
	NCT02475213	Safety Study of Enoblituzumab (MGA271) in Combination With Pembrolizumab or MGA012 in Refractory Cancer	Enoblituzumab (MGA271) +Pembrolizumab/MGA012	Phase I	Melanoma Head and Neck Cancer Non Small Cell Lung Cancer Urethelial Carcinoma	145	Completed

(*Continued*)

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Table 1 (Continued).

Drug Type	Trail Number	Study Title	Intervention/Treatment	Trail Phage	Tumor Type	Actual Enrollment/ Estimated Enrollment	Status
	NCT04129320	Enoblituzumab Plus MGA012 or MGD013 in Squamous Cell Carcinoma of the Head and Neck	Enoblituzumab (MGA271) +MGA012/MGD013	Phase II,III	Head and Neck Cancer Squamous Cell Carcinoma of Head and Neck	0	Withdrawn
	NCT04630769	FT516 and IL2 With Enoblituzumab for Ovarian Cancer	IP FT516+Enoblituzumab (MGA271) +IL-2	Phase I	Ovarian Cancer Fallopian Tube Adenocarcinoma Primary Peritoneal Cavity Cancer	3	Completed
	NCT05708924	MT2021-27 FT538 Recurrent Ovarian, Fallopian Tube, and Primary Peritoneal Cancer	FT538+Enoblituzumab (MGA271)	Phase I	Cancer Solid Tumor Ovarian Cancer Peritoneal Cancer Fallopian Tube Cancer	33	Suspended
	NCT04634825	Enoblituzumab Plus Retifanlimab or Tebotelimab in Head and Neck Cancer	Enoblituzumab (MGA271) +Retifanlimab/Tebotelimab	Phase II	Head and Neck Cancer Head and Neck Neoplasms Head and Neck Squamous Cell Carcinoma	62	Terminated
	NCT02381314	Safety Study of Enoblituzumab (MGA271) in Combination With Ipilimumab in Refractory Cancer	Enoblituzumab (MGA271) +Ipilimumab	Phase I	Melanoma Non Small Cell Lung Cancer	24	Completed

Bispecific Antibodies (BsAbs)	NCT02628535	Safety Study of MGD009 in B7-H3-expressing Tumors	Obrindatamab (MGD009)	Phase I	Mesothelioma Bladder Cancer Melanoma Squamous Cell Carcinoma of the Head and Neck Non Small Cell Lung Cancer Clear Cell Renal Cell Carcinoma Ovarian Cancer Thyroid Cancer Breast Cancer Pancreatic Cancer Prostate Cancer Colon Cancer Soft Tissue Sarcoma	67	Terminated
	NCT03406949	MGD009/MGA012 Combination in Relapsed/Refractory Cancer	Obrindatamab (MGD009) +Retifanlimab	Phase I	Advanced Solid Tumors	25	Completed
Antibody-drug Conjugates (ADCs)	NCT06227546	MGC018 in Patients With Relapsed or Refractory Extensive-Stage Small-Cell Lung Cancer (MGC018-SCLC)	Duocarmazine (MGC018)	Phase II	Extensive-stage Small-cell Lung Cancer	17	Recruiting

(*Continued*)

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Table 1 (Continued).

Drug Type	Trail Number	Study Title	Intervention/Treatment	Trail Phage	Tumor Type	Actual Enrollment/ Estimated Enrollment	Status
	NCT03729596	MGC018 With or Without MGA012 in Advanced Solid Tumors	Duocarmazine (MGC018) +Vobramitamab	Phase I,II	Squamous Cell Carcinoma of Head and Neck Triple Negative Breast Cancer Melanoma Advanced Solid Tumor, Adult Metastatic Castrate Resistant Prostate Cancer Non Small Cell Lung Cancer	143	Terminated
	NCT05293496	A Study of MGC018 in Combination With MGD019 in Participants With Advanced Solid Tumors	Vobramitamab+Duocarmazine (MGC018) +Lorigerlimab	Phase I	Advanced Solid Tumor Castration-Resistant Prostatic Cancer Malignant Melanoma Pancreatic Ductal Carcinoma Hepatocellular Cancer Epithelial Ovarian Cancer Renal Cell Carcinoma	278	Recruiting

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	NCT05551117	A Study of Vobramitamab Duocarmazine in Participants With Metastatic Castration Resistant Prostate Cancer and Other Solid Tumors (Tamarack)	Duocarmazine (MGC018) +Vobramitamab	Phase II	Castration-Resistant Prostatic Cancer Androgen-Independent Prostatic Cancer Androgen-Insensitive Prostatic Cancer Androgen-Resistant Prostatic Cancer Hormone Refractory Prostatic Cancer Anal Cancer Anal Neoplasm Carcinoma, Squamous Cell of Head and Neck Head and Neck Squamous Cell Carcinoma Laryngeal Squamous Cell Carcinoma Oral Squamous Cell Carcinoma Malignant Melanoma Melanoma Non-small Cell Lung Cancer Non-small Cell Carcinoma Small-cell Lung Cancer Small Cell Carcinoma	382	Active, not recruiting
	NCT05280470	Ifinatamab Deruxtecan (I-DXd) in Subjects With Pretreated Extensive-Stage Small Cell Lung Cancer (ES-SCLC) (IDeate-Lung01)	Ifinatamab Deruxtecan (I-DXd)	Phase II	Extensive-stage Small-cell Lung Cancer	180	Recruiting

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Table 1 (Continued).

Drug Type	Trail Number	Study Title	Intervention/Treatment	Trail Phage	Tumor Type	Actual Enrollment/ Estimated Enrollment	Status
	NCT06330064	A Study To Evaluate The Efficacy And Safety Of Ifinatamab Deruxtecan (I-DXD) In Subjects With Recurrent Or Metastatic Solid Tumors	Ifinatamab Deruxtecan (I-DXd)	Phase II	Recurrent or Metastatic Solid Tumors	260	Recruiting
	NCT06203210	A Study of Ifinatamab Deruxtecan Versus Treatment of Physician's Choice in Subjects With Relapsed Small Cell Lung Cancer (IDeate-Lung02)	Ifinatamab deruxtecan (I-DXd) / Topotecan /Amrubicin/Lurbinectedin	Phase III	Small Cell Lung Cancer	468	Not yet recruiting
	NCT04145622	Study of Ifinatamab Deruxtecan (I-DXd) in Participants With Advanced Solid Malignant Tumors	Ifinatamab Deruxtecan (I-DXd)	Phase I,II	Advanced Solid Tumor Malignant Solid Tumor	250	Recruiting
	NCT06362252	A Study of I-DXd in Combination With Atezolizumab With or Without Carboplatin as First-Line Induction or Maintenance in Subjects With Extensive Stage-Small Cell Lung Cancer (IDeate-Lung03)	Ifinatamab Deruxtecan (I-DXd) +Atezolizumab±Carboplatin ±Etoposide	Phase I,II	Extensive Stage-small Cell Lung Cancer	149	Not yet recruiting

Chimeric Antigen Receptor T Cells (CAR-T)	NCT04185038	Study of B7-H3-Specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/ Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors	SCRI-CARB7H3 (s); B7H3-CAR T cell	Phase I	Central Nervous System Tumor Diffuse Intrinsic Pontine Glioma Diffuse Midline Glioma Ependymoma Medulloblastoma, Childhood Germ Cell Tumor Atypical Teratoid/ Rhabdoid Tumor Primitive Neuroectodermal Tumor Choroid Plexus Carcinoma Pineoblastoma, Childhood Glioma	90	Recruiting
	NCT05835687	Loc3CAR: Locoregional Delivery of B7-H3-CAR T Cells for Pediatric Patients With Primary CNS Tumors	B7-H3-CAR T cells	Phase I	Central Nervous System Neoplasms Atypical Teratoid/ Rhabdoid Tumor Diffuse Midline Glioma, H3 K27M-Mutant Ependymoma High Grade Glioma Glioblastoma Medulloblastoma	36	Recruiting
	NCT04385173	Pilot Study of B7-H3 CAR-T in Treating Patients With Recurrent and Refractory Glioblastoma	B7-H3 CAR-T+Temozolomide	Phase I	Recurrent Glioblastoma Refractory Glioblastoma	12	Recruiting

(*Continued*)

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Table 1 (Continued).

Drug Type	Trail Number	Study Title	Intervention/Treatment	Trail Phage	Tumor Type	Actual Enrollment/ Estimated Enrollment	Status
	NCT05211557	Study of Fully Human B7H3 CAR-T in Treating Recurrent Malignant Ovarian Cancer	fhB7-H3 CAR-T	Phase I,II	Ovarian Cancer	15	Recruiting
	NCT05341492	EGFR/B7H3 CAR-T on Lung Cancer and Triple Negative Breast Cancer	EGFR/B7H3 CAR-T	Early Phase I	EGFR/ B7H3-positive Advanced Lung Cancer EGFR/ B7H3-positive Advanced Triple-negative Breast Cancer	30	Recruiting
	NCT04077866	B7-H3 CAR-T for Recurrent or Refractory Glioblastoma	Temozolomide+B7-H3 CAR-T	Phase I,II	Recurrent Glioblastoma Refractory Glioblastoma	40	Recruiting

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	NCT04897321	B7-H3-Specific Chimeric Antigen Receptor Autologous T-Cell Therapy for Pediatric Patients With Solid Tumors (3CAR)	Fludarabine+Cyclophosphamide +MESNA+B7-H3 CAR T cells	Phase I	Pediatric Solid Tumor Osteosarcoma Rhabdomyosarcoma Neuroblastoma Ewing Sarcoma Wilms Tumor Adrenocortical Cancer Desmoplastic Small Round Cell Tumor Germ Cell Cancer Rhabdoid Tumor Clear Cell Sarcoma Hepatoblastoma Melanoma Carcinoma Malignant Peripheral Nerve Sheath Tumors Soft Tissue Sarcoma	32	Recruiting

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Table 1 (Continued).

Drug Type	Trail Number	Study Title	Intervention/Treatment	Trail Phage	Tumor Type	Actual Enrollment/ Estimated Enrollment	Status
	NCT04483778	B7H3 CAR T Cell Immunotherapy for Recurrent/ Refractory Solid Tumors in Children and Young Adults	Second generation 4–1BBζ B7H3-EGFRt-DHFR (selected) +A second generation 4–1BBζ CD19-Her2tG+Pembrolizumab	Phase I	Pediatric Solid Tumor Germ Cell Tumor Retinoblastoma Hepatoblastoma Wilms Tumor Rhabdoid Tumor Carcinoma Osteosarcoma Ewing Sarcoma Rhabdomyosarcoma Synovial Sarcoma Clear Cell Sarcoma Malignant Peripheral Nerve Sheath Tumors Desmoplastic Small Round Cell Tumor Soft Tissue Sarcoma Neuroblastoma Melanoma	68	Active, not recruiting
	NCT05323201	Study Of B7H3 CAR-T Cells in Treating Advanced Liver Cancer	fhB7H3 CAR-Ts+Fludarabine +Cyclophosphamide	Phase I,II	Hepatocellular Carcinoma	15	Recruiting
	NCT06018363	Clinical Study on the Treatment of Malignant Brain Glioma by QH104 Cell Injection	Allogenic B7H3 CAR-γδT cell	Phase I,II	Clinical Study on the Treatment of Malignant Brain Glioma by QH104 Cell Injection	25	Recruiting
	NCT05241392	Safety and Efficacy Study of Anti-B7-H3 CAR-T Cell Therapy for Recurrent Glioblastoma	B7-H3-targeting CAR-T cells	Phase I	Glioblastoma	30	Recruiting
	NCT05474378	B7-H3 Chimeric Antigen Receptor T Cells (B7-H3CART) in Recurrent Glioblastoma Multiforme	B7-H3 CAR-T	Phase I	Brain and Nervous System	39	Recruiting

	NCT04185038	Study of B7-H3-Specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/ Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors	SCRI-CARB7H3 (s); B7H3-specific chimeric antigen receptor (CAR) T cell	Phase I	Central Nervous System Tumor Diffuse Intrinsic Pontine Glioma Diffuse Midline Glioma Ependymoma Medulloblastoma, Childhood Germ Cell Tumor Atypical Teratoid/ Rhabdoid Tumor Primitive Neuroectodermal Tumor Choroid Plexus Carcinoma Pineoblastoma, Childhood Glioma	90	Recruiting
	NCT06158139	Autologous CAR-T Cells Targeting B7-H3 in PDAC	iC9-CAR.B7-H3 T cell infusion	Phase I	Pancreas Cancer Relapse Resistant Cancer	27	Not yet recruiting
	NCT05562024	TAA06 Injection in the Treatment of Patients With B7-H3-positive Relapsed/ Refractory Neuroblastoma	T cell injection targeting B7-H3 chimeric antigen receptor	Phase I	B7-H3-positive Relapsed/ Refractory Neuroblastoma	24	Recruiting
	NCT06221553	Safety and Efficacy of Loco-regional B7H3 IL-7Ra CAR T Cell in DIPG (CMD03DIPG)	B7H3 specific CAR T cell with IL-7Ra signaling domain	Phase I	DIPG Brain Tumor Diffuse Intrinsic Pontine Glioma	9	Recruiting
	NCT06305299	Autologous CAR-T Cells Targeting B7H3 in Ovarian Cancer iC9-CAR.B7-H3 T Cells	iC9-CAR.B7-H3 T cells +Cyclophosphamide+Fludarabine	Phase I	Ovary Neoplasm Ovarian Cancer Epithelial Ovarian Cancer Recurrent	27	Not yet recruiting

(*Continued*)

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Table 1 (Continued).

Drug Type	Trail Number	Study Title	Intervention/Treatment	Trail Phage	Tumor Type	Actual Enrollment/ Estimated Enrollment	Status
	NCT05366179	Autologous CAR-T Cells Targeting B7-H3 in Recurrent or Refractory GBM CAR.B7-H3Tc	CAR.B7-H3T cells infusion	Phase I	Glioblastoma Multiforme	36	Recruiting
	NCT03198052	GPC3/Mesothelin/Claudin18.2/GUCY2C/B7-H3/PSCA/PSMA/MUC1/TGFβ/HER2/Lewis-Y/AXL/EGFR-CAR-T Cells Against Cancers	CAR-T cells targeting GPC3, Mesothelin, Claudin18.2, GUCY2C, B7-H3, PSCA, PSMA, MUC1, TGFβ, HER2, Lewis-Y, AXL, or EGFR	Phase I	Lung Cancer	30	Recruiting
	NCT04670068	Phase I Study of Autologous CAR T-Cells Targeting the B7-H3 Antigen in Recurrent Epithelial Ovarian	CAR.B7-H3+Fludarabine +Cyclophosphamide	Phase I	Epithelial Ovarian Cancer	21	Recruiting
	NCT06347068	Study of Autologous CAR-T Cells Targeting B7-H3 in TNBC iC9-CAR.B7-H3 T Cells	iC9-CAR.B7-H3 T Cell Therapy +Cyclophosphamide+Fludarabine	Phase I	Breast Cancer Relapse Resistant Cancer Triple Negative Breast Cancer	42	Not yet recruiting
	NCT05768880	Study of B7-H3, EGFR806, HER2, And IL13-Zetakine (Quad) CAR T Cell Locoregional Immunotherapy For Pediatric Diffuse Intrinsic Pontine Glioma, Diffuse Midline Glioma, And Recurrent Or Refractory Central Nervous System Tumors	SC-CAR4BRAIN	Phase I	Diffuse Intrinsic Pontine Glioma Diffuse Midline Glioma Recurrent CNS Tumor, Adult Recurrent, CNS Tumor, Childhood Refractory Primary Malignant Central Nervous System Neoplasm	72	Recruiting
	NCT05731219	UTAA06 Injection in the Treatment of Relapsed/ Refractory Acute Myeloid Leukemia	B7-H3 target, CAR gene modified gdT cell injection	Phase I	Relapsed/Refractory Acute Myeloid Leukemia	18	Recruiting

	NCT05515185	B7-H3 Targeting CAR-T Cells Therapy for B7-H3 Positive Solid Tumors	KT095 CAR-T injection	Early Phase 1	Advanced Solid Tumor	30	Not yet recruiting
	NCT04842812	Engineered TILs/CAR-TILs to Treat Advanced Solid Tumors	TILs and CAR-TILs targeting HER2, Mesothelin, PSCA, MUC1, Lewis-Y, GPC3, AXL, EGFR, Claudin18.2/6, ROR1, GD1, or B7-H3	Phase I	Liver Cancer Lung Cancer Breast Cancer Colo-rectal Cancer Brain Tumor Solid Tumor, Adult	40	Recruiting
	NCT05143151	CD276-targeted Chimeric Antigen Receptor T Cells in Treatment With Advanced Pancreatic Cancer (CAR-T)	CD276 CAR-T cells	Phase I,II	Advanced Pancreatic Carcinoma	10	Recruiting
	NCT05722171	Clinical Study of UTAA06 Injection in the Treatment of Relapsed/Refractory Acute Myeloid Leukemia	gdT cell injection targeting B7-H3 chimeric antigen receptor	Early Phase 1	Relapsed/Refractory Acute Myeloid Leukemia	10	Recruiting
	NCT04432649	Targeting CD276 (B7-H3) Positive Solid Tumors by 4SCAR-276	4SCAR-276	Phase I,II	Solid Tumor	100	Recruiting

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Traditional therapies often lack specificity for tumor cells, potentially causing severe side effects. In contrast, B7-H3-targeted CAR-T cells can specifically recognize and kill tumor cells expressing B7-H3, reducing damage to normal cells.[117] B7-H3-targeted CAR-T therapy has demonstrated significant potential in a series of preclinical model studies across various cancer types,[118–121] and clinical trials have confirmed its effectiveness. A Phase I clinical study of B7-H3 CAR-T therapy for diffuse intrinsic pontine glioma (NCT04185038) showed sustained improvement in clinical and radiographic symptoms in some patients, with repeated intracranial injections of CAR-T cells inducing local immune activation.[122] In vitro co-culture models and mouse xenograft models of acute myeloid leukemia have shown that B7-H3 CAR-T therapy is effective, exhibiting antigen-dependent toxicity with acceptable side effects.[123] Recently, iCas9.B7-H3 CAR-T have effectively killed uveal melanoma cells in vitro and eradicated liver metastasis of uveal melanoma in mouse model, outperforming B7-H3 mAbs.[124] This method embeds a caspase-9 (iCas9) suicide gene, regulated by the chemical inducer AP1903, into B7-H3 CAR-T cells.[124] This allows for rapid and conditional elimination of iC9.B7-H3 CAR-T cells via AP1903 administration in case of adverse effects, functioning as a "safety on/off switch". The findings support a Phase I clinical trial of iCas9.B7-H3 CAR-T cells to treat patients with metastatic uveal melanoma. However, CAR-T monotherapy may not achieve high cure rates for patients with solid tumors that are difficult to treat. This is possibly due to insufficient target antigen expression on the tumor surface, which impairs CAR-T cell recognition and attack, and the complex TME, where inhibitory cells and factors suppress CAR-T cell function and reduce their efficacy in solid tumors. Consequently, some scholars have used a novel high-content and high-throughput screening method to identify that ingenol-3-angelate enhances the activity of B7-H3 CAR-T cells by activating PKCα to upregulate B7-H3 on the target cell surface.[125] In addition, an increasing number of studies have focused on modifying B7-H3 CAR-T cells to improve their therapeutic efficacy, fostering the development of novel combination strategies for CAR-T immunotherapy.[126–131] Collectively, these studies demonstrate that B7-H3 CAR-T represents a promising therapeutic strategy for targeting human tumors.

In recent years, the number of trials evaluating B7-H3 targeted therapy has increased significantly with the accumulation of experimental evidence. These studies not only enhance our understanding of B7-H3's role in tumorigenesis but also provide insights into the potential therapeutic benefits of targeting this molecule, offering new alternatives and clinical benefits for tumor patients. However, the majority of B7-H3 targeted clinical trials are currently in Phase I/II, and the efficacy data that have been published are limited. Early results have primarily focused on safety and maximum tolerated dose, while biomarker-driven mechanistic data, such as the dynamics of immune cell changes, are rarely reported. Therefore, the unique expression patterns of B7-H3 in tumors make it a potential breakthrough target. Future research needs to conduct more in-depth mechanistic analyses. Targeting B7-H3 represents a new and feasible option for tumor treatment in the future.

Conclusions and Outlook

B7-H3, an emerging immune checkpoint molecule in the B7 family, plays a multifaceted role in cancer, encompassing a range of immunological and non-immunological functions. B7-H3 has a dual role in regulating adaptive and innate immune cells, underscoring its potential as a therapeutic target (Figure 2). At the same time, it is also involved in several biological processes central to tumor pathogenesis, including proliferation, migration, invasion, angiogenesis, and metabolism (Figure 3). Spanning from immunomodulatory to non-immunomodulatory functions, the pleiotropic characteristics of B7-H3 suggest extensive application potential in the therapeutic strategies against cancer. The expression of B7-H3 is typically associated with a poor prognosis and can be used alone or in combination with other molecules as a prognostic marker. Furthermore, the differential expression of B7-H3 across various tumor cell types suggests its potential significance in tumor heterogeneity. Although B7-H3 is predominantly identified as an inhibitory modulator in tumors, its functions may vary across different types of neoplasms. Therefore, caution should be exercised in interpreting the conclusions when translating the findings to other models.

Despite the expanding research on B7-H3, critical knowledge gaps persist in B7-H3 biology. The foremost issue is the unclear identification of the receptors and intracellular binding partners of B7-H3 in both immune and tumor cells, which hinders more profound investigations in this domain. Utilizing AI-driven protein interaction prediction tools, such as AlphaFold-Multimer, ESM-IF1, and DeepMSA2, can significantly accelerate the identification process of B7-H3 receptors and further enhance the accuracy and reliability of predictions. Secondly, post-transcriptional and post-translational modifications of B7-H3 play an exceedingly important role in its functional mechanisms, particularly in

the context of tumorigenesis. Notably, there is a significant gap in research on the post-translational modifications of B7-H3, which warrants further exploration, including studies on phosphorylation, acetylation, methylation, glycosylation, ubiquitination, and palmitoylation. Further study of the crosstalk between post-translational modifications will also be of great value. These investigations aim to broaden our in-depth comprehension of B7-H3, thereby aiding in the refinement of B7-H3-targeted therapeutic strategies and facilitating their clinical deployment. Moreover, several emerging technologies have offered unprecedented opportunities for biological research of B7-H3, such as single-cell multi-omics sequencing,[132] spatial functional genomics,[133] the combined application of single-cell and spatial genomics,[134] CRISPR-based screens (iScreen,[135] StAR[136]), and novel sequencing platforms (NIS-Seq,[137] UDA-seq[138]). Future studies can leverage these new technologies to further explore B7-H3's upstream regulatory mechanisms, downstream effector pathways, and its functions in normal physiology, thereby achieving a more comprehensive understanding of its mechanisms of action in tumor development and progression. Elucidating these mechanisms is essential for development of innovative immunotherapeutic strategies directed against B7-H3.

Therapeutic innovation is accelerating. Overexpression of B7-H3 in many tumors is associated with regulation by various non-coding RNAs, and targeting these naturally occurring non-coding RNAs shows promise in disrupting B7-H3 signaling. Targeting the pro-tumorigenic miRNAs, the introduction of synthetic anti-miRs that are complementary to the miRNAs into tumor cells may effectively prevent the binding of miRNAs to the mRNA of B7-H3, thereby inhibiting the progression of tumorigenesis.[139] Moreover, recent artificial lncRNA technology can precisely target and efficiently degrade proteins, effectively addressing the long-standing "undruggable" target issues that have plagued the scientific community.[140] Additionally, given the dual nature of B7-H3's immune and non-immune functions, simultaneous blocking of its immune checkpoint activity (such as antagonistic antibodies) and intrinsic tumor survival pathways (such as small molecule inhibitors disrupting B7-H3-mTOR interactions) may be required. And, given the complex role of B7-H3 in the TME, future research should explore the interactions between B7-H3 and other immune checkpoint molecules, as well as their potential synergistic effects on tumor immune evasion. Therapeutic strategies targeting B7-H3, including mAbs, BsAbs, ADCs, CAR-T therapies, and combinatorial strategies, are rapidly advancing and achieving significant breakthroughs. The development of monoclonal antibodies targeting the B7-H3 glycosylation site, as has been done with PD-1, may be a promising therapeutic approach. Additionally, inhibiting the glycosylation of B7-H3 may enhance the cytotoxic effects of CAR-T cells, thereby improving their anticancer activity in solid tumors.[141] And, local delivery strategies for B7-H3 CAR-T cells combined with oncolytic viruses are also a viable option.[142] Furthermore, high-throughput and virtual screening of compound libraries[143,144] can be used to explore the combination of B7-H3 with other therapeutic modalities, such as small-molecule inhibitors and chemotherapy, which may provide new treatment strategies for refractory tumors. Treatment strategies with B7-H3 as a target have shown promising efficacy and safety in the treatment of various tumor cells, suggesting that targeting B7-H3 could be a valuable strategy for cancer treatment. In terms of clinical trials, a broader evaluation of the safety and efficacy of B7-H3-targeted therapies is warranted. Notably, the clinical application of B7-H3 ADCs and CAR-T cell therapies across various types of cancer will be a focal point of future research. Ultimately, in-depth research on B7-H3 is poised to yield groundbreaking advancements in oncology. Integrating mechanistic insights with cutting-edge technologies will enable the development of more personalized and effective therapeutic regimens for patients.

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Author Contributions

All authors contributed to data collecting, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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