Perspective

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From tumor immunity to precision medicine: the next step in B7-H3/CD276 research

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Abstract: B7-H3 (CD276) is one of the immune checkpoint molecules at the forefront of cancer biology, plays a diverse role in immune regulation and cancer progression, while its immunosuppressive functions enable tumors to escape immune detection, its contribution to processes such as angiogenesis, metabolic reprogramming and chemoresistance underscores its broader impact on the tumor microenvironment (TME). These properties make B7-H3 an attractive target for cancer therapy. This perspective discusses the immune and non-immune related functions of B7-H3, the challenges in tapping its therapeutic potential.

Keywords: B7-H3/CD276; checkpoint inhibitors; cancer therapeutics; immune evasion; tumor microenvironment

Introduction

The B7 family is a group of structurally related immune checkpoint molecules which can transduce co-stimulatory and co-inhibitory signals [1]. Family members, such as B7-1 (*CD80*), B7-2 (*CD86*), PD-L1 (*CD274*) and B7-H3 (*CD276*), modulate T-cell activation and immune regulation. Though some, such as B7-1 and B7-2, are expressed mostly on antigen-presenting cells like dendritic cells and macrophages, others, like B7-H3 and B7-H6, are highly expressed by tumor cells and associated with immune evasion (Table 1) [2, 3]. B7-H3 displays a wide expression profile and performs multifunctional roles in tumor biology that distinguish it from other members of the B7 family, but its receptor is yet to be identified. B7-H3 was reported to be markedly overexpressed in the majority of cancers, including breast cancer, prostate cancer, lung cancer and colorectal cancer with limited expression in normal tissues [4]. It plays a complex role in tumor progression and immune evasion, in that it may stimulate or inhibit immune responses depending on the context. Besides its immunosuppressive action, B7-H3 has been implicated largely in tumor progression through its role in angiogenesis, metastasis, and resistance to chemotherapy [5]. This perspective discusses the molecular bases of B7-H3 functions, the possibility of therapeutic targeting of B7-H3 and their clinical implications regarding the potential impact they may have on the field of oncology.

The immuno-suppressive role of B7-H3 in tumor microenvironments

B7-H3 inhibits $CD8^+$ T-cell function by suppressing the production of granzyme B and IFN-γ, as demonstrated in ovarian and colorectal cancer models [6] (Figure 1). Recent studies show that mTORC1 directly upregulates the expression of B7-H3 could enhance its immunosuppressive function on antitumor T cells [7]. B7-H3 knockout mice harboring the E.G7 tumor showed a reduction of tumor-infiltrating natural killer (NK) cell activity has indicated by reduced expression of perforin and granzyme B. Anti-B7-H3 antibodies reduced tumor growth by boosting cytotoxic lymphocyte function [8]. In addition, it could also downregulate the STAT3/ULBP2 axis in colon cancer, resulting in reduced expression of ULBP2 and, consequently a reduction in γδ T-cell cytotoxicity [9]. B7-H3 deletion in trans-genic adenocarcinoma of the mouse prostate (TRAMP) mice led to enhanced infiltration and proliferation of $FoxP3^+$ Tregs within tumors, accompanied by higher levels of IL-10 and TGF-β, while the expression of effector cytokines in $CD8^+$ T cells was reduced [10]. B7-H3 increases the polarization of M2 macrophages through the CCL2-CCR2 axis, generating an immunosuppressive tumor microenvironment that increases the secretion of IL-10 and TGF-β [11] (Figure 1).

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Table 1: Overview of B7 Family.

B7 Molecule	Alias	Receptor	Function	Expression
B7-1	CD80	CTLA-4, CD28	Stimulatory/Inhibitory	DCs, macrophages, activated B cells
B7-2	CD86	CTLA-4, CD28	Stimulatory/Inhibitory	DCs, macrophages, monocytes, activated B cells
B7-H1	PD-L1, CD274	PD-1	Stimulatory	DCs, macrophages, activated $CD4^+$ T cells, activated $CD8^+$ T cells, tumor cells
B7-H2	ICOS-L, CD275	ICOS	Inhibitory	DCs, B cells, monocytes, tumor cells
B7-DC	PD-L2, CD273	PD-1	Inhibitory	DCs, macrophages, lung epithelial cells, tumor cells
B7-H3	CD276	Not identified	Stimulatory/Inhibitory	DCs, monocytes, activated $CD4^+$ T cells, activated $CD8^+$ T cells, tumor cells, endothelial cells
B7-H4	B7x, B7S1, VTCN1	BTLA	Inhibitory	DCs, macrophages, tumor-associated fibroblasts, tumor cells
B7-H5	VISTA, Gi24	PSGL-1	Inhibitory	Macrophages, monocytes, neutrophils, $CD4^+$ T cells, $CD8^+$ T cells
B7-H6	NCR3LG1	NKp30	Stimulatory	NK cells, tumor cells
B7-H7	HHLA2	CD28H	Stimulatory/Inhibitory	Macrophages, monocytes, activated $CD4^+$ T cells, activated $CD8^+$ T cells, tumor cells, endothelial cells

This table provides a summary of key B7 family molecules, detailing their aliases, known receptors, and primary functions in immune modulation, and expression. DCs = dentritic cells.

The non-immune role of B7-H3 in tumor microenvironments

Besides regulating immune cell function, B7-H3 contributes to tumor development by promoting epithelial-mesenchymal transition (EMT), metastasis, metabolic reprogramming and cell proliferation [12] (Figure 1). B7-H3 activates NF-κB and the mTOR pathway, promoting angiogenesis via vascular endothelial growth factor A (VEGF-A), which facilitates tumor survival and proliferation [7]. Soluble B7-H3 was identified in the plasma of healthy individuals and elevated in cancer patients [13]. Exosome B7-H3 activates the NF-κB pathway, increasing VEGFA expression and angiogenesis in colorectal cancer. B7-H3 knockdown reduced p-p65 phosphorylation, and NF-κB inhibition with BAY11–7082 decreased VEGFA expression and micro-vessel density [14]. B7-H3 regulates lipogenesis in lung cancer through the SREBP1/FASN pathway, with silencing B7-H3 leading to decreased SREBP1 and FASN levels, thus inhibiting lipid synthesis [15]. Additionally, B7-H3 stabilizes HIF-1α by increasing ROS, promoting glycolysis through HIF-1α targets like LDHA and PDK1 [16]. Thus, it supports tumor growth, acidification of TME, and immune impairment. Moreover, B7-H3 mediates chemotherapy resistance through the STAT3 and PI3K/Akt pathway and enhances anti-apoptotic protein expression like Bcl-2 and Mcl-1 [17].

Emerging therapeutic strategies targeting B7-H3 in cancer treatment

B7-H3 has emerged as a promising therapeutic target due to its overexpression in multiple cancer types and its low expression in normal tissues. Its role in immune evasion and tumor progression has led to several therapeutic strategies,

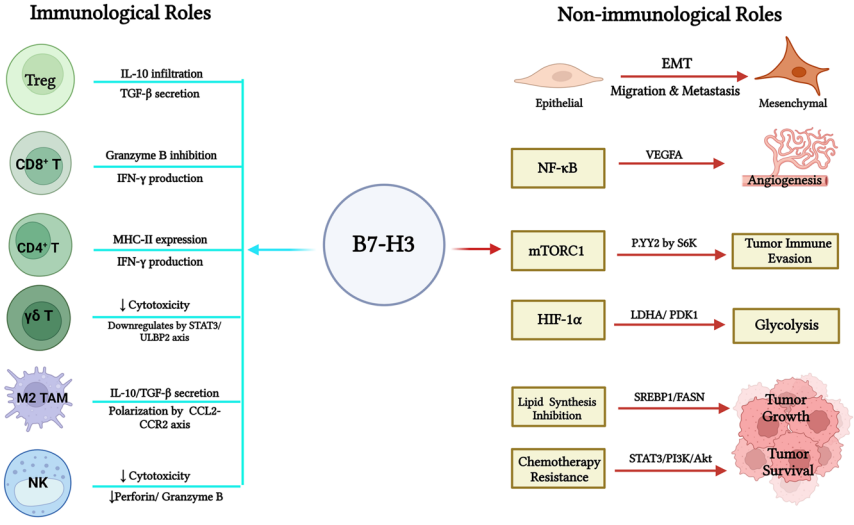

Figure 1: Roles of B7-H3 in tumor immunosuppression and progression. This figure shows the immunological and non-immunological roles of B7-H3 in tumor microenvironment. The left-hand side represents how B7-H3 exerts its immunosuppressive functions by interacting with T cells, marcophages and NK cells, hence promoting immune evasion. The right-hand side shows B7-H3 promotes tumor development through EMT, metabolic reprogramming, and activation of the NF-κB and mTOR pathways, enhancing angiogenesis, cell survival, and chemoresistance. EMT: Epithelial-mesenchymal transition.

Table 2: Overview of B7-H3-Targeted Therapies.

Agent	Strategy	Mechanism	Status	Advantages	Challenges
Enoblituzumab (MGA271)	Monoclonal antibodies	ADCC-mediated tumor cell lysis	Phase II trials	Specific, manageable safety	Limited efficacy as monotherapy
B7-H3 × CD28 B7-H3 × PD-L1	Bispecific antibodies	Activates T cells, blocks immune escape pathways	Preclinical studies	Dual targeting, enhanced specificity	Complex design, off-target effects
B7-H3 × 4-1BB	Bispecific antibodies	Stimulates $CD8^+$ TILs, leads to tumor regression	Preclinical studies	Enhances T-cell activation, better antitumor effect	Limited penetration, durability issues
TX103	CAR-T therapy	T Cells targeting B7-H3	Phase I/II trials	Tumor-specific, minimal toxicity	Tumor penetration, persistence issues
B7-H3-targeted NK cells	Adoptive NK cell therapy	Enhances cytotoxicity in non-small cell lung cancer	Preclinical studies	Amplified immune response	Delivery and expansion challenges
Ifinatamab deruxtecan (DS-7300)	ADC	Delivers topoisomerase I inhibitor to tumor cells	Phase III trials	Precise delivery, bystander effect, favorable safety	Limited validation in tumor types
MGC018	ADC	Inhibits DNA replication in tumor cells	Phase I/II trials	Bystander effect	Limited in other cancer types
B7-H3-conjugated isotopes	Radioimmunotherapy	Delivers targeted radiation to tumor	Preclinical studies	Localized effects, tumor-specific	Radiotoxicity, penetration issues
B7-H3/Dox@GNCs	Nanoparticles	pH-responsive drug release in tumor environment	Preclinical studies	Enhanced targeting, reduced toxicity	Clearance by liver macrophages

This table summarizes major therapeutic strategies targeting B7-H3; a description of their mechanisms of action and current clinical/preclinical status, together with advantages and challenges. ADCC = antibody-dependent cellular cytotoxicity; ADCs = antibody-drug conjugates; TILs = tumor-infiltrating lymphocytes; CAR-T = chimeric antigen receptor T cell therapy; NK = natural killer cells; NSCLC = non-small cell lung cancer; GNCs = gold nanocages; 4-1BB = a T-cell co-stimulatory receptor (CD137); PD-L1 = programmed death-ligand 1.

including CAR-T cells, bispecific antibodies (BsAbs), antibody-drug conjugates (ADCs) and nanoparticle. However, while these approaches demonstrate potential, their efficacy often remains constrained by TME complexity (Table 2).

Enoblituzumab (MGA271) is the first developed humanized IgG1 monoclonal antibody targeting against B7-H3. It induces antibody-dependent cellular cytotoxicity (ADCC) in B7-H3-positive tumors and has demonstrated encouraging safety and efficacy in clinical trials, Ifinatamab deruxtecan (DS-7300), a B7-H3-targeted ADC conjugated to a topoisomerase I inhibitor, exhibits potent antitumor activity against lung and breast cancer models while minimizing systemic toxicity [18]. While MGC018 is another duocarmycin-based ADC, uses a vc-seco-DUBA payload to inhibit DNA replication in tumor cells [19]. DS-7300 has shown promising results in small-cell lung cancer (SCLC), whereas MGC018 is more effective in breast and ovarian cancers. CAR-T therapies, such as TX103, show tumor infiltration and regression in glioblastoma and neuroblastoma but face challenges with stromal barriers and persistence [20]. There is no related death in TX103-CAR-T therapy. However, some adverse events and treatment-related AEs (AE) like cytokine release syndrome, increased intracranial pressure were experienced in patients [20]. Furthermore, adoptive transfer chimeric antigen receptor-modified NK cells targeting B7-H3 showed amplified cytotoxic effect against B7-H3 in non-small lung cancer cells, hence further indicating the vital role for B7-H3 in immune evading [21]. Bispecific antibodies targeting B7-H3 × CD28 enhance T-cell co-stimulation, improving immune responses, while other bi-specific antibodies targeting B7-H3 × PD-L1 show superior antitumor activity in head and neck squamous cell carcinoma (HNSCC) and laryngeal squamous cell carcinoma (LSCC) [22]. For B7-H3 × 4-1BB bispecific antibodies, stimulating $CD8^+$ TILs leads to tumor regression in colorectal cancer, melanoma, and breast cancer models, with even greater antitumor effects when combined with PD-1 blockade [23]. Radioimmunotherapy conjugates radioactive isotopes to B7-H3 antibodies, achieving localized glioblastoma ablation but requiring better delivery systems to reduce radiotoxicity [24].

While there have been promising therapeutic developments, there are still important areas for improvement related to the complex role of B7-H3 in cancer progression. For example, Targeting B7-H3 alone does not completely eradicate tumor, one reason could be upregulation of IFN-γ-induced genes which have been shown to be involved in immunotherapy resistance [7]. The combination of B7-H3 inhibitors with drugs that target interconnected pathways like PD-1 or CTLA-4 may therefore show synergistic effects, but patient stratification and biomarker-driven approaches should be used to maximize such benefit. Secondly, many strategies focus on advanced-stage cancers, leaving early-stage applications underexplored. Enhancing real-time monitoring with delivery

systems such as MMP-2-sensitive nanoparticles carrying anti-B7-H3 × CD3 bispecific antibodies and dEGCG (S-biAb/dEGCG@NPs) could enhance the precision of treatments and avoid unnecessary toxicities [25]. By addressing these challenges and further developing novel strategies, B7-H3 can transform its role from an emerging target to a cornerstone of cancer therapy.

Future directions

Identifying receptors is still a top priority for understanding B7-H3's mechanism of action. Combination therapies that target B7-H3, along with other immune checkpoint inhibitors, metabolic modulators, or angiogenesis inhibitors, may achieve greater therapeutic efficacy and potentially overcome certain therapeutic resistance. Assessing relevant biomarker responses could help predict outcomes and guide treatment strategies. Artificial intelligence and big data analytics can also be further used to optimize patient stratification and make B7-H3-targeting therapies much more precise and effective.

B7-H3 exemplifies complex immune checkpoint biology, demonstrating both cell-autonomous and non-cell-autonomous functions. While challenges are being acknowledged in identifying its receptors and resistance to therapy, given its wide expression pattern, B7-H3 still represents an intriguing cancer therapy target.

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