Am J Transl Res 2025;17(4):2835-2849
www.ajtr.org /ISSN:1943-8141/AJTR0160544

Review Article

The relevance of B7-H3 and tumor-associated macrophages in the tumor immune microenvironment of solid tumors: recent advances

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Received September 14, 2024; Accepted March 19, 2025; Epub April 15, 2025; Published April 30, 2025

Abstract: B7 homolog 3 (B7-H3) is a member of the B7 ligand family. It is highly expressed in various human cancers, especially mesenchymal malignancies. B7-H3 regulates cancer progression through multiple signaling pathways such as JAK2/STAT3, NF-κB, PI3K/AKT, and ERK. It also has the ability to downregulate $CD8^+$ T-cell infiltration and drive immune evasion. Tumor-associated macrophages (TAMs) are the primary immune infiltrating cells in diverse solid tumors, dominating the immune environment of these malignancies. B7-H3 may have connections to TAMs through the induction of polarization and immunosuppression by the CCL2-CCR2-M2 macrophage axis. This mechanism can inhibit antitumor immunotherapy and promote tumor progression in non-small cell lung cancer, ovarian cancer, colorectal cancer, and osteosarcoma. The inducibility of B7-H3 in TAMs provides novel insight into the targeting of checkpoints for tumor immunotherapy. In general, B7-H3 represents a promising immune therapeutic target and should be considered an immunologic adjuvant for activating the tumor immune microenvironment. Therefore, combination therapies based on anti-B7-H3 agents hold great potential for improving the solid tumor microenvironment to enhance the initiation of the cancer-immunity cycle.

Keywords: B7-H3, macrophages, tumor microenvironment, immunotherapy

Introduction

In recent years, immune checkpoint inhibitors (ICIs) have emerged as a highly promising treatment option, enabling the clinical cure of unresectable solid tumors by producing a lasting response. Nevertheless, the objective response rates to anti-PD-1/PD-L1 or anti-CTLA-4 drugs remain somewhat unsatisfactory and limited in many solid tumors [1]. Therefore, efforts have been directed to identify effective tumor targets that cover a broader range of tumors and exhibit wider expression patterns. B7-H3, a member of the B7 ligand family, represents an attractive target because it is commonly overexpressed on various malignant cells. For decades, the precise mechanism of B7-H3 in immune evasion has remained ambiguous, due to an unknown receptor for its extracellular domain, which consequently hampers our understanding of its biological function. Some researchers have found that B7-H3 has close interactions with TAMs, suggesting its important role in modulating suppressive myeloid immune cells in the tumor immune microenvironment (TIME). Thus, further studies are urgently needed to provide additional insight for this theory and explore key molecules involved in these signaling pathways to guide clinical practice. The aim of this article is to review the histologic literature on the specific interactions between B7-H3 and TAMs, which act to modulate the TIME.

Basic profiles of B7-H3

B7-H3, also known as CD276 or B7RP-2, contains 316 amino acids, and its gene is located on 15q24.1 in human cells. It is a type I transmembrane glycoprotein with two isoforms, namely 2IgB7-H3 and 4IgB7-H3, where 4IgB7-H3 is the most frequent in humans, while mice only express 2IgB7-H3 (**Figure 1**) [2, 3]. B7-H3 is highly expressed on the surfaces of T cells, anti-

https://doi.org/10.62347/ILTR3848

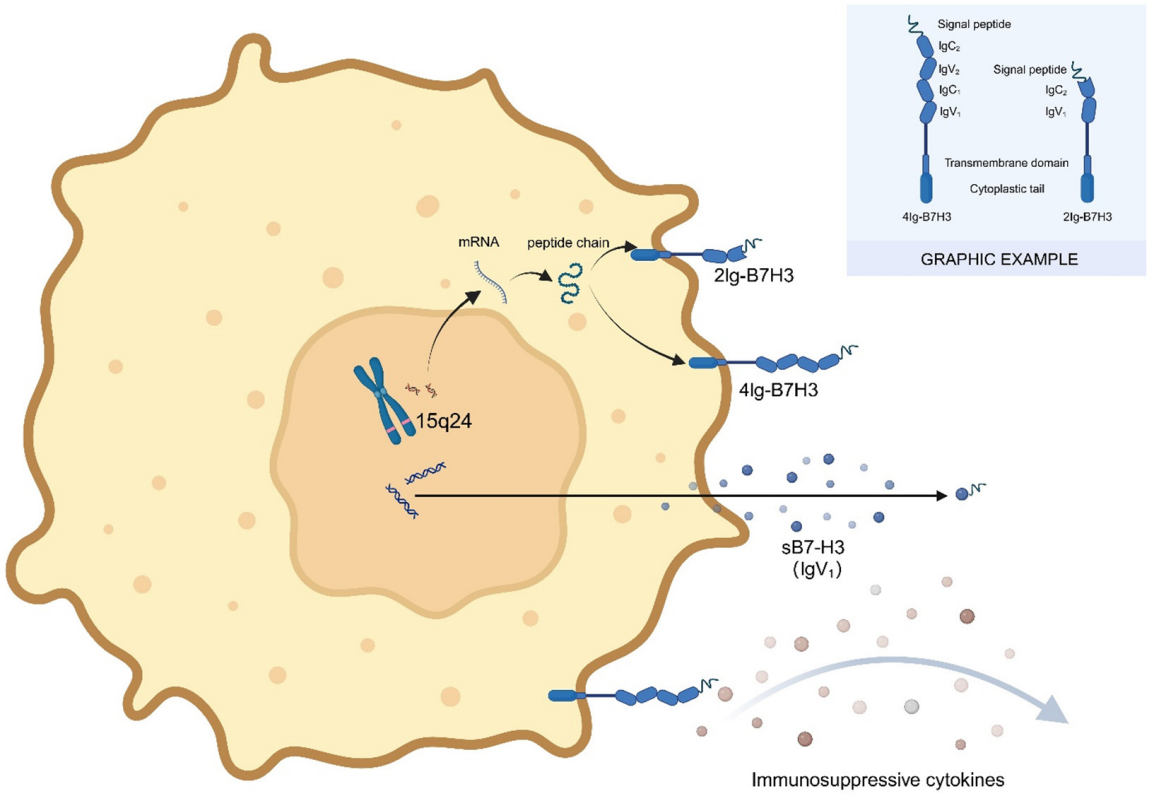

Figure 1. The genetic background and molecular structure of B7-H3. B7-H3 is a type I transmembrane glycoprotein with two isoforms, namely 2IgB7-H3 and 4IgB7-H3. 2IgB7-H3 consists of IgV_1 and IgC_2 while 4IgB7-H3 consists of IgV_1, IgC_1, IgV_2 and IgC_2. Both also have a transmembrane domain, a cytoplastic tail and a signal peptide. 4IgB7-H3 is the most frequent in humans while mice express only 2IgB7-H3. Its gene is located in 15q24.1 in human cells. sB7-H3: soluble B7-H3.

gen-presenting cells (APCs), and tumor cells, and it can affect immune inflammation, material metabolism, angiogenesis, and composition of TIME, to promote the growth of tumor cells and metastasis. The receptor for B7-H3 has not been identified, but possible candidates include TLT-2, IL-20RA, and PLA2R1 [4]. Previous studies have shown that the binding affinity between B7-H3Ig and TLT-2 is similar to that of PD-1 and PD-L1, leading to enhanced T-cell response and IFN-γ production [4]. The function of IL20RA toward B7-H3 is still under investigation, but it is possible that the interaction between IL20RA and B7-H3 negatively regulates inflammatory and immune responses [5]. B7-H3 has initially been considered a T-cell positive regulator that stimulates the proliferation of $CD4^+$ and $CD8^+$ T cells, enhances cytotoxic lymphocyte (CTL) function, and induces IFN-γ production [6]. So far, B7-H3 has been deemed to play an influential immunosuppressive role in most solid tumors. B7-H3 may affect immune function by modulating glycolysis, leading to alterations in HK2 and HIF-α levels, which promotes lactate production, ultimately contributing to the regulation of the tumor immunosuppressive microenvironment [7]. Furthermore, under the influence of B7-H3, $CD14^+$ monocytes can promote tumor-associated vessel (TAV) formation and differentiate into vascular endothelial cells [8].

In addition to its role in immune function, recent studies have demonstrated that B7-H3 can directly affect the growth and metastasis of tumor cells. B7-H3 has been shown to facilitate endothelial-to-mesenchymal transition (EMT), thereby expediting tumor progression. Furthermore, B7-H3 has been reported to modulate the effects of 5-Fluorouracil (FU) in colorectal cancer [9] and gemcitabine in pancreatic cancer [10] by inhibiting autophagy, apoptosis, and DNA-break repair in baseline cells, ultimately leading to enhanced radioresistance [11]. The

available evidence highlights a significant role of B7-H3 in tumor initiation, progression, and immune evasion.

Distinction from other B7 members

Comparison with PD-L1: PD-L1, also known as B7-H1, is an important protein for maintaining immune homeostasis [12]. The PD-1/PD-L1 signaling pathway can inhibit excessive activation of immune cells to prevent autoimmune diseases [13], and may even be hijacked to assist tumor to escape immune surveillance [14]. The combination of PD-L1 on cancer cells and PD-1 on tumor-infiltrating lymphocytes (TILs) activates Src homology region 2 domain-containing phosphatase (SPH2), leading to the suppression of T-cell receptor (TCR) and T-cell function [15]. Furthermore, the transcription of PD-L1 can be regulated by a large number of signaling pathways, such as mitogen-activated protein kinase (MAPK), anaplastic lymphoma kinase (ALK), phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR, Janus kinase 2/signal transducer and activator of transcription 3 (JAK/STAT3), and nuclear factor-κB (NF-κB). Unlike PD-L1, expression of B7-H3 on tumor cells is wider, whether in non-small cell lung cancer, melanoma, gastrointestinal cancers, or sarcomas. Nevertheless, while the function and mechanism of PD-L1 have been relatively clear, the function and mechanism of B7-H3 are still under investigation. Currently, suppression of the PD-1/PD-L1 signaling pathway is a significant strategy to restore the normal regulatory condition of TIME [16]. As B7-H3 has both immunosuppressive and immunostimulatory functions, it is important to explore its mechanism.

Comparison with other B7 members: In addition to B7-H3 and PD-L1, there are eight more members of the B7 ligand family, namely B7-1, B7-2, B7-H2, B7-DC, B7-H4, B7-H5, B7-H6, and B7-H7 (**Figure 2**) [17]. B7-1 and B7-2 are primarily expressed on professional APCs such as dendritic cells and macrophages. They can specifically interact with ligands on the T cell surface such as CD28 or CTLA-4, which play a key role in T-cell activation, maintenance of steady state, and self-tolerance [18]. For example, it was reported that the interaction between B7-1 and PD-L1 expressed by dendritic cells (DCs), T cells, B cells, and macrophages could suppress the activation of T cells and the production of cytokines [19]. Some investigators have begun to investigate chemical agents (e.g., belatacept) and monoclonal antibodies (e.g., galiximab) that target B7-1 to modulate immunity [20, 21]. B7-H2 is a ligand of the inducible co-stimulator (ICOS), serving as a co-stimulatory signal to induce T-cell proliferation and B-cell differentiation into plasma cells while also facilitating the secretion of antitumor cytokines. B7-DC, also known as PD-L2, primarily contributes to tumor's evasion of the immune system through the interaction with PD-1. However, it is less efficient than PD-L1, whose function on tumor progression and prognosis in TIME in osteosarcoma has been studied before [2]. V-domain Ig-containing suppressor of T-cell activation (VISTA), also known as B7-H5, is a member of the B7 family of negative checkpoint regulators and represents a new target for immunotherapy. VISTA shows the highest expression in myeloid cells, including macrophages, conventional DCs, monocytes, and circulating neutrophils. Among conventional T cells, expression of VISTA is the highest in naïve cells and FoxP3+ regulatory T cells (Tregs), and memory $CD4^+$ T cells also express VISTA to some extent. This unique surface expression pattern suggests that VISTA may function to restrict T-cell immunity at different stages compared with the PD-1/PD-L1 and CTLA-4 axes [22]. B7-H6 can facilitate or suppress immune reaction by interacting with TMIGD2 or KIR3DL3, respectively [23]. The B7 family members have immune regulatory functions, specifically in the interaction with T cells. B7-H3, in contrast to other B7 family members, is expressed in a wide range of tumor cells and plays a dual role in immune response modulation, both stimulatory and inhibitory.

Mechanisms of B7-H3 in cancer signaling pathways

So far, many immune signaling mechanisms of B7-H3 in tumors have been explored, highlighting its critical and debated role in TIME (**Figure 3**). B7-H3 has been shown to promote immune evasion, thereby inhibiting antitumor responses. The depletion or inhibition of B7-H3 is likely to hinder the progression, invasion, angiogenesis, and metastasis of gastrointestinal tract (GIT) tumors, weakening their resistance. The overexpression of B7-H3 can activate a large

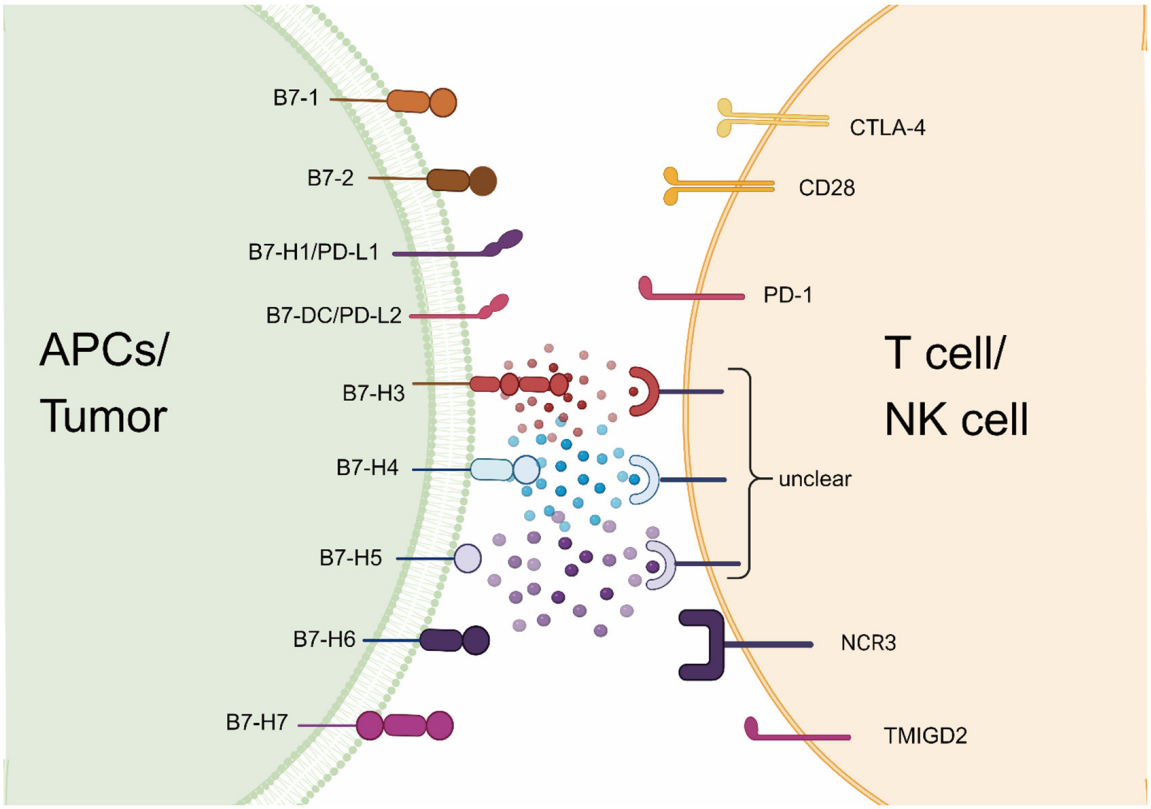

Figure 2. The B7 family members and its receptor. This picture provides a summary of research findings on the B7 family members and their corresponding receptors. The family includes B7-1, B7-2, B7-H1 (also known as PD-L1 or Programmed Death-Ligand 1), B7-DC (also referred to as PD-L2 or Programmed Death-Ligand 2), B7-H3, B7-H4, B7-H5, B7-H6, and B7-H7. Notably, B7-H3, B7-H4, and B7-H5 have both membrane surface expression and soluble forms, although the identity of their ligands remains unclear. CTLA4: The cytotoxic T-lymphocyte-associated antigen 4; PD-1: Programmed cell death protein 1; NCR3: Natural cytotoxicity receptor 3; TMIGD2: Transmembrane and immunoglobulin domain containing 2.

number of signaling pathways to inhibit apoptosis genetically and control the activity of cell cycle-controlling proteins and DNA-repair mechanisms [24].

It is suggested that FOSL1, YY2, eIF4F complex, and inflammatory cytokines can directly influence the expression of B7-H3. A key component of FOSL1, AP-1, binds to the superenhancer (SE) region upstream of B7-H3 to promote B7-H3 transcription. The expression of FOSL1 is influenced by B7-H3 through the activation of AP-1, creating a positive feedback loop between B7-H3 and FOSL1 [25]. mTORC1 regulates B7-H3 expression by directly phosphorylating the transcription factor YY2. More specifically, the downstream effector of mTORC1, S6K, directly phosphorylates Thr336 on YY2. This phosphorylation inhibits the ubiquitin-mediated degradation of YY2, leading to increased stability and enhanced expression of YY2 protein. In mice with mTORC1 hyperactivity, inhibition of B7-H3 increases $CD38^{+}CD39^{+}CD4^{+}$ cytotoxic T-cell infiltration, activates the IFN-γ response, and enhances the expression of MHC-II [26]. Eukaryotic translation initiation factor 4E (eIF4E) plays a crucial role in the translation of B7-H3 by assembling an eIF4F complex with eIF4A and eIF4G. Phosphorylation of PI3K/AKT/mTOR and extracellular signal-regulated kinase (ERK) or p38MAPK-MNK1/2 regulates the expression of B7-H3, and loss of SP20H and stimulation of TNF-α in cancer upregulates it. For example, deficiency of S20H can induce an eIF4E-dependent translation of B7-H3, enhancing the antitumor activity of APCs. Some inflammatory cytokines such as GM-CSF, LPS, and IFN-γ can also induce DCs and monocytes to express B7-H3 [27]. In addition, there are some genes that can affect the expression of B7-H3, but the

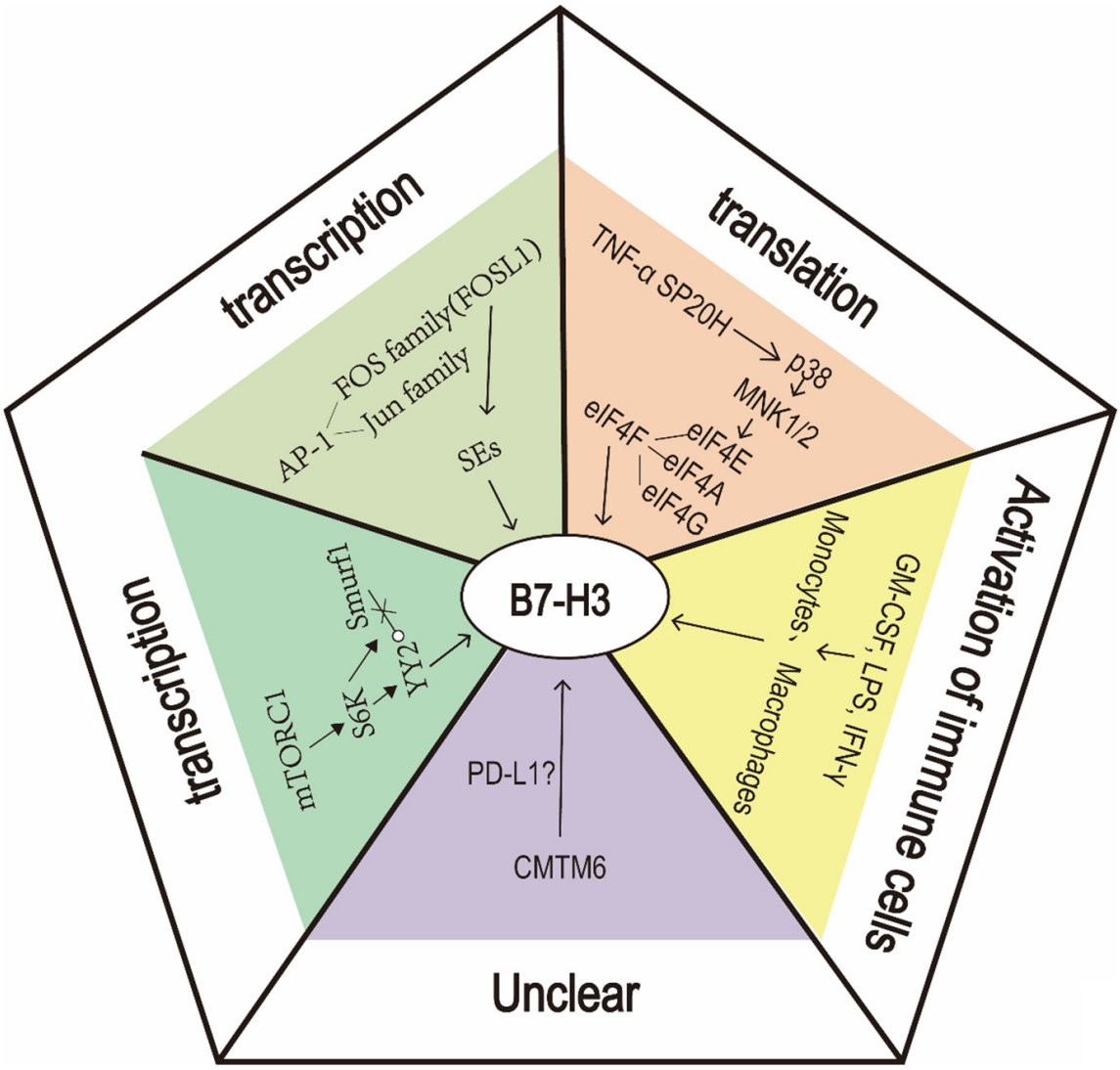

Figure 3. Control factors of B7-H3 expression. In this picture, we summarize the existing literature on the signaling pathways influencing B7-H3 expression, covering aspects such as transcription, translation, and immune cell involvement. Throughout the picture, the arrow-headed lines denote induction, the circles-headed line denote ubiquitination degradation, and crosses denote blockade. mTORC1: The mechanistic/mammalian target of rapamycin complex I; S6K: S6 kinase; YY2: Yin yang 2; Smurf1: SMAD specific E3 ubiquitin protein ligase 1; AP-1: Activating protein-1; FOSL1: Fos-like antigen 1; SEs: Super-enhancers; TNF-α: Tumor necrosis factor α; SP20H: SPT20 homolog; MAPK: Mitogen-activated protein kinases; MNK1/2: MAPK interacting protein kinases 1 and 2; eIF4E: eukaryotic translation initiation factor 4E; eIF4A: eukaryotic translation initiation factor 4A; eIF4G: eukaryotic translation initiation factor 4G; eIF4F: eukaryotic translation initiation factor 4F; GM-CSF: Granulocyte/macrophage colony stimulating factor; LPS: Lipopolysaccharide; IFN-γ: Interferon-γ; CMTM6: The CKLF-like MARVEL transmembrane domain-containing protein 6; PD-1: Programmed cell death protein 1.

mechanism is still unclear. CMTM6, a regulator of PD-L1, can affect tumorigenesis and interfere with the maintenance of cancer stem cell (CSC) and TGF-β-induced EMT through the Wnt/β-catenin signaling pathway. Knocking down CMTM6 in TILs results in downregulation of B7-H3, leading to an antitumor action [28], and overexpression of B7-H3 may adjust the level of HK2 and HIF-α to reprogram cancer glucose metabolism.

TAMs in the TIME

The TIME comprises a variety of immune and nonimmune cells, including CTLs, NK cells, cancer-associated fibroblasts (CAFs), and endo-

thelial cells (ECs), among others. Additionally, the TIME contains significant non-tumor stromal cells that have an effect on tumor immune evasion and the immune response [29]. Macrophages are a type of versatile immune cell capable of phagocytosis, antigen presentation, and secretion of signaling molecules [30-34], and they can also modulate tissue homeostasis and promote wound healing [35]. In the tumor, TAMs can magnify immune signals and start the antitumor immune response, and can also restore homeostasis and auxiliary tumor tissue remodeling and repair.

Generation of macrophages

Macrophages can be induced to two contrasting groups through polarization, namely M1 macrophages, which are activated classically, and M2 macrophages, which are activated alternatively [36]. M1 macrophages are typically induced by bacterial products and proinflammatory factors, whereas M2 macrophages are often induced by immunoregulatory cytokines. Commonly, M1 macrophages produce antitumor angiostatic factors such as IL-12 and CXCL10, and M2 macrophages generate tissue-remodeling factors and pro-angiogenic factors such as MMP and VEGF. Nevertheless, the binary classification of macrophages to M1 and M2 phenotypes is becoming less clear, leading to the more frequent use of terms such as “M1-like” or “M2-like” [37]. There is another view that macrophages can be regarded as “beneficial”, “harmful”, and “bystander” toward the immune system. Because M2 and a minority of M1 macrophages are involved in tumor initiation, progression, angiogenesis, and metastasis [38], they are collectively known as TAMs.

Relationship with the TIME

The interaction between TAMs and immune cells enables an immunosuppressive microenvironment. T cells, myeloid cells, and tumor cells can regulate TAMs. Tregs also have some influence on TAMs. For example, Tregs can adjust lipid metabolism of M2-like TAMs by preventing IFN-γ secreted by $CD8^+$ T cells from cutting of the activation of sterol regulatory element by binding ptotein-1 (SREBP-1)-mediated fatty acid synthesis, and sustain survival, metabolic fitness, and mitochondrial integrity of M2-TAMs [39]. LILRB4 is a myeloid inhibitory receptor from leukocyte Ig-like receptor superfamily. It is usually expressed on myeloid cells, especially on $CD45^+$ cells, and is expressed more than PD-1 in the TIME. The PD-1/PD-L1 axis also affects the antitumor ability of TAMs. Specifically, when PD-1/PD-L1 signaling is blocked by anti-PD-1 antibodies or PD-L1 inhibitors, antitumor responses are observed even in the absence of T cells, B cells, and NK cells. The interactions between MHC II and macrophages-LILRB1 can affect the function of TAMs. Through combination with LILRB1, MHC I causes cancer cells to resist phagocytosis [40].

TAMs can regulate the TIME by releasing cytokines and regulating membrane receptors. For example, macrophages can express CSF1R to activate the CSF1-CSF1R signaling pathway, accelerating initiation and proliferation of macrophage precursors, and recruitment and retention within inflamed sites [37, 41]. Moreover, TAMs upregulate PD-L1 and PD-L2 on their surface, leading to T-cell exhaustion. TAMs produce IL-10 and TGF-β, directly inhibit the function of $CD8^+$ T cells, and stimulate $CD4^+$ T cells to differentiate into Tregs [39]. TAMs-derived IL-10 activates PD-L1(+) TAMs to induce $CD8^+$ T-cell dysfunction in hepatocellular carcinoma (HCC) [42, 43], and TREM-1(+) TAMs-derived CCL-20 facilitates $CC6^+$ $FOXP3^+$ Tregs infiltration through the ERK/NF-κB signaling pathway in response to tumor metabolites and hypoxia [44, 45]. PI3Kγ is located in a signaling bottleneck in TAMs, integrating external reprogramming signals to control the switch from immune stimulation to immune suppression. In the case of PI3Kγ gene deletion or inhibition, the lack of catalytic subunit p110 promotes the degradation of IκBα, thereby enhancing the activity of NF-κB, which results in the increased expression of immunostimulatory molecules such as MHC II and IL-12, and decreased expression of immunosuppressive molecules such as IL-10 and arginase [46].

Interaction between B7-H3 and TAMs in cancer

During the development and progression of cancer, there are abundant interactions between B7-H3 and TAMs to support or impede tumor cells jointly (Supplementary Table 1). Tumor-expressed B7-H3 can influence the polarization of human monocytic cell line THP-1 toward an anti-inflammatory M2-like pheno-

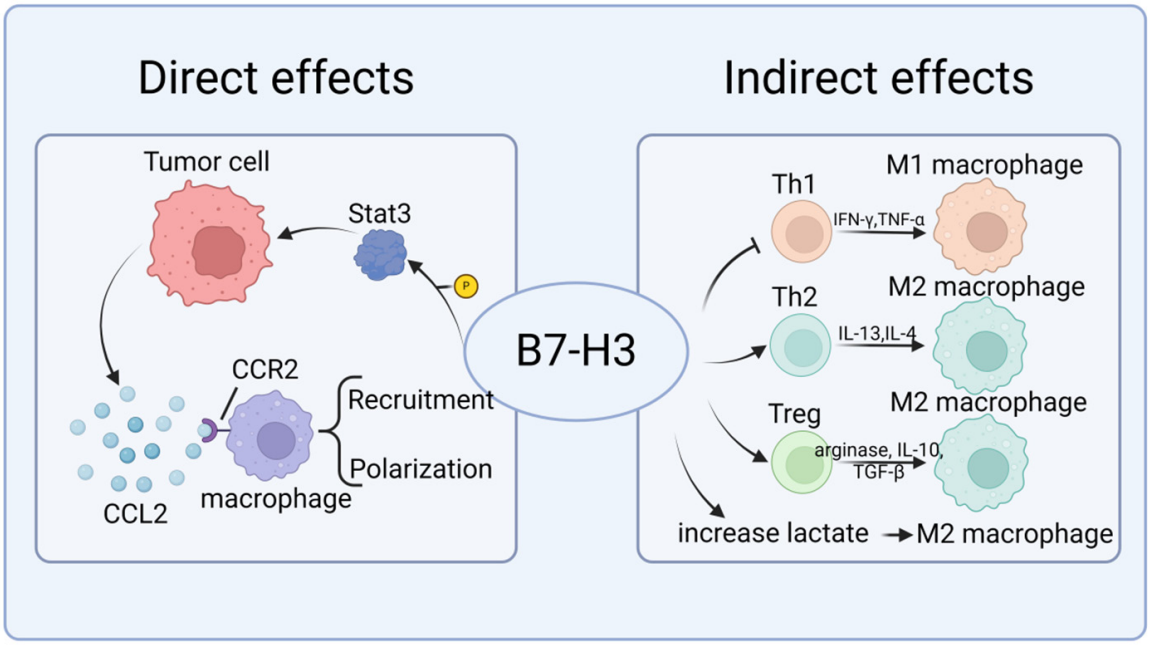

Figure 4. Effect of B7-H3 on macrophage polarization. B7-H3 can affect the CCL2-CCR2-M2 pathway through STAT3, promoting the recruitment and polarization of monocytes to macrophages. Additionally, B7-H3 can indirectly influence macrophage polarization through its effects on T cells or lactate production. Stat3: Signal transducer and activator of transcription 3; CCL2: C-C motif ligand 2; CCR2: C-C chemokine receptor type 2; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor α; IL-4: Interleukin-4; IL-13: Interleukin-13; IL-10: Interleukin-10; TGF-β; Transforming growth factor β.

type, thereby creating an immunosuppressive and tumor-promoting TIME (**Figure 4**). The expression of B7-H3 in tumor spheroids is closely associated with the infiltration of macrophages. Depletion of B7-H3 can lead to the differentiation of monocytes into macrophages in the presence of GM-CSF and M-CSF. Activated monocytes and macrophages can upregulate B7-H3, but this does not aid in the differentiation and polarization of monocyte-derived macrophages (MDMs). B7-H3 may promote tumor progression by inducing immunosuppression through the CCL2-CCR2-M2 macrophage axis. αCD276-based immunotherapy can selectively act on macrophages, reducing B7-H3 and facilitating macrophages infiltration [47].

Pathways significant for cell polarization

CCL2-CCR2-M2 macrophage axis: CCL2 (also known as MCP-1) is a chemokine that attracts monocytes to sites of inflammation and tumor by binding to its receptor CCR2. Once monocytes are recruited to these regions, they may further differentiate into M2 macrophages, forming an immunosuppressive microenvironment conducive to tumor progression. Recent studies have shown that spondin 2 (SPON2), high-mobility gene group A2 (HMGA2), cytoplasmic polyadenylation element binding protein 3 (CPEB3), and miR-106b produced by tumor cells can affect the secretion of CCL2. SPON2, an extracellular matrix glycoprotein, can activate TAM migration and infiltration and induce M2 polarization indirectly by upregulating several cytokines such as IL-10, CCL2, and CSF1, perhaps through the ERK/AP1 pathway activated by integrin β1. HMGA2 is an overexpressed oncoprotein, and it can stimulate recruitment and M2 polarization of macrophages in the TIME by inducing CCL2 secretion by binding directly to STAT3 promoter [48]. A decrease of CPEB3 is associated with fewer $CD86^+$ TAMs and more $CD163^+$ TAMs, and CPEB3 can suppress M2-TAMs polarization by downregulating CCL2 and inhibit TAMs-induced EMT via IL-6 to impair tumor progression [49]. Conversely, EMT-Exos-derived miR-106b can induce M2 polarization to activate the PI3Kγ/AKT/mTOR signaling cascade by decreasing PDCD4 at the posttranscription level, which assists M2 polarization, thereby forming a vicious circle to push the migration, invasion,

and metastasis [50]. B7-H3 can affect the CCL2-CCR2-M2 macrophage pathway by partially affecting STAT3.

B7-H3 indirectly affects macrophage polarization: B7-H3 has an effect on the infiltration and function of $CD4^+$ T cells, particularly Tregs, Th1 cells, and Th2 cells. Research on prostate cancer has demonstrated that B7-H3 influences the invasion of all three cell types, especially regarding the presence of Tregs in B7-$H3_{high}$ TAMs to facilitate tumor accumulation [51]. Additionally, B7-H3 affects the function of these three T-cell types, with the deletion of B7-H3 resulting in increased granzyme B, IFN-γ, and IL-2 production in $CD4^+$ T cells, indicating an enhanced cytotoxic effect [51]. B7-H3 also plays a role in negatively regulating Th1-driven immune responses and affecting the production of Th2 cytokines (IL-4, IL-5, and IL-13) [52, 53]. These T cells influence the polarization of macrophages, with Th1 cytokines such as IFN-γ and TNF-α inducing M1 polarization and Th2 cytokines such as IL-4 and IL-13 inducing M2 polarization [54]. Tregs can induce M2 macrophage polarization through arginase, IL-10, and TGF-β pathways [54, 55]. Although there is no direct evidence showing that B7-H3 can affect macrophage polarization through $CD4^+$ T cells, there is a strong association between them. In addition, B7-H3 can affect the glycolytic process of tumor cells and increase the formation of lactate [7]. High levels of lactic acid can promote M2 macrophage polarization [56].

Relationship between B7-H3 or TAMs in several common cancers

Non-small cell lung cancer (NSCLC): NSCLC accounts for the majority of lung cancer cases. It is usually treated with anti-PD-1 or anti-PD-L1 agents, which have a response rate of less than 20% given that only 25%-37% of tumor cells are positive for PD-L1 in NSCLC [57]. However, about 76% of NSCLC cases are positive for B7-H3 [58]. Even in pulmonary sarcomatoid carcinoma (PSC), an NSCLC with a high frequency of driver mutations, B7-H3 is positive in 73% of PSC and in 100% of sarcomatoid components [59]. B7-H3 is associated with prognosis in NSCLC, which may be due to its immunomodulatory and immune-independent function. Overexpression of B7-H3 is associated with tumor-infiltrated cytotoxic lymphocytes and pDC upregulation in NSCLC. The proportion of $CD3^-$ $CD45^+$ macrophages is downregulated in B7-H3-high tumor tissues and non-tumor tissues [60]. In samples which have close proximity and interaction between malignant cells and T cells, macrophages expressing B7-H3 and B7-H4 actively interact with malignant cells, which may increase the risk of tumor recurrence [61].

Ovarian cancer (OC): OC is a highly aggressive tumor that is closely linked to the immune checkpoint protein B7-H3, and B7-H3 is significantly associated with tumor subtypes and TIME [62]. B7-H3 is predominantly expressed on M2 macrophages and MACRO+ macrophages, which have a tumor-promoting phenotype in OC [62]. According to the TCGA, B7-H3 expression in mesenchymal and proliferative subtypes is greater than that in immunoreactive subtype [63]. Analysis of the learning resource (LR)-network suggests that B7-H3 may play a role in anchoring macrophage clusters to carry out its functions within TIME through macrophage signaling [62]. Compared to normal tissues, the expression level of B7-H3 in OC is significantly enhanced and correlates with immune cell infiltration. It positively correlates with M0 and M2 macrophages and negatively correlates with infiltrating memory B cells and plasma cells [62]. Similar results have been found for high-grade serous OC (HGSOC). For example, in patients with HGSOC, B7-H3 expression is positively correlated with the abundance of M2 macrophages [63]. This phenomenon may be attributed to the positive correlation between B7-H3 expression and various immune-related genes, immune checkpoint genes, and mismatch repair (MMR) genes in OC [62]. Additionally, B7-H3 may promote tumor progression by inducing immunosuppression through the CCL2-CCR2-M2 macrophage axis. Specifically, CCL2 produced by tumor cells by the STAT3 pathway is inhibited by B7-H3, thereby suppressing the polarization and migration of M2 macrophages and monocytes [63]. These findings indicate that B7-H3 may be a promising therapeutic target, particularly in tumors with high M2 infiltration and B7-H3 expression [64].

Colorectal cancer (CRC): CRC is tightly associated with B7-H3 and TAMs. CRC tumor cells can affect SPON2, HMGA2, CPEB3, and miR-106b to influence the CCL2-CCR2-M2 pathway, which affects macrophage polarization and distribution. It has also been shown that B7-H3 is relat-

ed to M2 macrophage polarization. Factor 1 from principal component analysis (PCA) for cytokines with M2 macrophages is positively associated with the percentage of B7-H3 immunohistochemistry (IHC) expression and B7-H3 concentrations in tumor tissue homogenates. B7-H3 can support tumor progression by forming an immunosuppressive TIME induced by M2-like macrophages and anti-inflammatory cytokines, and CD163 expression and the immune scores of macrophage regulation both improve in B7-$H3_{high}$ CRC [65].

Glioma: In glioma, the expression of B7-H3 is significantly higher than that of normal tissue, with approximately 97% of cases showing detection. Also, in supratentorial ependymoma, a rare form of glioma, B7-H3 is positive in TIME. The expression of B7-H3 in glioma is positively associated with the WHO grade of glioma, patient age, greater recurrence, and a poor prognosis. In gliomas, B7-H3 has a strong association with immune cells, especially TAMs. The risk score of glioma established by five screened immune gene-related lncRNAs is tightly associated with B7-H3 [66]. While there is no significant difference in B7-H3 expression and TAMs abundance between pediatric diffuse gliomas (pDGs) and adult diffuse gliomas (aDGs), there is a strong correlation between TAMs and B7-H3 expression and PD-L1 levels in patients with aDGs and pDGs. Additionally, the expression of B7-H3 in pDGs may affect the anatomic location and prognosis of the tumors. High expression of B7-H3 is found in patients with pDGs located in the posterior capsule, and external capsule is composed of white matter fibers, which are thought to assist malignant behavior, such as the proliferation of glioma [67]. Thus B7-H3 may be a therapeutic target for glioma.

Breast cancer: B7-H3 is expressed on tumor cells in over 70% of breast cancer cases [47], and plays an important role in breast cancer. Since B7-H3 is overexpressed in different subtypes of breast cancer, it may be a potential target for ultrasound molecular imaging of breast cancer. For example, affibody (ABY)-based ultrasound molecular imaging of vascular B7-H3 by using the ABY-B7-H3 to recognize B7-H3 tissue sections of breast cancer can improve cancer detection [68]. B7-H3 has also been implicated in immune regulation of breast cancer. Previous research has shown that high expression of B7-H3 on TAMs is associated with poor prognosis and exerts a significant pro-metastatic function in triple-negative breast cancer (TNBC). B7-$H3_{high}$ TAMs aggravate the immunosuppressive TIME by supporting the accumulation of myeloid-derived suppressor cells (MDSCs) and pro-tumoral Tregs, and suppressing the infiltration of NK cells and $CD8^+$ T cells. This increases tumor angiogenesis and mediates extracellular matrix (ECM) degradation. Furthermore, blocking B7-H3 can improve the therapeutic efficacy of many drugs such as anti-PD-1 and paclitaxel in TNBC, indicating that targeting B7-H3 can combine with other antitumor therapies to reduce TAMs-related ineffective treatment toward TNBC [69]. Although there is little evidence for the interaction between B7-H3 and TAMs in breast cancer, it is likely of great significance in immunotherapy for breast cancer.

Relationship between B7-H3 or TAMs in sarcomas

B7-H3 is expressed in diverse sarcomas, such as osteosarcoma, rhabdomyosarcoma, liposarcoma, chondrosarcoma, and synovial sarcoma, promoting tumor growth and metastasis. B7-H3-targeting monoclonal antibodies (mAbs) can improve the cytotoxicity and degranulation of NK cells almost in all sarcoma cell lines, and increase IFN-γ, TNF, IL-4, IL-10, and granzyme A and B [70]. Research on the relationship between TAMs and B7-H3 is less abundant in sarcomas than in solid cancers, which may be related to the relative rarity of sarcomas.

Osteosarcoma (OS): B7-H3 is expressed in 91.8% of OS lesions, and its expression intensity is higher than in adjacent normal tissues. The expression of B7-H3 negatively correlates with the density of infiltrating $CD8^+$ T lymphocytes [71]. In addition, the expression of B7-H3 is associated with tumor Ennecking stage/metastasis status. B7-H3-sr39tk and B7-H3 CAR-T cells both have antitumor effects on 143B OS cells naturally expressing B7-H3 [72]. Anti-B7-H3 monoclonal antibody conjugated with FITC can penetrate tumor tissue and bind with 143B OS tumor cells, enhancing their recognition by CAR-T cells and preventing their suppression and exhaustion. This interaction can also enhance the antitumor activity of anti-FITC CAR-T cells, which can be stimulated to migrate to OS, leading to upregulation of IFN-γ

and TNF-α, and ultimately improving antitumor efficacy. Another study has shown that M1-like macrophages activated by IFN-γ can inhibit the growth of OS cells [73]. There is no direct evidence that TAMs and B7-H3 are related, but both are associated with IFN-γ. Further studies are needed to verify the relationship between the two.

Rhabdomyosarcoma (RMS): B7-H3 has been shown to be a specific target in RMS [74]. High expression of B7-H3 is associated with low density of $CD8^+$ T cells. M1 macrophages and NK cells are enriched in tumors with high B7-H3 expression. In *PAX3/7-FOXO1* fusion-negative RMS, B7-H3 correlates positively and significantly with M1 macrophages and neutrophils, and moderately negatively correlates with M2 macrophages and monocytes [75]. B7-H3 CAR-T cells incubated with $fLuc^+$ RD and Rh4 cells can almost eradicate all $fLuc^+$ RMS cells and release substantial IL-2, IFN-γ, granzyme B, and B7-H3, particularly [76]. Canine MGA271 CARs, a type of B7-H3 CAR-T cells, have extremely lethal function on tumor spheroids in RMS through increasing serum ALP and ALT and upregulating CCL2 after lymphodepletion [77]. There is not yet enough conclusive evidence to support an immune connection between B7-H3 and TAMs in the TIME.

Ewing sarcoma (ES): B7-H3 mRNA is also highly expressed in ES, but lower than in OS and Wilms tumor [78]. There is a higher B7-H3 expression in low-risk than in high-risk ES, probably associated with the immune-related 11-lncRNA. In ES, plasma cells positively correlate with M1 macrophages and negatively correlate with M2 macrophages, infiltration of which generally implies a poor prognosis [79]. It has been shown that the population of macrophages in ES is less abundant than that of OS and RMS, and ES has a tendency of low M2 macrophage gene signatures. However, the population of CD163/CD68 double-positive M2 macrophages in metastatic ES is higher than that of local recurring ES [80]. At present, diverse mAbs of immune checkpoints including B7-H3 are applied in immunotherapy of sarcomas [81], which may provide new targeting opportunities for ES.

Others

In numerous cancers, B7-H3 is associated with TAMs. Fibrolamellar carcinoma (FLC) is a liver carcinoma, belonging to HCC. About 91% of FLC cases have B7-H3-positive TAMs in the TIME, and B7-H3 expression significantly correlates with high abundance of $CD8^+$ T cells [82]. In sarcomatoid HCC (sHCC), B7-H3 expression in peritumor tissue is lower than that in tumor tissue, and B7-H3 expression in the sarcomatoid component is higher than that of the conventional HCC component. However, there is no difference in $CD68^+$ TAMs abundance between the sarcomatoid and conventional components [83]. Furthermore, B7-H3 CAR-T cells play an efficient antitumor therapeutic role in many solid tumors [84].

Concluding remarks

B7-H3 and M2 TAMs have a consistent immunosuppressive tendency in tumor immunotherapy. B7-H3 is overexpressed in a number of cancers, inducing macrophages to polarize from M1 to M2 and facilitating pro-tumor roles of TAMs in the TIME. Various molecules are tightly associated with B7-H3 expression and its specific effect in many cancers, so it is important to search for their binding ligands or regulatory sites to enable drug development for immunotherapy.

T cells and macrophages are both immune cells, and thus implanting the technology of chimeric antigen receptor into TAMs and other immune cells may be useful. Although we have collected and summarized the probable complex characteristics and mechanisms of B7-H3, its exact action is still unclear, preventing optimization of a strategy of combining drugs. The M2 polarization of TAMs in the TIME induced by B7-H3 has been discussed in diverse tumors and involves various signaling pathways, mostly NF-κB and STAT3. However, there is still no unified signaling pathway or clear downstream receptor. It is worth pondering whether those receptors exist on the surface or inside of immune cells, or endocytosis is involved in the corresponding process of the interactions between B7-H3 and TAMs, making receptors or targets blurry. Furthermore, the pro-tumor function of M2 TAMs mainly matters not at the terminal of cancer-immunity cycle, but during antigen presentation, the most critical stage. This may explain why clinical trials of B7-H3 mAbs have not been very successful. As an immune checkpoint, B7-H3 does not have an equal therapeutic efficacy of single drugs or mAbs, as enabled by PD-L1 in many solid tumors, indicat-

ing that the function of this checkpoint is rather auxiliary and supplementary. In other words, it is not the final part of the cancer-immunity cycle. In our opinion, it probably exists at the beginning of this cycle, which mainly enables the presence of antibodies as well as modulates the TIME into a "cold" state. B7-H3 dominates targets on the surface of many sarcomas and requires more reasonable drug combinations to play an immune regulatory role. If this is true, it is even more necessary to clarify the signaling pathways and receptors managed by this checkpoint. Furthermore, the above research mainly focuses on the influence of myeloid cells on TIME, but perhaps the secretion of anti-inflammatory cytokines and the infiltration of Tregs caused by M2 polarization are the chief reasons for immunosuppression. Thus, further cell and mouse experiments should demonstrate whether the increase of M1 macrophages in TIME by inhibition of B7-H3 could lead to more infiltration of $CD8^+$ T cells and more cytotoxicity of NK cells. An immune checkpoint that works on the myeloid system and is highly expressed on the cell membrane surface will have great prospects. Accordingly, we can predict that target inhibition and blockade of B7-H3, combined with mAbs against CD47, PD-1/PD-L1, or CTLA-4, can reform the distribution of cytokines, reverse the situation of drug insensitivity or low response rate of the PD-1/PD-L1 axis, and bring revolutionary immunotherapeutic efficacy, only if toxic side effects (such as anemia and cytokine release syndrome) are acceptable. In conclusion, B7-H3 has many complicated and close relationships with TAMs in cancers, especially sarcomas. B7-H3 may mediate M2 polarization of TAMs in TIME to support tumor progression through diverse molecular signaling pathways. Thus, both B7-H3 and TAMs are promising immune therapeutic targets for combination therapy.

Acknowledgements

One of the corresponding authors, Lu Xie, was supported by the Scientific and technological innovation talent funding project of Tongzhou District in Beijing (No. JCQN2023008) and the Beijing Natural Science Foundation-Changping Innovation Collaborative Fund (No. L234041). We thank LetPub (www.letpub.com.cn) for its linguistic assistance during the preparation of this manuscript.

Disclosure of conflict of interest

None.

Abbreviations

B7-H3, B7 homolog 3; TAMs, tumor-associated macrophages; ICIs, immune checkpoint inhibitors; TIME, tumor immune microenvironment; APCs, antigen-presenting cells; CTL, cytotoxic lymphocyte; TAV, tumor-associated vessel; EMT, endothelial-to-mesenchymal transition; FU, fluorouracil; TILs, tumor-infiltrating lymphocytes; SPH2, Src homology region 2 domain-containing phosphatase; TCR, T-cell receptor; MAPK, mitogen-activated protein kinase; ALK, anaplastic lymphoma kinase; PI3K, phosphatidylinositol 3-kinase; JAK/STAT3, janus kinase 2/signal transducer and activator of transcription 3; NF-κB, nuclear factor-κB; DCs, dendritic cells; ICOS, inducible co-stimulator; VISTA, V-domain Ig-containing suppressor of T-cell activation; Tregs, regulatory T cells; GIT, gastrointestinal tract; ERK, extracellular signal-regulated kinase; SE, superenhancer; eIF4E, eukaryotic translation initiation factor 4E; CSC, cancer stem cell; CAFs, cancer-associated fibroblasts; ECs, endothelial cells; SREBP-1, sterol regulatory element by binding ptotein-1; HCC, hepatocellular carcinoma; MDMs, monocyte-derived macrophages; SPON2, spondin 2; HMGA2, high-mobility gene group A2; CPEB3, cytoplasmic polyadenylation element binding protein 3; NSCLC, non-small cell lung cancer; PSC, pulmonary sarcomatoid carcinoma; OC, ovarian cancer; LR, learning resource; HGSOC, high-grade serous OC; MMR, mismatch repair; CRC, colorectal cancer; PCA, principal component analysis; IHC, immunohistochemistry; pDGs, pediatric diffuse gliomas; aDGs, adult diffuse gliomas; ABY, affibody; TNBC, triple-negative breast cancer; MDSCs, myeloid-derived suppressor cells; ECM, extracellular matrix; mAbs, monoclonal antibodies; OS, osteosarcoma; RMS, rhabdomyosarcoma; ES, Ewing sarcoma; FLC, fibrolamellar carcinoma; sHCC, sarcomatoid HCC.

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References

[1] Mortezaee K, Majidpoor J and Najafi S. VISTA immune regulatory effects in bypassing cancer immunotherapy: updated. Life Sci 2022; 310: 121083.

[2] Chapoval AI, Ni J, Lau JS, Wilcox RA, Flies DB, Liu D, Dong H, Sica GL, Zhu G, Tamada K and Chen L. B7-H3: a costimulatory molecule for T cell activation and IFN-γ production. Nat Immunol 2001; 2: 269-274.

[3] Steinberger P, Majdic O, Derdak SV, Pfistershammer K, Kirchberger S, Klauser C, Zlabinger G, Pickl WF, Stöckl J and Knapp W. Molecular characterization of human 4Ig-B7-H3, a member of the B7 family with four ig-like domains. J Immunol 2004; 172: 2352-2359.

[4] Hashiguchi M, Kobori H, Ritprajak P, Kamimura Y, Kozono H and Azuma M. Triggering receptor expressed on myeloid cell-like transcript 2 (TLT-2) is a counter-receptor for B7-H3 and enhances T cell responses. Proc Natl Acad Sci 2008; 105: 10495-10500.

[5] Ungaro F, Garlatti V, Massimino L, Spinelli A, Carvello M, Sacchi M, Spanò S, Colasante G, Valassina N, Vetrano S, Malesci A, Peyrin-Biroulet L, Danese S and D'Alessio S. mTOR-dependent stimulation of IL20RA orchestrates immune cell trafficking through lymphatic endothelium in patients with Crohn's disease. Cells 2019; 8: 924.

[6] Sun X, Vale M, Leung E, Kanwar JR, Gupta R and Krissansen GW. Mouse B7-H3 induces antitumor immunity. Gene Ther 2003; 10: 1728-1734.

[7] Lim S, Liu H, Madeira da Silva L, Arora R, Liu Z, Phillips JB, Schmitt DC, Vu T, McClellan S, Lin Y, Lin W, Piazza GA, Fodstad O and Tan M. Immunoregulatory protein B7-H3 reprograms glucose metabolism in cancer cells by ROS-Mediated stabilization of HIF1α. Cancer Res 2016; 76: 2231-2242.

[8] Li M, Zhang G, Zhang X, Lv G, Wei X, Yuan H and Hou J. Overexpression of B7-H3 in CD14+ monocytes is associated with renal cell carcinoma progression. Med Oncol 2014; 31: 349.

[9] Jiang B, Liu F, Liu Z, Zhang T and Hua D. B7-H3 increases thymidylate synthase expression via the PI3k-Akt pathway. Tumour Biol 2016; 37: 9465-9472.

[10] Zhao X, Zhang GB, Gan WJ, Xiong F, Li Z, Zhao H, Zhu DM, Zhang B, Zhang XG and Li DC. Silencing of B7-H3 increases gemcitabine sensitivity by promoting apoptosis in pancreatic carcinoma. Oncol Lett 2013; 5: 805-812.

[11] Li Y, Yang X, Yao P, Shen W, Wu Y, Ye Z, Zhao K, Chen H, Cao J and Xing C. B7-H3 increases the radioresistance of gastric cancer cells through regulating baseline levels of cell autophagy. Am J Transl Res 2019; 11: 4438-4449.

[12] Akinleye A and Rasool Z. Immune checkpoint inhibitors of PD-L1 as cancer therapeutics. J Hematol Oncol 2019; 12: 92.

[13] Sun C, Mezzadra R and Schumacher TN. Regulation and function of the PD-L1 checkpoint. Immunity 2018; 48: 434-452.

[14] Li X, Shao C, Shi Y and Han W. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. J Hematol Oncol 2018; 11: 31.

[15] Cha JH, Chan LC, Li CW, Hsu JL and Hung MC. Mechanisms controlling PD-L1 expression in cancer. Mol Cell 2019; 76: 359-370.

[16] Sanmamed MF and Chen L. A paradigm shift in cancer immunotherapy: from enhancement to normalization. Cell 2018; 175: 313-326.

[17] Liu S, Liang J, Liu Z, Zhang C, Wang Y, Watson AH, Zhou C, Zhang F, Wu K, Zhang F, Lu Y and Wang X. The role of CD276 in cancers. Front Oncol 2021; 11: 654684.

[18] Melvin G, Sandhiya S and Subraja K. Belatacept: a worthy alternative to cyclosporine? J Pharmacol Pharmacother 2012; 3: 90-92.

[19] Butte MJ, Keir ME, Phamduy TB, Sharpe AH and Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007; 27: 111-122.

[20] Bhat S and Czuczman MS. Galiximab: a review. Expert Opin Biol Ther 2010; 10: 451-458.

[21] Czuczman MS, Thall A, Witzig TE, Vose JM, Younes A, Emmanouilides C, Miller TP, Moore JO, Leonard JP, Gordon LI, Sweetenham J, Alkuzweny B, Finucane DM and Leigh BR. Phase I/II study of galiximab, an anti-CD80 antibody, for relapsed or refractory follicular lymphoma. J Clin Oncol 2005; 23: 4390-4398.

[22] Xu W, Hiếu T, Malarkannan S and Wang L. The structure, expression, and multifaceted role of immune-checkpoint protein VISTA as a critical regulator of anti-tumor immunity, autoimmunity, and inflammation. Cell Mol Immunol 2018; 15: 438-446.

[23] Li Y, Lv C, Yu Y, Wu B, Zhang Y, Lang Q, Liang Z, Zhong C, Shi Y, Han S, Xu F and Tian Y. KIR3DL3-HHLA2 and TMIGD2-HHLA2 pathways: the dual role of HHLA2 in immune responses and its potential therapeutic approach for cancer immunotherapy. J Adv Res 2023; 47: 137-150.

[24] Rasic P, Jovanovic-Tucovic M, Jeremic M, Djuricic SM, Vasiljevic ZV, Milickovic M and Savic D. B7 homologue 3 as a prognostic biomarker and potential therapeutic target in gastrointestinal tumors. World J Gastrointest Oncol 2021; 13: 799-821.

[25] Wang C, Li Y, Jia L, Kim JK, Li J, Deng P, Zhang W, Krebsbach PH and Wang CY. CD276 expression enables squamous cell carcinoma stem cells to evade immune surveillance. Cell Stem Cell 2021; 28: 1597-1613, e1597.
[26] Liu HJ, Du H, Khabibullin D, Zarei M, Wei K, Freeman GJ, Kwiatkowski DJ and Henske EP. mTORC1 upregulates B7-H3/CD276 to inhibit antitumor T cells and drive tumor immune evasion. Nat Commun 2023; 14: 1214.
[27] Zhao S, Wang Y, Yang N, Mu M, Wu Z, Li H, Tang X, Zhong K, Zhang Z, Huang C, Cao T, Zheng M, Wang G, Nie C, Yang H, Guo G, Zhou L, Zheng X and Tong A. Genome-scale CRISPR-Cas9 screen reveals novel regulators of B7-H3 in tumor cells. J Immunother Cancer 2022; 10: e004875.
[28] Chen L, Yang QC, Li YC, Yang LL, Liu JF, Li H, Xiao Y, Bu LL, Zhang WF and Sun ZJ. Targeting CMTM6 suppresses stem cell-like properties and enhances antitumor immunity in head and neck squamous cell carcinoma. Cancer Immunol Res 2020; 8: 179-191.
[29] Ilyas SI, Wang J and El-Khoueiry AB. Liver cancer immunity. Hepatology 2021; 73 Suppl 1: 86-103.
[30] Murray PJ and Wynn TA. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol 2011; 11: 723-737.
[31] Balmer ML, Slack E, de Gottardi A, Lawson MA, Hapfelmeier S, Miele L, Grieco A, Van Vlierberghe H, Fahrner R, Patuto N, Bernsmeier C, Ronchi F, Wyss M, Stroka D, Dickgreber N, Heim MH, McCoy KD and Macpherson AJ. The liver may act as a firewall mediating mutualism between the host and its gut commensal microbiota. Sci Transl Med 2014; 6: 237ra66.
[32] Schmall A, Al-tamari HM, Herold S, Kampschulte M, Weigert A, Wietelmann A, Vipotnik N, Grimminger F, Seeger W, Pullamsetti SS and Savai R. Macrophage and cancer cell crosstalk via CCR2 and CX3CR1 is a fundamental mechanism driving lung cancer. Am J Respir Crit Care Med 2015; 191: 437-447.
[33] Ruffell B and Coussens LM. Macrophages and therapeutic resistance in cancer. Cancer Cell 2015; 27: 462-472.
[34] Krenkel O and Tacke F. Liver macrophages in tissue homeostasis and disease. Nat Rev Immunol 2017; 17: 306-321.
[35] Wynn TA, Chawla A and Pollard JW. Macrophage biology in development, homeostasis and disease. Nature 2013; 496: 445-455.
[36] Guillot A and Tacke F. Liver macrophages: old dogmas and new insights. Hepatol Commun 2019; 3: 730-743.
[37] Qian BZ and Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell 2010; 141: 39-51.
[38] Mantovani A, Marchesi F, Malesci A, Laghi L and Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017; 14: 399-416.
[39] Feng M, Jiang W, Kim BYS, Zhang CC, Fu YX and Weissman IL. Phagocytosis checkpoints as new targets for cancer immunotherapy. Nat Rev Cancer 2019; 19: 568-586.
[40] Sharma N, Atolagbe OT, Ge Z and Allison JP. LILRB4 suppresses immunity in solid tumors and is a potential target for immunotherapy. J Exp Med 2021; 218: e20201811.
[41] Lin EY, Nguyen AV, Russell RG and Pollard JW. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. J Exp Med 2001; 193: 727-740.
[42] Gerhard GM, Bill R, Messemaker M, Klein AM and Pittet MJ. Tumor-infiltrating dendritic cell states are conserved across solid human cancers. J Exp Med 2021; 218: e20200264.
[43] Andreatta M, Corria-Osorio J, Müller S, Cubas R, Coukos G and Carmona SJ. Interpretation of T cell states from single-cell transcriptomics data using reference atlases. Nat Commun 2021; 12: 2965.
[44] Hughes R, Qian BZ, Rowan C, Muthana M, Keklikoglou I, Olson OC, Tazzyman S, Danson S, Addison C, Clemons M, Gonzalez-Angulo AM, Joyce JA, De Palma M, Pollard JW and Lewis CE. Perivascular M2 macrophages stimulate tumor relapse after chemotherapy. Cancer Res 2015; 75: 3479-3491.
[45] Movahedi K, Laoui D, Gysemans C, Baeten M, Stangé G, Van den Bossche J, Mack M, Pipeleers D, In't Veld P, De Baetselier P and Van Ginderachter JA. Different tumor microenvironments contain functionally distinct subsets of macrophages derived from Ly6C(high) monocytes. Cancer Res 2010; 70: 5728-5739.
[46] Zheng W and Pollard JW. Inhibiting macrophage PI3Kγ to enhance immunotherapy. Cell Res 2016; 26: 1267-1268.
[47] Durlanik S, Fundel-Clemens K, Viollet C, Huber HJ, Lenter M, Kitt K and Pflanz S. CD276 is an important player in macrophage recruitment into the tumor and an upstream regulator for PAI-1. Sci Rep 2021; 11: 14849.
[48] Wang X, Wang J, Zhao J, Wang H, Chen J and Wu J. HMGA2 facilitates colorectal cancer progression via STAT3-mediated tumor-associated macrophage recruitment. Theranostics 2022; 12: 963-975.
[49] Zhong Q, Fang Y, Lai Q, Wang S, He C, Li A, Liu S and Yan Q. CPEB3 inhibits epithelial-mesenchymal transition by disrupting the crosstalk between colorectal cancer cells and tumor-associated macrophages via IL-6R/STAT3 signaling. J Exp Clin Cancer Res 2020; 39: 132.

[50] Yang C, Dou R, Wei C, Liu K, Shi D, Zhang C, Liu Q, Wang S and Xiong B. Tumor-derived exosomal microRNA-106b-5p activates EMT-cancer cell and M2-subtype TAM interaction to facilitate CRC metastasis. Mol Ther 2021; 29: 2088-2107.

[51] Shi W, Wang Y, Zhao Y, Kim JJ, Li H, Meng C, Chen F, Zhang J, Mak DH, Van V, Leo J, St Croix B, Aparicio A and Zhao D. Immune checkpoint B7-H3 is a therapeutic vulnerability in prostate cancer harboring PTEN and TP53 deficiencies. Sci Transl Med 2023; 15: eadf6724.

[52] Suh WK, Gajewska BU, Okada H, Gronski MA, Bertram EM, Dawicki W, Duncan GS, Bukczynski J, Plyte S, Elia A, Wakeham A, Itie A, Chung S, Da Costa J, Arya S, Horan T, Campbell P, Gaida K, Ohashi PS, Watts TH, Yoshinaga SK, Bray MR, Jordana M and Mak TW. The B7 family member B7-H3 preferentially down-regulates T helper type 1-mediated immune responses. Nat Immunol 2003; 4: 899-906.

[53] Nagashima O, Harada N, Usui Y, Yamazaki T, Yagita H, Okumura K, Takahashi K and Akiba H. B7-H3 contributes to the development of pathogenic th2 cells in a murine model of asthma. J Immunol 2008; 181: 4062-4071.

[54] Biswas SK and Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 2010; 11: 889-896.

[55] Liu G, Ma H, Qiu L, Li L, Cao Y, Ma J and Zhao Y. Phenotypic and functional switch of macrophages induced by regulatory CD4+CD25+ T cells in mice. Immunol Cell Biol 2011; 89: 130-142.

[56] Ohashi T, Aoki M, Tomita H, Akazawa T, Sato K, Kuze B, Mizuta K, Hara A, Nagaoka H, Inoue N and Ito Y. M2-like macrophage polarization in high lactic acid-producing head and neck cancer. Cancer Sci 2017; 108: 1128-1134.

[57] John P, Pulanco MC, Galbo PM Jr, Wei Y, Ohaegbulam KC, Zheng D and Zang X. The immune checkpoint B7x expands tumor-infiltrating Tregs and promotes resistance to anti-CTLA-4 therapy. Nat Commun 2022; 13: 2506.

[58] Liu J, Yang S, Cao B, Zhou G, Zhang F, Wang Y, Wang R, Zhu L, Meng Y, Hu C, Liang H, Lin X, Zhu K, Chen G, Luo KQ, Di L and Zhao Q. Targeting B7-H3 via chimeric antigen receptor T cells and bispecific killer cell engagers augments antitumor response of cytotoxic lymphocytes. J Hematol Oncol 2021; 14: 21.

[59] Wang F, Cali Daylan AE, Deng L, Yang J, Sharma J, Su C, Li S, Zang X, Halmos B, Borczuk A and Cheng H. Heterogeneous expression of PD-L1, B7x, B7-H3, and HHLA2 in pulmonary sarcomatoid carcinoma and the related regulatory signaling pathways. Cancers (Basel) 2023; 15: 3372.

[60] Yim J, Koh J, Kim S, Song SG, Ahn HK, Kim YA, Jeon YK and Chung DH. Effects of B7-H3 expression on tumour-infiltrating immune cells and clinicopathological characteristics in non-small-cell lung cancer. Eur J Cancer 2020; 133: 74-85.

[61] Parra ER, Ferrufino-Schmidt MC, Tamegnon A, Zhang J, Solis L, Jiang M, Ibarguen H, Haymaker C, Lee JJ, Bernatchez C and Wistuba II. Immuno-profiling and cellular spatial analysis using five immune oncology multiplex immunofluorescence panels for paraffin tumor tissue. Sci Rep 2021; 11: 8511.

[62] Ding J, Sun Y, Sulaiman Z, Li C, Cheng Z and Liu S. Comprehensive analysis reveals distinct immunological and prognostic characteristics of CD276/B7-H3 in pan-cancer. Int J Gen Med 2023; 16: 367-391.

[63] Miyamoto T, Murakami R, Hamanishi J, Tanigaki K, Hosoe Y, Mise N, Takamatsu S, Mise Y, Ukita M, Taki M, Yamanoi K, Horikawa N, Abiko K, Yamaguchi K, Baba T, Matsumura N and Mandai M. B7-H3 suppresses antitumor immunity via the CCL2-CCR2-M2 macrophage axis and contributes to ovarian cancer progression. Cancer Immuno Res 2022; 10: 56-69.

[64] Du H, Hirabayashi K, Ahn S, Kren NP, Montgomery SA, Wang X, Tiruthani K, Mirlekar B, Michaud D, Greene K, Herrera SG, Xu Y, Sun C, Chen Y, Ma X, Ferrone CR, Pylayeva-Gupta Y, Yeh JJ, Liu R, Savoldo B, Ferrone S and Dotti G. Antitumor responses in the absence of toxicity in solid tumors by targeting B7-H3 via chimeric antigen receptor T cells. Cancer Cell 2019; 35: 221-237, e228.

[65] Mielcarska S, Dawidowicz M, Kula A, Kiczmer P, Skiba H, Krygier M, Chrabańska M, Piecuch J, Szrot M, Ochman B, Robotycka J, Strzałkowska B, Czuba Z, Waniczek D and Świętochowska E. B7H3 role in reshaping immunosuppressive landscape in MSI and MSS colorectal cancer tumours. Cancers (Basel) 2023; 15: 3136.

[66] Wang X, Gao M, Ye J, Jiang Q, Yang Q, Zhang C, Wang S, Zhang J, Wang L, Wu J, Zhan H, Hou X, Han D and Zhao S. An immune gene-related five-incRNA signature for to predict glioma prognosis. Front Genet 2020; 11: 612037.

[67] Zhang L, Zhang B, Dou Z, Wu J, Iranmanesh Y, Jiang B, Sun C and Zhang J. Immune checkpoint-associated locations of diffuse gliomas comparing pediatric with adult patients based on voxel-wise analysis. Front Immunol 2021; 12: 582594.

[68] Bam R, Lown PS, Stern LA, Sharma K, Wilson KE, Bean GR, Lutz AM, Paulmurugan R, Hackel BJ, Dahl J and Abou-Elkacem L. Efficacy of affibody-based ultrasound molecular imaging of

vascular B7-H3 for breast cancer detection. Clin Cancer Res 2020; 26: 2140-2150.
[69] Cheng N, Bei Y, Song Y, Zhang W, Xu L, Zhang W, Yang N, Bai X, Shu Y and Shen P. B7-H3 augments the pro-angiogenic function of tumor-associated macrophages and acts as a novel adjuvant target for triple-negative breast cancer therapy. Biochem Pharmacol 2021; 183: 114298.
[70] Hagelstein I, Engel M, Hinterleitner C, Manz T, Märklin M, Jung G, Salih HR and Zekri L. B7-H3-targeting Fc-optimized antibody for induction of NK cell reactivity against sarcoma. Front Immunol 2022; 13: 1002898.
[71] Wang L, Zhang Q, Chen W, Shan B, Ding Y, Zhang G, Cao N, Liu L and Zhang Y. B7-H3 is Overexpressed in patients suffering osteosarcoma and associated with tumor aggressiveness and metastasis. PLoS One 2013; 8: e70689.
[72] Murty S, Labanieh L, Murty T, Gowrishankar G, Haywood T, Alam IS, Beinat C, Robinson E, Aalipour A, Klysz DD, Cochran JR, Majzner RG, Mackall CL and Gambhir SS. PET reporter gene imaging and ganciclovir-mediated ablation of chimeric antigen receptor T cells in solid tumors. Cancer Res 2020; 80: 4731-4740.
[73] Pahl JH, Kwappenberg KM, Varypataki EM, Santos SJ, Kuijjer ML, Mohamed S, Wijnen JT, van Tol MJ, Cleton-Jansen AM, Egeler RM, Jiskoot W, Lankester AC and Schilham MW. Macrophages inhibit human osteosarcoma cell growth after activation with the bacterial cell wall derivative liposomal muramyl tripeptide in combination with interferon-γ. J Exp Clin Cancer Res 2014; 33: 27.
[74] Timpanaro A, Piccand C, Uldry AC, Bode PK, Dzhumashev D, Sala R, Heller M, Rössler J and Bernasconi M. Surfaceome profiling of cell Lines and patient-derived xenografts confirm FGFR4, NCAM1, CD276, and highlight AGRL2, JAM3, and L1CAM as surface targets for rhabdomyosarcoma. Int J Mol Sci 2023; 24: 2601.
[75] Lavoie RR, Gargollo PC, Ahmed ME, Kim Y, Baer E, Phelps DA, Charlesworth CM, Madden BJ, Wang L, Houghton PJ, Cheville J, Dong H, Granberg CF and Lucien F. Surfaceome profiling of rhabdomyosarcoma reveals B7-H3 as a mediator of immune evasion. Cancers (Basel) 2021; 13: 4528.
[76] Timpanaro A, Piccand C, Dzhumashev D, Anton-Joseph S, Robbi A, Moser J, Rössler J and Bernasconi M. CD276-CAR T cells and Dual-CAR T cells targeting CD276/FGFR4 promote rhabdomyosarcoma clearance in orthotopic mouse models. J Exp Clin Cancer Res 2023; 42: 293.
[77] Zhang S, Black RG, Kohli K, Hayes BJ, Miller C, Koehne A, Schroeder BA, Abrams K, Schulte BC, Alexiev BA, Heimberger AB, Zhang A, Jing W, Ng JCK, Shinglot H, Seguin B, Salter AI, Riddell SR, Jensen MC, Gottschalk S, Moore PF, Torok-Storb B and Pollack SM. B7-H3 specific CAR T cells for the naturally occurring, spontaneous canine sarcoma model. Mol Cancer Ther 2022; 21: 999-1009.
[78] Kendsersky NM, Lindsay J, Kolb EA, Smith MA, Teicher BA, Erickson SW, Earley EJ, Mosse YP, Martinez D, Pogoriler J, Krytska K, Patel K, Groff D, Tsang M, Ghilu S, Wang Y, Seaman S, Feng Y, Croix BS, Gorlick R, Kurmasheva R, Houghton PJ and Maris JM. The B7-H3-targeting antibody-drug conjugate m276-SL-PBD is potently effective against pediatric cancer preclinical solid tumor models. Clin Cancer Res 2021; 27: 2938-2946.
[79] Ren EH, Deng YJ, Yuan WH, Zhang GZ, Wu ZL, Li CY and Xie QQ. An immune-related long noncoding RNA signature to predict the prognosis of ewing's sarcoma based on a machine learning iterative lasso regression. Front Cell Dev Biol 2021; 9: 651593.
[80] Thakur MD, Franz CJ, Brennan L, Brouwer-Visser J, Tam R, Korski K, Koeppen H, Ziai J, Babitzki G, Ranchere-Vince D, Vasiljevic A, Dijoud F, Marec-Bérard P, Rochet I, Cannarile MA and Marabelle A. Immune contexture of paediatric cancers. Eur J Cancer 2022; 170: 179-193.
[81] Qi L, Jiang K, Zhao FF, Ren P and Wang L. Identification of therapeutic targets and prognostic biomarkers in the siglec family of genes in tumor immune microenvironment of sarcoma. Sci Rep 2024; 14: 577.
[82] Kim AK, Gani F, Layman AJ, Besharati S, Zhu Q, Succaria F, Engle EL, Bhaijee F, Goggins MB, Llosa NJ, Pawlik TM, Yarchoan M, Jaffee EM, Simons HC, Taube JM and Anders RA. Multiple immune-suppressive mechanisms in fibrolamellar carcinoma. Cancer Immunol Res 2019; 7: 805-812.
[83] Luo C, Xin H, Yin D, Zhao T, Hu Z, Zhou Z, Sun R, Yao N, Sun Q, Fan J, Huang X, Zhou J and Zhou S. Characterization of immune infiltration in sarcomatoid hepatocellular carcinoma. Aging (Albany NY) 2021; 13: 15126-15138.
[84] Lei X, Ou Z, Yang Z, Zhong J, Zhu Y, Tian J, Wu J, Deng H, Lin X, Peng Y, Li B, He L, Tu Z, Chen W, Li Q, Liu N, Zhang H, Wang Z, Fang Z, Yamada T, Lv X, Tian T, Pan G, Wu F, Xiao L, Zhang L, Cai T, Wang X, Tannous BA, Li J, Kontos F, Ferrone S and Fan S. A pan-histone deacetylase inhibitor enhances the antitumor activity of B7-H3-specific CAR T cells in solid tumors. Clin Cancer Res 2021; 27: 3757-3771.

Supplementary Table 1. Functions of B7-H3 in various tumors

Tumor	B7-H3 Expression	TAMs Relevance	Effects on Patients	Reference
NSCLC	76%	$CD3^-CD45^+$ macrophages downregulation macrophages interaction with malignant cells	tumor-infiltrated cytotoxic lymphocytes and pDCs upregulation immune-regulatory function poor prognosis increased tumor recurrence risk	[58, 60, 61]
OC	high mRNA levels	high expression on M2 or $MACRO^+$ macrophages macrophage clusters anchoring M2 macrophages polarization and migration	tumor progression via CCL2-CCR2-M2 macrophage axis	[62, 63]
CRC	higher expression compared with normal tissues	positive correlation with factor 1 with M2 macrophages support for an immunosuppressive TIME induced by M2 macrophages improvement in macrophage regulation	tumor progression via an immunosuppressive TIME	[65]
Glioma	97%	strong correlation with B7-H3 levels	influence on anatomical location and assistance for malignant behavior association with Glioma risk correlation with prognosis	[66, 67]
BC	over 70%	aggravation of immunosuppressive TIME, increased tumor angiogenesis and mediation to ECM degradation in $B7\text{-}H3_{high}$ TAMs	a significant pro-metastatic function assistance for BC detection, screening and diagnosis	[47, 68, 69]
OS	91.8%	association with IFN-γ which is associated with TAMs	negative correlation with density of infiltrating $CD8^+$ T lymphocytes association with tumor Ennecking stage/metastasis status	[71]
RMS	known target	positive correlation with M1 macrophages negative correlation with M2 macrophages	association with low density of $CD8^+$ T cells abundance of NK cells positive correlation with neutrophils negative correlation with monocytes	[74, 75]
ES	high expression, lower than OS and RMS	NA	NA	[78]
FLC	40%	91% percentages with $B7\text{-}H3^+$ TAMs	significant correlation with high $CD8^+$ T cells	[82]
sHCC	higher expression compared with peritumoral tissues	NA	NA	[83]

BC, breast cancer; CRC, colorectal cancer; ECM, extracellular matrix; CCL2, Chemokine (C-C motif) ligand 2; CCR2, chemokine (C-C motif) receptor 2; ES, Ewing sarcoma; FLC, fibrolamellar carcinoma; NA, not available; NK, natural killer; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, osteosarcoma; pDCs, plasmacytoid endritic cells; RMS, rhabdomyosarcoma; sHCC, sarcomatoid hepatocellular carcinoma; TAMs, tumor-associated macrophages; TIME, tumor immune microenvironment.