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Review Article

B7-H3 role in the immune landscape of cancer

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Abstract: The field of immunotherapy is a continually expanding niche in cancer biology research. In the last two decades, there has been significant progress in identifying better targets and creating more specific agents for therapy in the field. B7-H3 (CD276) is an immune checkpoint from the B7 family of molecules, many of whom interact with known checkpoint markers including CTLA4, PD-1, and CD28. This is an exciting molecule that is overexpressed in many cancers, although the receptor of B7-H3 has not been characterized. Initially, B7-H3 was thought to co-stimulate the immune response, but recent studies have shown that it has a co-inhibitory role on T-cells, contributing to tumor cell immune evasion. Therefore, its overexpression has been linked to poor prognosis in human patients and to invasive and metastatic potential of tumors in *in vitro* models. Moreover, recent evidence has shown that B7-H3 influences cancer progression beyond the immune regulatory roles. In this review, we aim to characterize the roles of B7-H3 in different cancers, its relationship with other immune checkpoints, and its non-immunological function in cancer progression. Targeting B7-H3 in cancer treatment can reduce cell proliferation, progression, and metastasis, which may ultimately lead to improved therapeutic options and better clinical outcomes.

Keywords: B7-H3 (CD276), CTLA4, PD-1, immune checkpoints, cancer, invasion, migration, angiogenesis

Introduction

The typical protective mechanism of the immune system involves a set of complex molecular interactions modulated by immune checkpoints that mechanistically inhibit or excite host immunophenotypic cells to kill foreign agents while protecting native cells [1, 2]. When these checkpoints receive aberrant signaling, they have the potential to allow for unchecked proliferation, invasion and eventually metastasis into non-native tissue, comprising the hallmarks of malignant neoplastic growth. Fate-determining interactions largely occur on the surface of adjacent immunophenotypic cells [3]. To date, 371 different surface glycoproteins have been identified [4] and are named in order of discovery as clusters of differentiation (CDs). The various CDs play different roles in the immunoregulatory processes that occur in the human body. This review focuses on one such CD, commonly known as B7-H3 (CD276), a membrane protein that is encoded for on chromosome 15. It is a major glycoprotein expressed on antigen-presenting cells (APC) that most literature considers to be involved in the inhibition of T-cells [2, 3, 5], though when initially characterized by Chapoval *et al*. (2001), it was found to stimulate the T-cell response and IFN-γ production [6]. Due to its role in immune evasion, B7-H3 has become an interesting target for new immunotherapeutic treatments. Even more intriguing, studies have shown that B7-H3 plays a role in cancer progression outside of immune evasion, including invasion and migration, angiogenesis, as well as gene regulation via epigenetic modifiers. These varied roles make B7-H3 a prime target for novel immunotherapeutic strategies. In this review, we will delineate the roles of B7-H3 in the various immune checkpoints, discuss its roles generally in carcinogenesis, and finally, discuss the work that has been done so far in a range of cancers and characterize its role in the aberrant modulation of cancer progression.

B7-H3's relationship with other immune checkpoints

When the scientific community discusses neoplasia, the typical 5 hallmarks of neoplasia are invasive abilities, metastatic potential, angiogenic properties, unchecked proliferation, and finally, evasion of apoptosis and immune checkpoints. This latter characteristic relates most to the goal of immunotherapy, and it is therefore important to discuss the well-characterized immune checkpoints prior to looking at how B7-H3 plays into these checkpoints and how it ultimately contributes to neoplastic growth.

B7-H3 and programmed cell death-1 checkpoint

As we have previously mentioned, immune evasion is a crucial adaptation for the progression of cancer, including that of metastasis [7]. Programmed cell death-1 (PD-1) is an immune inhibitory receptor that was first reported in 1992 [8]. PD-1, also known as CD279, is a receptor expressed on the surface of T-cells and B-cells. This receptor is a protein encoded by the PDCD1 gene, located on chromosome 2. PD-1 is a member of the CD28 superfamily, which delivers inhibitory signals once it interacts with its ligand, and is important in the regulation of T-cell activity. This regulatory receptor is not expressed on the surface of resting T-cells, but T-cell activation induces the expression of this surface receptor [9]. PD-1 interacts with two ligands, PD-L1 (B7-H1) or PD-L2 (B7-DC), which exert a range of roles in the immunoregulation of T-cells [10]. PD-1 is mainly involved in regulating effector T-cell activity within tissues and tumors. The activation of PD-1 by its ligand is responsible for downregulating activity of T-cells [11]. PD-1 knockout experiments have shown the development of lupus-like autoimmune complications in mice, highlighting the crucial role PD-1 plays in immunoregulation [12].

The role of PD-1 as an immune-checkpoint receptor has also been linked to the ability of tumor to escape the immune system. This has made PD-1 a promising target in immunotherapy. Understanding of the PD-1/PD-L1/PD-L2 pathway has emerged as an encouraging target in immunotherapy for cancer. The blockade of PD-1 is believed to enhance the activity of the effector T-cell in the microenvironment of tissues. As an adaptive modification, cancer cells have been found to express PD-L1, which allows them to escape immune detection and destruction. Interference with PD-1 or its ligands increases antitumor immunity. As a result, anti-PD-1 and anti-PD-L2 human monoclonal antibodies are under clinical development. Refractory solid tumors like melanoma, colorectal cancer, and renal cell carcinoma have been found to have positive clinical response to treatment with nivolumab, an IgG4 monoclonal antibody against PD-1 [13]. Although PD-1 is just one of a small list of immune checkpoint to be identified as a high value target for immunotherapy, the need for the identification of specific immune checkpoint target is promising for the treatment of cancer. Moreover, members of the same family as PD-1 and its ligand have a similar influence on tumor growth and microenvironment modification. B7-H3 is also a member of the B7/CD28 superfamily. B7-H3 and PD-L1 induce an inhibitory effect on T-cells and change their microenvironment to escape the anti-tumor immune response. Initially, B7-H3 was described as a co-stimulatory molecule and inducer of IFN-γ [6]. However, recent studies have made a strong case for B7-H3 as an immune inhibitory molecule, as B7-H3 was found to inhibit T-cell proliferation [14-16]. The molecule has also been linked to the decrease in secretion of IFN-γ, TNF-α, and other cytokines, which allows for immune escape [17]. The similarities between B7-H3 and PD-L1 have given researchers reason to target B7-H3 in novel immunotherapeutic treatments. Indeed, 8H9, an antibody developed to inhibit B7-H3 function, was used in a clinical trial for treating patients with recurrent metastatic neuroblastoma showing positive results [18]. 8H9 is also currently being investigated in a Phase I clinical trial involving desmoplastic small round cell tumors found in the peritoneum [19].

B7-H3 and the CTLA4 checkpoint

Another molecule essential to immune regulation is CTLA4, also known as CD152. CTLA4 is an intracellular glycoprotein that acts as a functional suppressor of T-cell response [20]. In normal T-cell activation, CD80 or CD86 on the dendritic APC bind CD28 on the adjacent T-cell, thus activating the T-cell and resulting in T-cell

cytokine production. This interaction mediates various acute and chronic inflammatory processes in the body, including atherosclerosis [21], autoimmune disorders [22], and cancer [23]. Despite the fact that activation of the T-cell in part requires CD28-CD80/86 interactions, T-cells also express a CD28 homolog that binds the APC's CD80 and CD86 with a much higher affinity. This molecule is known as CTLA4, and it is largely responsible for the attenuation of T-cell activation that cause the APC to bind to it in lieu of CD28 [24]. Some studies suggest that the mechanism of CTLA4's inhibition of the T-cell response additionally includes a decreased contact time between the T-cell and its complementary APC, thus decreasing the time during which the stimulatory CD28-CD80/86 interaction can potentially occur [25].

Normally, B7-H3 is expressed on APC; its function is to further inhibit the T-cell activation. Thus, B7-H3 and CTLA4 may act synergistically with one another, just as B7-H3 does in the PD-1 pathway. Leitner *et al*. (2009) characterizes B7-H3 as a potent inhibitor of the T-cell response via IL-2 suppression, which can then be rescued by the addition of exogenous IL-2, demonstrating B7-H3 as an upstream effector of IL-2 release [26]. Additionally, B7-H3 is expressed largely on tumor and tumor-associated cells despite its more minor role in inflammatory and immune homeostatic processes, whereas CTLA4 is found in normal tissue, normal immune cells, and tumor cells [27]. Because of the prevalence among cancer types but not healthy cells, B7-H3 has become an increasingly enticing immunotherapeutic target. Before delving into the work that has been carried out with this molecule in specific tumor types, a discussion of its roles in cancer needs to be adequately discussed.

Function of B7-H3 in cancer progression

B7-H3 in migration and invasion

It may be apparent from our above discussions that B7-H3 as an immune regulator has attracted most of the attention in cancer investigations. However, this molecule has recently been linked to other aspects of cancer progression. The roles of B7-H3 in non-immunological systems are important to study for the purpose of knowing the full scale of its function in cancer, as its roles in this capacity have been recently linked to the progression of many cancers apart from the aforementioned immune checkpoint functions. *In vitro* studies have found that reducing the expression of B7-H3 decreases cell adhesion to fibronectin and reduced migration and matrigel invasion abilities [28]. Recent studies have also implicated B7-H3 in contributing to the metastatic potential of cancer cells. One study examined B7-H3 in melanoma cells. Silencing of B7-H3 using shRNA reduced the matrigel invasion capacity of these cells, and prolonged symptom-free survival of mice and rats injected with these cells [29]. The authors also showed that B7-H3 silencing reduced the expression of metastasis-associated proteins such as matrix metalloproteinase (MMP)-2, signal transducer and activator of transcription 3 (STAT3), and the level of secreted interleukin-8 (IL-8) [29]. Matrix Metalloproteinase-2 (MMP-2) was also found to be downregulated in B7-H3 knockdown cells [30]. MMP-2 breaks down extracellular matrix, which allows cells to migrate from the primary tumor to the surrounding environment. In addition, silencing of B7-H3 in MDA-MB-435 and FEMX-I cells reduced STAT3 phosphorylation level, which is interesting because of STAT3 importance in cell signaling pathways that are typically linked with metastasis via induction of MMP-2 expression [30]. An additional mechanism proposed by Kang et al. suggests that B7-H3 also influences liver cancer aggressiveness and invasive abilities through the JAK3/STAT3/SLUG signaling pathway [31]. Here, the relationship between B7-H3 and MMP2 was again observed. Next, the expression of E-cadherin was significantly increased in B7-H3 knockdown of hepatocellular carcinoma samples, a property lost in cancers that undergo epithelial-mesenchymal transition (EMT). B7-H3 plays a key role in EMT, which ultimately increases the metastatic abilities of hepatocellular carcinoma. Moreover, STAT3 was also found to induce NF-κB activity in tumors [32]. NF-κB influences the expression of IL-8, VEGF, and MMPs in the tumor microenvironment, again related to inflammatory, angiogenic, and metastatic properties of the cancer [33, 34]. Xie *et al*. links B7-H3 with an increase in NF-κB activity, which stimulates *in vitro* and *in vivo* invasion of pancreatic cancer cells [35].

As an additional note, exosomes are membranous vesicles released by cancer cells that are known to promote cancer growth and increase tumor invasion and migration [36]. Marimpietri *et al*. analyzed exosomes derived from neuroblastoma cell lines. They found a variety of molecules associated with cancer cell proliferation and progression, including cytoskeleton-related proteins, heat shock protein, fibronectin, as well as immune checkpoints like CD133, CD147, and B7-H3 [36]. These observations suggest that B7-H3 likely plays a role in tumor dissemination via exosomal activity and cell-cell interactions, which promotes cancer phenotypes.

B7-H3 in angiogenesis

For cancer cells to proliferate, a stable source of nutrients and oxygen is essential. Blood vessels are necessary for transportation of these nutrients to the tumor microenvironment. Therefore, tumor angiogenesis has been described as another one of the hallmarks of cancer. The ability to manipulate blood supply is essential for tumors to expand beyond a normal size that cannot be supported by the normal blood supply [37]. Targeting this mechanism may reduce tumor progression. The ability of tumors to generate new blood vessels was confirmed in glioblastoma models [38]. Moreover, tumor reduction and degeneration was observed by selectively targeting endothelial cells generated by tumor stem cells [39]. This confirms that angiogenesis serves as a target of interest for cancer therapy. Recently, B7-H3 has been linked to angiogenesis in cancer. Multiple studies have shown the presence of B7-H3 in tumor endothelial cells. A recent study detected B7-H3 in kidney tumor vasculature [40]. This is consistent with previous reports in which B7-H3 was found in the endothelium of colon, lung, and breast cancers [41]. This protein was present only in pathological angiogenesis and did not play a role in physiological vascular development. In addition to being found in the tumor vasculature, B7-H3 has been found to influence the cancer microenvironment as soluble B7-H3 (sB7-H3). A recent study published on B7-H3 in pancreatic cells showed that cells could release sB7-H3 to the extracellular medium. ELISA analysis showed an increase in sB7-H3 in the supernatant of pancreatic cells cultures. The same study exposed pancreatic carcinoma cells to sB7-H3 [35]. This exposure lead to a significant increase in the migration and invasion of these cells measured using fluorescence-based scratch wound healing assay. B7-H3 also leads to an increase in NF-κB activity. This up-regulation in the activation of NF-κB was mediated through a TLR4-dependent mechanism. This pathway leads to a significant increase in VEGF and IL-8 expression. The increase of VEGF and IL-8 in cancer stimulates tumor invasion and angiogenesis [42]. Therefore, understanding the role of B7-H3 in angiogenesis is of significant interest. This knowledge may result in agents that target B7-H3 in different aspects of cancer simultaneously, resulting in potentially improved therapeutic efficacy and better prognosis.

Role of B7-H3 in different cancers

Now that we have generally covered how B7-H3 functions at a mechanistic level in cancer, we can discuss the work that has been carried out in *in vivo* and *in vitro* models of specific carcinomas. B7-H3 has been studied in several solid neoplasms, and its presence has been correlated with worse prognosis and increased potential to metastasize. B7-H3's ability to confer enhanced invasive and migratory properties has been further studied in *in vitro* cancer models and will be highlighted below.

B7-H3 in Non-small-cell lung cancer

B7-H3 has been studied in non-small cell lung cancer. Combined, non-small cell and small cell lung cancers are the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) is responsible for the majority of new cases of lung cancer every year. Overall, less than 20% of patients diagnosed with NSCLC survive past the 5-year mark, a significantly poor prognosis despite expansion of our current knowledge of the disease [43, 44]. This class of lung cancer is known for its insensitivity to chemotherapy and radiation therapy. Many studies have tried to identify molecules in this class of lung cancers that can potentially serve as targets of anti-neoplastic treatments. One such study found B7-H3 expression at the transcriptional and translational levels across 6 different non-small cell lung cancer (NSCLC) cell lines [45]. In NSCLC, there was a positive correlation in the expression between B7-H1

(CD80), and B7-H3 [46]. In the same study, B7-H1/B7-H3 expression was found to be associated with NSCLC lymph node metastasis and advanced TNM stage compared to those without metastasis. This study found that B7-H3 has an inhibitory effect on the immune system in NSCLC. Another study analyzed cell lines and tumors from 70 different patients, and found B7-H3 expression at the transcriptional and translational level. This study also found the overexpression of this molecule to have a significant positive correlation with lymph node metastasis. The study suggested that B7-H3 contributes to suppression of the normal immune response, which allows the progression of cancer in NSCLC patients. In another study using 110 NSCLC tumor patient tissue samples, it was observed that high B7-H3 expression was associated with high tumor grade and shorter overall survival [47]. The study also found that B7-H3 expression levels correlated with heightened regulatory T-cell (Tregs) levels across the tumor samples, indicating a potential relationship between B7-H3 and Treg inhibition of T-cell activity [48]. Together, these studies point to the presence of B7-H3 in NSCLC as a prognostic marker whose overexpression contributes to the ability of these malignant neoplasms to progress and metastasize.

B7-H3 in breast cancer

Additionally, B7-H3 has been studied in breast cancer, the most frequently diagnosed cancer in women worldwide [49], and the second deadliest cancer in the United States. Immunologic investigation revealed the expression of B7-H3 was present in primary breast cancer. A recent study looked at American Joint Committee on Cancer stage I to III primary breast cancers and normal breast specimens, noting the expression of B7-H3 in 32 of 82 primary breast tumors [50]. This study concluded that B7-H3 expression in primary tumors had a significant correlation with increase tumor size and lymphovascular invasion compared to normal breast tissue. In another recent publication, the authors proposed B7-H3 as a potential biomarker for breast cancer detection. Using immunostaining, B7-H3 expression was present in over 80% of patient samples, whereas less than 15% of normal breast tissue showed positive expression for the marker [51]. Additionally, the authors were able to use B7-H3 as a target marker for antibody-mediated detection using ultrasound technology. In continuity with the previously conducted immunohistochemistry, presence of B7-H3 was significantly higher in breast cancer tissue compared to normal breast tissue in the ultrasound study [51]. Thus, the case for B7-H3 as a marker in many diverse cancer environments, including that of breast cancer, continues to build.

B7-H3 in prostate cancer

Prostate cancer research has also focused its interests on B7-H3. Yuan et al. silenced B7-H3 via siRNA in an *in vitro* prostate cancer resection-resistant metastatic disease [52]. Interestingly, the authors identified a potential upstream regulator of B7-H3, NR3C4, an androgen receptor [52]. In conclusion, B7-H3 knockdown studies in prostate cancer were observed to reduce the cells' ability to adhere to fibronectin, migrate and invade as effectively, when compared to control prostate cancer cells [53]. Furthermore, in an additional study profiling 2781 prostate human patient samples, the authors found high B7-H3 expression positively correlated with high tumor grade and ileitis, and that it may be controlled by upstream molecules including NR3C4.

B7-H3 in renal cell carcinoma

B7-H3 has additionally been studied in renal cell carcinoma (RCC). RCCs typically originate in the renal cortex and constitute the majority of primary kidney cancers [54]. Unfortunately, RRCs do not become symptomatic until the disease is at an advanced stage, with metastasis at presentation in a significant number of patients [55]. The expression of B7-H3 was found to be expressed in both tumor mesenchyme and supporting vasculature in clear cell renal cell carcinomas [56]. Tumors from 743 patients treated for clear cell renal cell carcinoma were studied and 95% of the tumor specimens were found to be B7-H3-positive [56]. An interesting component of this study that was not seen (or perhaps looked for) in the studies on other carcinomas is that 17% of the tumor vasculature studies in clear cell RCC also expressed the molecule. Similarly, to the other cancer types, however, the expression of B7-H3 in the RCC patients was associated with significantly higher mortality risk compared to those

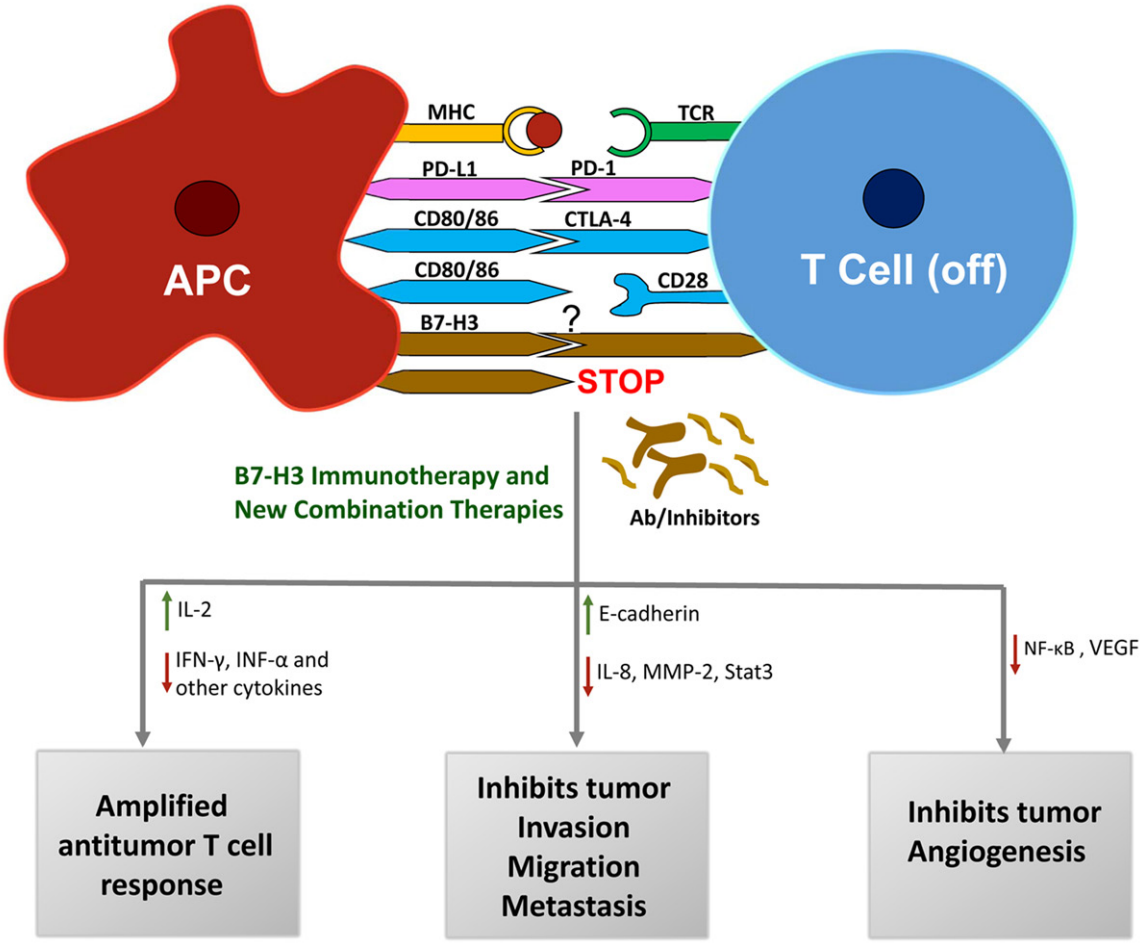

Figure 1. A graphic presentation of an antigen-presenting cell or tumor cell interacting with a T-cell. Inhibitory immune checkpoints, such as PD-L1, PD-1, CTLA-4 and B7-H3 binding with their associated interacting partners induce an inhibitory response that prevent stimulatory immune checkpoints from prompting a signaling cascade leading to T-cell activity, including pathogen identification and APC death. By preventing the interaction of these inhibitory immune checkpoints and their receptors, such as B7-H3 and its receptor, via direct inhibition or reduced surface expression, immunotherapeutic treatments can decrease tumorigenicity while increasing anti-tumor protein expression.

who had tumors in which B7-H3 was not expressed [56]. In a continuation of the notion that B7-H3 was being expressed in tumor vasculature, another study of RCC examined the relationship between B7-H3 and angiogenesis. The authors found that in RCC tumors, B7-H3 expression was elevated in tumor stroma around the blood vessels relative to other tumor areas. They also found that higher B7-H3 expression correlated with higher tumor grade [57]. These results are interesting and unexplored in previously mentioned papers, but ultimately may indicate that B7-H3 expression allows for enhanced tumor invasiveness, migratory potential, and in this case, the ability to provide additional vasculature for supportive measure.

B7-H3 in brain cancers

Multiple studies showed the presence of B7-H3 across a range of brain cancers. One study utilized immunohistochemical staining with 5B14, or CD19, antibody, an antibody that binds to B7-H3. They found that 76% of neuroblastoma samples and 100% of medulloblastoma samples showed a positive immunohistochemical stain for B7-H3 [58]. Castriconi *et al*. found that B7-H3 expression was high across 3 MB cell lines [59]. B7-H3 was more common and prevalent than other target immune checkpoints such as CD146 and CD133 [59]. Additionally, Baral *et al*. found that high B7-H3 expression levels in tumors of glioma patients correlated with a high-grade tumor [60]. Interestingly, the

measured expression levels were in the cerebrospinal fluid of patients, showing that soluble B7-H3 may play a vital role in increasing the metastatic potential of brain tumors. In diffuse intrinsic pontine glioma (DIPG), B7-H3 expression level correlated with histological tumor grade and was overexpressed in tumor samples compared to normal samples [61]. Because of the ubiquitous expression of B7-H3 in medulloblastoma, there is particular interest in studying the molecule in the context of this pediatric tumor-particularly in types 3 & 4 medulloblastoma, as these carry with them extremely poor prognosis without a good chemotherapeutic option available.

Clinical trials targeting B7-H3

As we mentioned in our PD-1 section, the antibody 8H9 inhibits B7-H3 [18]. 8H9 is currently being investigated in a Phase I clinical trial involving desmoplastic small round cell tumors found in the peritoneum [19]. Additionally, the antibody enoblituzumab (MGA271) directly and specifically targets B7-H3 [27]. It is currently in Phase I trials as well for a number of different solid tumors, including refractory tumors and pediatric tumors. Results from these studies must still be gathered and analyzed, but they may provide convincing evidence that B7-H3 is a viable target for future combination immunotherapies.

Conclusion

In summary, recent research has focused on the range of roles that B7-H3 has in different cancers. The prevalence of B7-H3 overexpression across lung, breast, brain, kidney, and prostate cancers make B7-H3 a particularly intriguing target for developing combination immunotherapeutic treatments. While previously controversial, current studies have provided greater evidence for classifying B7-H3 as a co-inhibitory molecule of T-cell activity as opposed to a co-stimulatory molecule. Observing the success of immunotherapies targeting similar immune checkpoints, like PD-1 and CTLA4, provides researchers with reasons to focus on developing new combination therapies that target B7-H3. In studying its role in cancer, B7-H3 appears to be widely associated with different proteins that contribute to cancer migration, invasion, and angiogenesis. Because of this, it appears that B7-H3 has a much greater role in cancer progression than immune evasion (**Figure 1**). Effective cancer treatments involve multifaceted approaches that target cancer from different check-points. Future work focusing on B7-H3 should integrate a holistic approach to determining the role of B7-H3 in cancer. This will lead to more appropriate therapies featuring this new, yet prominent contributor to the cancer phenotype.

Disclosure of conflict of interest

None.

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