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REVIEW

B7 homologue 3 as a prognostic biomarker and potential therapeutic target in gastrointestinal tumors

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Abstract

The most common digestive system (DS) cancers, including tumors of the gastrointestinal tract (GIT) such as colorectal cancer (CRC), gastric cancer (GC) and esophageal cancer (EC) as well as tumors of DS accessory organs such as pancreatic and liver cancer, are responsible for more than one-third of all cancer-related deaths worldwide, despite the progress that has been achieved in anticancer therapy. Due to these limitations in treatment strategies, oncological research has taken outstanding steps towards a better understanding of cancer cell biological complexity and heterogeneity. These studies led to new molecular target-driven therapeutic approaches. Different *in vivo* and *in vitro* studies have revealed significant expression of B7 homologue 3 (B7-H3) among the most common cancers of the GIT, including CRC, GC, and EC, whereas B7-H3 expression in normal healthy tissue of these organs was shown to be absent or minimal. This molecule is able to influence the biological behavior of GIT tumors through the various immunological and nonimmunological molecular mechanisms, and some of them are shown to be the result of B7-H3-related

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induction of signal transduction pathways, such as Janus kinase 2/signal transducer and activator of transcription 3, phosphatidylinositol 3-kinase/protein kinase B, extracellular signal-regulated kinase, and nuclear factor-κB. B7-H3 exerts an important role in progression, metastasis and resistance to anticancer therapy in these tumors. In addition, the results of many studies suggest that B7-H3 stimulates immune evasion in GIT tumors by suppressing antitumor immune response. Accordingly, it was observed that experimental depletion or inhibition of B7-H3 in gastrointestinal cancers improved antitumor immune response, impaired tumor progression, invasion, angiogenesis, and metastasis and decreased resistance to anticancer therapy. Finally, the high expression of B7-H3 in most common cancers of the GIT was shown to be associated with poor prognosis. In this review, we summarize the established data from different GIT cancer-related studies and suggest that the B7-H3 molecule could be a promising prognostic biomarker and therapeutic target for anticancer immunotherapy in these tumors.

Key Words: B7 homologue 3; Gastrointestinal tumors; Colorectal cancer; Gastric cancer; Esophageal cancer; Targeted therapy

Core Tip: Limitations related to oncotherapy and poor survival of patients with advanced forms of the most common malignant tumors of the gastrointestinal tract, including colorectal, gastric, and esophageal cancers (ECs), have led researchers to investigate new molecular target-driven therapeutic approaches. B7 homologue 3 (B7-H3) was shown to be significantly overexpressed among various malignancies and associated with their progression, metastasis and resistance to anticancer therapy. In this review, we analyze the results of different studies related to B7-H3 in colorectal, gastric, and ECs and suggest that this molecule could be a promising prognostic biomarker and therapeutic target in these tumors.

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INTRODUCTION

The digestive system (DS) consists of the gastrointestinal tract (GIT) and accessory organs, although the DS and GIT are often considered synonyms. The GIT comprises the oral cavity, pharynx, esophagus, stomach, small intestine, and large intestine. The accessory organs of the DS are the teeth, tongue, salivary glands, pancreas, liver, and gallbladder[1]. DS cancers represent more than one-quarter of the global cancer incidence and over one-third of all cancer-related deaths. The most common malignant DS tumors are colorectal, gastric, liver, esophageal, and pancreatic cancers, with nearly 4.8 million new cases in 2018[2].

The survival of the patients with the most common GIT tumors, including colorectal cancer (CRC), gastric cancer (GC), and esophageal cancer (EC), has improved in the last few decades, especially in developed countries. This is mainly a result of better screening programs for some gastrointestinal tumors and advancement in multimodal treatment, including surgery, chemotherapy, radiotherapy and targeted immunotherapy. However, the survival of patients with advanced CRC, GC, and EC is still poor, and the therapeutic options in these cases remain limited[3-5].

Given its proven value in numerous cancer treatments, antibody-based targeted immunotherapy has been developed into an eminent approach over the past few years. However, recently developed immune checkpoint inhibitors have only been successful in select types of cancer. Therefore, the necessity for new biomarkers is

urgently required in order to establish new potential targets suitable for anticancer therapy[6].

Recent studies have revealed that the B7 homologue 3 (B7-H3) molecule is overexpressed in various malignancies and involved in their progression, invasion and resistance to anticancer therapy[7]. This review aimed to analyze the expression of the B7-H3 molecule in the most common malignant tumors of the GIT (CRC, GC and EC), its correlation with prognosis, and the molecular mechanisms that may influence prognosis. B7-H3 is also analyzed as a potential therapeutic target in these gastrointestinal tumors.

B7-H3

The B7 family contains proteins that have a crucial role in triggering stimulatory and inhibitory pathways that regulate immune response[8]. These molecules are structurally similar and usually can be found on the cell surface as ligands able to bind to the receptors on lymphocytes[9]. In general, the effective activation of naïve T cells requires two signals: The first signal is provided by the binding of the antigen-specific T cell receptor to the major histocompatibility complex (commonly known as MHC) of the antigen-presenting cells carrying antigenic peptides, while the second signal represents the interaction of the various receptors on T cells, such as CD28 and cytotoxic T lymphocyte antigen 4 (also known as CTLA-4) and their ligands on antigen-presenting cells (such as CD80 and CD86), which may have costimulatory or coinhibitory effects[10]. The B7 family molecules regulate T-cell activation, tolerance and autoimmunity by providing crucial positive (costimulatory) or negative (coinhibitory) secondary signals[8]. Ten members of this family have been reported so far: CD80 (B7-1), CD86 (B7-2), programmed death-ligand (PD-L)1 (B7-H1), PD-L2 (B7-DC or CD273), ICOSL (B7-H2), CD276 (B7-H3), B7S1 (B7-H4, B7x, or Vtcn1), VISTA (B7-H5, GI24, or PD-1H), B7-H6 and B7-H7 (HHLA2)[11].

B7-H3 (CD276), a type I transmembrane glycoprotein encoded by chromosome 15, was identified as a homolog of the B7 family in 2001. This molecule shares 20%–27% amino acid identity with other B7 family members and has two isoforms in humans: 2Ig-B7-H3 and 4Ig-B7-H3[11-13]. Although the expression of B7-H3 mRNA is ubiquitously found in multiple normal tissues, B7-H3 protein is relatively rarely expressed in physiological conditions, probably due to posttranscriptional regulatory mechanisms[11,14]. B7-H3 is found to be expressed on endothelial cells, nonimmune resting fibroblasts, amniotic fluid stem cells and osteoblasts. In addition, B7-H3 expression could be induced on T cells, B cells, natural killer (commonly referred to as NK) cells, and specifically antigen-presenting cells, such as dendritic cells and macrophages[13-15].

However, B7-H3 was found to be overexpressed among various kinds of human cancer cells and has significant influence on their biological behavior[16-20]. Although B7-H3 is structurally a transmembrane protein, immunohistochemical studies on B7-H3 in cancer reported that it was also found in the cytoplasm and nucleus of tumor cells[18,21]. This molecule can modulate the biological functions of immune cells, including $CD4^+$ T cells, $CD8^+$ T cells, macrophages, and NK cells, and plays an essential role in regulating the innate and adaptive immune responses[13,22,23]. However, the receptor that B7-H3 binds to still has not been precisely determined, although a potential receptor, TREM-like transcript 2 (TLT-2), was detected on activated immune cells. Nevertheless, TLT-2 may not be the only receptor of B7-H3 because B7-H3 was shown to exert many contradictory roles[7,13]. Most available data demonstrate that B7-H3 has coinhibitory effects on T cell responses, which may allow cancer cells to avoid immune destruction[22,24-26]. However, B7-H3 was previously recognized as a costimulatory molecule that promotes T cell activation and interferon-gamma (IFN-γ) production[12]. Apart from its immunological function, B7-H3 may be involved in the regulation of cancer progression *via* nonimmunological functions, such as modifying cancer metabolism and promoting invasion, metastasis and drug resistance[27-30]. Therefore, the presence of B7-H3 has been correlated with a worse prognosis in many solid malignant tumors, such as CRC[18], GC[31], EC[26], pancreatic cancer[19], liver cancer[32], breast cancer[33], lung cancer[34], and central nervous system tumors[35]. The association between B7-H3 expression and survival of cancer patients is described through the various mechanisms that tumors use to overcome the immune system, survive and spread. These are known as the "hallmarks of cancer"[36]: Evading immune destruction[22], reprogramming of energy metabolism[27], resisting cell death[37], inducing angiogenesis[38], activating invasion

and metastasis[28].

B7-H3 IN CRC

CRC is the second most deadly and third most diagnosed cancer worldwide[2]. It is also the most prevalent GIT malignancy[39]. With over 1.8 million new CRC cases, it caused 881000 deaths in 2018[2].

CRC can be classified as sporadic, inherited, and familial. Sporadic cancer rises from point mutations and accounts for 70% of all CRCs. Inherited CRC is found in about 5% of CRC cases, and it is caused by germline mutations that affect one of the alleles of the mutated gene. If the point mutation in the other allele occurs, it triggers further carcinogenesis. Inherited CRC comprises two types[40]. The polypus type results from the germline mutations in the *adenomatous polyposis coli* gene, which leads to the development of familial adenomatous polyposis, with the formation of multiple potentially malignant polyps in the colon[41]. In contrast, hereditary non-polyposis CRC is related to the inherited mutations in one of the alleles that code proteins responsible for DNA repair mechanisms, such as MSH2, MLH1, MLH6, PMS1, and PMS2. Familial CRC accounts for approximately 25% of all cases and is also caused by inherited mutations. However, these germline mutations do not occur in any of the genes associated with known inherited CRC syndromes, which is why familial CRC is classified separately[40].

Various risk factors have been associated with CRC development, including age (past the fifth decade of life), inflammatory bowel disease, positive familial history of CRC, sedentary lifestyle, obesity, unhealthy nutritional habits (such as overconsumption of red meat), smoking, and alcohol consumption[40]. Survival rates have improved over the past decade as a result of advancements in the understanding of tumor biology, screening programs, better referral pathways, centralization of services, effective primary surgery, and the development of new chemotherapy and targeted immunotherapy agents[3]. Nevertheless, 20% of patients present with synchronous metastases, and up to 60% of patients develop distant metastases within five years [42]. Unfortunately, the 5-year survival rate of CRC patients with distant metastases is only 14%[43].

Screening programs have led to the increased number of CRC cases identified in early stages, and some of them could be treated endoscopically[44]. However, surgery, including tumor excision with or without bowel resection, is the most common treatment for all stages of CRC. Advanced stages of CRC are additionally treated with chemotherapy, radiotherapy, targeted therapy or the combination of these therapeutic modalities[40,44]. Unfortunately, chemotherapy and radiotherapy are characterized by low specificity and significant systemic cytotoxicity as well as by unsatisfying recurrence rates. Therefore, research has been directed to better knowing CRC immunogenic potential and the development of targeted therapy[45].

During the past decade great efforts have been made to find novel therapeutic agents for cancer treatment. The B7 family molecules and their receptors are promising targets. Extensive research of molecular mechanisms involved in carcinogenesis revealed that cancer cell progression is driven by mutagenesis[46]. Today, a high mutation burden is considered as both a hallmark of cancer cells and a marker of responsiveness to immunotherapy in several tumor types[47]. Although metastatic CRC is categorized as immunogenic, immune checkpoint therapy has only been shown to be an eligible intervention therapy strategy to treat deficient mismatch repair (referred to as dMMR) or microsatellite instability-high (referred to as MSI-H) metastatic CRC. Unfortunately, only 15% of CRCs are MSI-H or dMMR. Most proficient mismatch repair or MSI-low CRCs are unresponsive to treatment with the current immune checkpoint inhibitors[11]. Although the checkpoint inhibitors pembrolizumab and nivolumab that interrupt programmed death 1 (PD-1) binding to PD-L1 (B7-H1) and PD-L2 (B7-DC) have shown great effectiveness in the management of advanced solid tumors such as non-small lung cancer[48] and melanoma[49], their use in CRC treatment is very limited[11]. These unsatisfactory results have stimulated the development of many studies regarding the involvement of other members of the B7 family on the biological behavior of CRC, their influence on prognosis and the possibility to be used in targeted therapy.

B7-H3 in tumor cells and immune cells of CRC

The B7-H3 protein has been found on the membrane, in the cytoplasm[18], within the nucleus[21], the vasculature[21,50], and on interstitial infiltrating immune cells in CRC

[11,51]. Many studies have found the association of B7-H3 overexpression with poor prognosis in CRC, which is explained by different immunological and nonimmunological molecular mechanisms[18,21,51,52]. The meta-analysis published by Fan *et al* [52] that included 1202 cases from six published studies showed that even though the expression of B7-H3 was not associated with lymph node metastasis in CRC patients, it was significantly associated with 24-mo and 72-mo overall survival (OS), indicating that CRC patients overexpressing B7-H3 may have a poor survival rate. Similarly, Tang *et al*[53] revealed that CRC patients with high B7-H3 mRNA expression had significantly worse OS and disease-free survival. Better OS in CRC patients with low expression of B7-H3 in tumor cells was also confirmed by Mao *et al*[54]. Notwithstanding, in the large cohort that included 805 CRC tissue microarrays, B7-H3 overexpression was independently associated with decreased disease-free survival, but not OS. This may indicate that CRC patients expressing B7-H3 are more likely to experience relapses[18].

B7-H3 subcellular localization is especially important for understanding its possible roles in carcinogenesis. Ingebrigtsen *et al*[21,55] were first to report that B7-H3 could be found in the nucleus of CRC cells. These data suggested that B7-H3 could affect gene expression. Initially, it was shown that B7-H3 nuclear expression in colon cancer patients was independently and significantly associated with reduced OS, disease-free survival and metastasis-free survival[21]. In the next study, Ingebrigtsen *et al*[55] detected only the association with reduced recurrence-free survival in tumor, node, metastasis (commonly known as TNM) I CRC patients. Nuclear localization of B7-H3 in CRC cells was also identified by immunohistochemical staining in a study that also detected B7-H3 in the cell membrane and cytoplasm, but no association of subcellular site expression with prognosis was analyzed independently[54].

Furthermore, B7-H3 is found in tumor infiltrating cells in CRC. Nonmalignant cells in the tumor microenvironment play critical roles in all the stages of carcinogenesis by stimulating and facilitating uncontrolled cell proliferation. In addition to malignant cells, adipocytes, fibroblasts, tumor vasculature, lymphocytes, macrophage, dendritic cells, and cancer-associated fibroblasts are present in the tumor microenvironment. Each of these cell types has unique immunological capabilities that determine whether the tumor will survive and affect neighboring cells[56]. Research data shows that effector/cytotoxic $CD3^+$ and $CD8^+$, as well as memory $CD45RO^+$ T cells, play essential roles in antitumor immune response. A significant relationship between elevated $CD45RO^+$ T cell infiltration and improved CRC prognosis was observed previously [57]. Lu *et al*[18] showed a positive correlation between B7-H3 tumor cell expression and $CD45RO^+$ T cell density in CRC but not with $CD3^+$ and $CD8^+$ T cell densities. However, this study also revealed that B7-H3 expression in primary tumors was significantly related to advanced overall stage and worse prognosis. This may indicate that the immune activity of $CD45RO^+$ T cells is impaired by the coinhibitory effects of B7-H3.

γδ T cells account for about 5% of all circulating T cells and have an important role in innate and adaptive immune surveillance. Vγ9Vδ2 (Vδ2) T cells, which represent 50%-90% of human peripheral blood γδ T cells, exert a strong anticancer capability because they have MHC-independent recognition of antigens and can release abundant proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IFN-γ and interleukin-17 (IL-17). The study of Lu *et al*[22] showed that the proportions of γδ T cells were reduced in the peripheral blood mononuclear cells of patients with colon cancer compared to healthy donors. At the same time, the proportions of B7-H3 expressing γδ T cells were distinctly increased in the peripheral blood of colon cancer patients compared to healthy individuals. In addition, the proportions of infiltrating γδ T cells were lower in tumor areas than in neighboring noncancerous areas, whereas the proportions of B7-H3 expressing γδ T cells were significantly higher. These results suggested that B7-H3 serves as an important negative immune checkpoint molecule that regulates the activity and biological function of γδ T cells in colon cancer. It is also revealed that B7-H3 negatively impacts the proliferation, activation, and IFN-γ production of Vδ2 T cells and inhibits their cytotoxic activity through the downregulation of IFN-γ and perforin/granzyme B expression. In contrast, neutralizing B7-H3 by MIH35, an anti-B7-H3 monoclonal antibody (mAb), significantly enhanced the cytotoxic effect of Vδ2 T cells on colon cancer cells *in vitro* and *in vivo*.

Furthermore, it was shown that tumor-associated macrophages were associated with a poor prognosis and outcome in numerous human malignancies due to their involvement in tumor growth, invasion and metastasis[58,59]. In the study by Mao *et al*[54], the level of cancer cell expression of B7-H3 was found to be positively associated with the density of infiltrated macrophages in CRC tissue. Besides, B7-H3 expression in cancer tissue and the infiltrating density of macrophages were negatively

associated with the OS.

In addition to the cellular localization of B7-H3, the soluble form of this molecule (sB7-H3) can be released by monocytes, activated T cells, dendritic cells and B7-H3-positive tumor cells. Many studies have demonstrated a relationship between sB7-H3 and the poor prognosis of patients with malignant tumors[60]. Sun *et al*[61] revealed that patients with CRC had higher serum levels of sB7-H3 than healthy individuals, and the secretion of B7-H3 was enhanced by TNF-α, an important cancer-promoting inflammatory cytokine. Moreover, the results of this study also confirmed the role of B7-H3 in suppressing immune surveillance because B7-H3 expression in tumor specimens obtained from patients who underwent surgery for CRC was negatively correlated with the density of infiltrating $CD3^+$ T cells in both tumor stroma and tumor nest.

B7-H3 antiapoptotic activity in CRC

Resisting cell death is one of the most important characteristics of cancer cells, and it is often achieved by limiting or circumventing apoptosis. This is most commonly provided by the loss of TP53 tumor suppressor function, but it can also be the result of deregulation of pro- and antiapoptotic factors[36].

In 2016, Sun *et al*[62] reported in their *in vitro* study that overexpression of B7-H3 upregulates BRCA1/BRCA2-containing complex subunit 3 (BRCC3) expression and antagonizes the anticancer activity of 5-fluorouracil (5-FU). BRCC3 (previously known as BRCC36) is a deubiquitinating enzyme encoded by the *BRCC3* gene and represents a subunit of the BRCA1/BRCA2-containing complex, which plays a vital role in the DNA damage response[63,64]. BRCA1 or BRCA2 are activated as a part of the DNA damage response machinery and exert their activity in homologous recombination, which represents a pathway for DNA double-strand break repair[65,66]. Previous studies indicated that the BRCC3 molecule directly interacts with BRCA1, and it is required for the recruitment of BRCA1 to DNA damage sites[64,67,68]. It was shown that the downregulation of BRCC3 expression caused glioma cells to become more sensitive to temozolomide, an alkylating agent[64].

Despite all modern drugs, 5-FU alone or in combination with other chemotherapeutic agents or radiation is still recognized as the mainstay in CRC treatment[40,69]. 5-FU blocks the synthesis of thymidine, which leads to interruption of DNA replication[62]. In addition, this drug can cause DNA damage by antagonizing homologous recombination repair and sensitizing CRC cells towards double-stranded DNA breaks[62,69]. The cell damage caused by chemotherapy or radiation may lead to cell cycle arrest and activation of DNA damage response proteins, or if damage overrides cellular repair mechanisms, it could activate programmed cell death, which is a favorable outcome in anticancer therapy[70]. Sun *et al*[62] revealed that the overexpression of B7-H3 is associated with the improved ability of the tumor cell to overcome the DNA damage, which is provided by the induction of the DNA repair complex protein BRCC3. This directly allows CRC cells to resist the cytotoxic activity of 5-FU. Moreover, this study proved that the knockdown of B7-H3 increased CRC sensitivity to 5-FU, which can be used in further therapy.

In accordance with this report, another group of researchers observed that overexpression of B7-H3 in CRC reduced drug-induced DNA damage caused by chemotherapy[71]. Oxaliplatin (L-OHP) is the first platinum-based drug with proven activity against CRC. L-OHP exerts its antitumor effects by creating DNA lesions, interstrand and intrastrand platinum-DNA adducts that inhibit gene transcription, DNA repair and synthesis[71,72]. Zhang *et al*[71] reported that B7-H3 promotes L-OHP resistance in CRC cells by upregulating the expression of the X-ray repair cross-complementing group 1 (*XRCC1*) gene. XRCC1 is one of many proteins of the DNA repair machinery that promotes the efficient repair of DNA single-strand breaks and plays a key role in drug resistance by promoting the DNA damage repair ability in cancer cells. Also, they found that B7-H3-mediated upregulation of XRCC1 was conducted *via* the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (also known as Akt) pathway, one of the pivotal intracellular signal transduction pathways that promote proliferation, cell survival, metabolism, growth and angiogenesis[71,73]. On the other hand, transient silencing of B7-H3 enhanced L-OHP sensitivity by increasing L-OHP-induced DNA damage[71].

Studies revealed that B7-H3 induced activation of other prosurvival signaling pathways, the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3), and extracellular signal-regulated kinase 1/2 (ERK1/2)[37,74].

The JAK2/STAT3 signaling pathway is hyperactivated in many types of tumors and has a prominent role in cancer cell proliferation, invasion, metastasis, and suppressive effects on antitumor immunity and apoptosis[75-77]. In general, hyperactivation of the

JAK2/STAT3 pathway is associated with a poor clinical prognosis in many types of cancer. JAK-mediated phosphorylation of STAT3 induces dimerization of the STAT3 protein and its translocation to the nucleus[75,78,79]. Once in the nucleus, STAT3 dimers induce transcription of many genes including regulators of cellular proliferation, prosurvival and angiogenesis-promoting genes[75]. Interestingly, Zhang *et al* [37] showed in their *in vitro* CRC study that overexpression of B7-H3 inhibited apoptosis in a JAK2/STAT3-dependent manner by augmented expression of antiapoptotic proteins B cell lymphoma 2 (Bcl-2) and B cell lymphoma-extra-large (referred to as Bcl-xl) and downregulation of proapoptotic protein Bax. These proteins, Bcl-2, Bcl-xl, and Bax, belong to the same Bcl-2 family of proteins. This family of proteins has an important role in controlling the mitochondrial outer membrane permeabilization and induction of programmed cell death. Once the mitochondrial outer membrane permeabilization happens, it leads to irreversible release of intermembrane space proteins, subsequent caspase activation and induction of apoptosis[80]. This could explain why B7-H3-JAK2/STAT3-mediated activation of the antiapoptotic proteins Bcl-2 and Bcl-xl in the study of Zhang *et al*[37] made CRC cells become more resistant to drug-induced apoptosis. In contrast, B7-H3 knockdown increased drug-induced apoptosis, once again marking this molecule as a potential therapeutic target[37].

In addition to B7-H3-dependent upregulation of antiapoptotic proteins, Ma *et al*[29] revealed that the B7-H3/STAT3 axis further potentiated chemoresistance by modifying the cell division checkpoint *via* increasing the expression of cell division cycle 25A protein (CDC25A). The cell cycle is a set of strictly conserved events by which eukaryotic cells replicate their genome during the S phase and segregate into two new daughter cells during mitosis or M phase[81,82]. Between these two phases, there are two preparatory gaps: G1, which separates M from S and G2 between S and M[81], and three cell cycle checkpoints that occur at the G1/S boundary, in S-phase and during the G2/M phases[82]. These checkpoints are regulatory mechanisms that cells use to assure that proliferation occurs only in the presence of stimulatory signals and to guarantee the fidelity of replicated genetic material[82]. Deregulation of checkpoint mechanisms is often found in human malignancies and can induce chemoresistance[83,84]. CDC25A is a dual-specificity protein phosphatase and one of the most crucial cell cycle regulators, which removes the inhibitory phosphorylation in cyclin-dependent kinases (CDKs), such as CDK2, CDK4, and CDK6, and positively regulates the activities of CDKs that lead to cell cycle progression. In addition, CDC25A also acts as a regulator of apoptosis. Furthermore, the overexpression of this protein promotes tumorigenesis and is frequently observed in various types of cancer [85]. Ma *et al*[29] reported that B7-H3 promotes chemoresistance to L-OHP and 5-FU by reducing the G2/M phase arrest in a STAT3/CDC25A-dependent manner in CRC cells, confirming the oncogenic potential of both B7-H3 and CDC25A.

B7-H3 can also upregulate the kinesin family member 15 (KIF15) protein[74]. KIF15 maintains the bipolar microtubule spindle apparatus in all dividing cells and promotes spindle assembly, whereas downregulation of KIF15 induces G1/S phase cell cycle arrest and inhibits cell growth and mitosis[86,87]. Moreover, Ma *et al*[74] illustrated that the upregulation of B7-H3 in CRC promotes radioresistance *via* the KIF15/ERK signaling pathway. As we mentioned above, B7-H3 affects several signaling cascades, and ERK is one of those pathways. ERK represents one of the terminal kinases in serine/threonine mitogen-activated protein kinase (MAPK) cascades. It has an important role in signaling pathways involved in cell proliferation, differentiation, and survival. Also, the substantial body of experimental observations demonstrates that the mutational activation and/or overexpression of upstream signaling components that activate ERK participate in oncogenesis, migration, invasion, and metastasis in CRC[88]. While confirming previous findings on the involvement of B7-H3 overexpression in CRC, Ma *et al*[74] showed that the ERK signaling pathway was required for B7-H3/KIF15 axis-mediated radioresistance in CRC cells. On the contrary, B7-H3 blockade by 3E8, a specific B7-H3 antibody, significantly sensitized CRC cells to irradiation *in vivo*.

B7-H3 promotes progression in CRC

Beyond its role in immune response and in chemotherapy and radiotherapy resistance, mounting evidence has revealed that B7-H3 is involved in the progression and metastasis of CRC by playing a key role in epithelial-to-mesenchymal transition (EMT), invasion, migration, and angiogenesis.

EMT is a normal biologic process, which occurs during normal embryonic development, tissue regeneration, organ fibrosis, and wound healing. However, this process is involved in tumor progression and considers disruption of cell-cell adhesion and cellular polarity, remodeling of the cytoskeleton, and changes in cell-matrix

adhesion[89]. Jiang *et al*[28] clarified the role of B7-H3 in promotion of CRC cell transformation into a mesenchymal phenotype with cancer stem cell characteristics. Results obtained in that study revealed that B7-H3 overexpression was apparently accompanied by downregulated expression of epithelial markers (E-cadherin and β-catenin) and enhanced expression of mesenchymal marker proteins (N-cadherin and vimentin). Also, their data revealed that B7-H3 triggered EMT in a PI3K/Akt-dependent manner, confirming the importance of the B7-H3-PI3K/Akt signaling pathway in CRC. In addition, it has been shown that B7-H3 was coexpressed with matrix metalloproteinase (MMP) 2 and MMP9. The MMPs are extracellular proteinases required for numerous developmental and disease-related processes[90, 91]. In cancer, MMPs mediate many changes in the microenvironment during tumor progression by promoting extracellular matrix remodeling, unregulated tumor growth, angiogenesis, inflammation, tissue invasion, and metastasis[91]. Thus, these results suggested an additional mechanism by which B7-H3 promoted tumor invasion and metastasis. Finally, Jiang *et al*[28] confirmed that invasion and metastasis capabilities of CRC cells were decreased after B7-H3 was knocked down.

In accordance with previous studies, Liu *et al*[30] reported that enhanced expression of B7-H3 in CRC elevated MMP9 levels in a JAK2/STAT3-dependent manner, thus bestowing CRC cells with promigratory and proinvasive potential.

Besides EMT, angiogenesis is one of the essential steps in the pathway of tumor metastasis. Wang *et al*[38] investigated the role of B7-H3 in angiogenesis and showed that B7-H3 upregulated vascular endothelial growth factor A (VEGFA), a signaling protein that stimulates the formation of new blood vessels. Their study also revealed that this process was mediated by activation of inducible transcription factor, nuclear factor-kappa B (NF-κB)[38], which is known to regulate the expression of a large array of genes involved in different processes of the immune and inflammatory responses [92]. Also, they showed in a series of *in vitro* and *in vivo* experiments that conditioned medium from B7-H3 knockdown CRC cells significantly inhibited the migration, invasion, and tube formation of human umbilical vein endothelial cells, which were used as a vascular cell laboratory model[38].

B7-H3 role in CRC cell metabolism

Cancer cell metabolism is no longer considered to be synonymous with the Warburg effect. Nowadays, it is described by remarkable diversity and flexibility of anabolic and catabolic pathways in order to satisfy bioenergetic, biosynthetic and redox demands of malignant cells[93]. The underlying mechanisms of CRC cell metabolism have yet to be elucidated. Because B7-H3 is broadly overexpressed by multiple cancers and plays a key role in their progression, several studies examined whether it influences metabolism in CRC.

Indeed, in 2018, Wu *et al*[94] revealed a positive correlation between the expression of B7-H3 and isocitrate dehydrogenase 1 (IDH1). IDH1 is $NADP^+$-dependent and a crossroad enzyme in cell metabolism, involved in lipogenesis and glucose sensing, epigenetic regulation, and DNA repair. IDH1 contributes to the cellular defense against reactive oxygen species generated during lipid oxidation and other processes by generating NADPH[95]. Mutations or aberrant expression of *IDH1* have been described in various types of malignancies[96]. Wu *et al*[94] analyzed IDH1 and B7-H3 expression levels in tumor tissues of 225 CRC patients by immunochemistry. Results showed that coexpression of IDH1 and B7-H3 significantly correlated with the prognosis of CRC patients. Moreover, their *in vitro* study confirmed this correlation. Although this study showed that IDH1 and B7-H3 were not independent prognostic factors in CRC patients, their coexpression significantly correlated with a worse survival rate and may serve as a combined predictive marker.

Another study also reported the influence of B7-H3 on the metabolism of CRC cells. Shi *et al*[27] revealed that B7-H3 could regulate glucose metabolism and chemoresistance by promoting glycolytic enzyme hexokinase 2 (HK2) expression in CRC. HK2 phosphorylates glucose to glucose-6-phosphate. HK2 prevents glucose from leaving the cell and provides the 'pull' for glucose entry into the cell[97]. In their *in vitro* study, Shi *et al*[27] showed that B7-H3 promoted glucose consumption and aerobic glycolysis in CRC cells by upregulating expression of HK2 *via* STAT3. They found that the B7-H3/STAT3-HK2 axis induced CRC cell chemoresistance by upregulation of antiapoptotic protein Bcl-2 and reduced Bax expression. Moreover, *in vivo* experiments confirmed that B7-H3-induced HK2 promoted CRC cell chemoresistance as well. Finally, the analysis of CRC patient tumor tissue specimens revealed that the levels of B7-H3 and HK2 were higher in advanced clinical stages.

In addition, Zhang *et al*[98] discovered a linear relationship between B7-H3 expression and levels of fasting blood glucose with the depth of tumor invasion (T3/4), lymph node metastasis (N0), and TNM stage (I/II). These results indicated a significant correlation between the expression of B7-H3 and fasting blood glucose in the early stage of CRC, once again suggesting that B7-H3 has an important role in CRC cell metabolism.

B7-H3 IN GC

Based on GLOBOCAN 2018 data, GC is the fifth most common malignancy worldwide with an annual incidence of 1000000 new cases. It is also the third most common cause of cancer-related deaths with 784000 deaths globally in 2018[2]. Anatomic classification of malignant stomach tumors is based on location and comprises two entities: Cardia GC (having the epicenter in cardia, more than 2 cm distal from the esophago-gastric junction) and non-cardia GC (which involves other parts of stomach, distal from cardia)[99,100]. GC occurs two times more frequently in males than in females, and various factors have been associated with increased risk for its development[2,101,102]. *Helicobacter pylori* (*H. pylori*) infection has been noted as the main risk factor for GC development (especially in the non-cardia type), whereas the other predisposing factors are N-nitroso compound consumption, salt-preserved, smoked and cured food consumption, low fruit intake, Epstein-Barr virus infection, and smoking[2,103]. Furthermore, gastroesophageal reflux disease was recognized as an additional risk factor associated with cardia GC, although not all patients with this type of cancer have a history of gastroesophageal reflux disease[104]. The most common histological type of GC is gastric adenocarcinoma (GA), a malignant epithelial neoplasm of the gastric mucosa with glandular differentiation[100].

Radical surgery represents the standard and the only potentially curative form of therapy for GC[103,105]. Tumor excision in early-stage disease could be achieved by open surgery, laparoscopic surgery, and endoscopically *via* endoscopic mucosal resection and endoscopic submucosal dissection[106]. However, the prognosis of patients with locally advanced GC remains poor despite radical surgical resection [107]. In these cases, a slight improvement in survival could be achieved by perioperative and adjuvant chemotherapy as well as by chemoradiation[108]. Moreover, most newly diagnosed patients are at an advanced stage, and approximately 50% of them have already lost their chance for surgery[109]. Despite the multimodal therapeutic approaches, the 5-year OS of locally advanced GC is less than 30%, and in metastatic disease, the prognosis remains poor with a median OS of 1 year[105].

The last decade has been characterized by a better understanding of molecular mechanisms of pathogenesis and biology of GC, which led to the development of new targeted therapy drugs. To date, a few targeted therapy agents have been approved for metastatic GC. Trastuzumab, the anti-human epidermal growth factor receptor-2 (HER2) mAb, has been the first targeted therapy drug that received approval for HER2 high expressing advanced GCs and gastroesophageal junction cancer, while the VEGF receptor 2 (VEGFR-2) mAb, ramucirumab, has been approved in the second-line setting as a monotherapy or in combination with chemotherapeutic agent paclitaxel. Recently, in some Asian countries and North America, PD-1 checkpoint inhibitors have been approved for patients with heavily pretreated advanced GC[103,105].

Like in CRC, the involvement of the B7 family molecules has been recognized in tumorigenesis of GC as well. A novel bioinformatics study conducted by Li *et al*[110] analyzed the data obtained from The Cancer Genome Atlas and Genotype-Tissue Expression databases. They revealed that B7-H3, B7-H4, B7-H5, B7-H6, and B7-H7 were significantly upregulated in GC.

B7-H3 in tumor cells and immune cells of GC

Studies on B7-H3 expression in GC have indicated that aberrant expression of this molecule is closely related to tumor progression and poor prognosis[20,111]. It was confirmed that patients with high B7-H3 expression in both tumor cells and stromal cells of GA tissue had significantly poorer OS[31]. Arigami *et al*[20] observed that B7-H3 expression was related to tumor aggressiveness. In addition, they demonstrated that B7-H3 was expressed in circulating gastric tumor cells, and the blood specimen analyses of GC patients showed significantly more copies of B7-H3 mRNA than those from healthy volunteers. These results indicated that B7-H3 expression levels might be a useful blood marker for predicting tumor progression in patients with GC. However, Wu *et al*[112] showed that the survival of GC patients with high intratumor B7-H3

expression was twice as high than those with low intratumor B7-H3 expression. These contradictory results call for caution in implementing B7-H3 as a prognostic marker for GC.

GA develops through a sequence of precursor lesions. The first step of multistage GA carcinogenesis is chronic superficial gastritis, which progresses within years or decades to chronic atrophic gastritis. Further progression leads to intraepithelial neoplasia and finally invasive carcinoma[113,114]. Guo *et al*[113] examined B7-H3 expression and clinical significance in gastric tumor/parenchymal tissues and infiltrating immune cells at different stages of gastric carcinogenesis, including chronic superficial gastritis, chronic atrophic gastritis, low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia and GA. The B7-H3 expression in tumor/parenchymal cells was mainly detected in the GA stage and rarely detected in the other stages, indicating an important role of this molecule in gastric carcinogenesis.

In infiltrating $CD68^+$ macrophages and $CD8^+$ lymphocytes, B7-H3 expression showed a significant increasing trend with disease progression. Almost no B7-H3 expression was detected in the inflammatory phase, but B7-H3 expression began and gradually increased during the neoplastic stage, with a more drastic increase in the GA stage than in the neoplastic stage. These findings clearly indicate that B7-H3 is closely related to cancer progression[113]. Furthermore, the results of that study discovered that in the neoplastic and GA stages, the density of $CD8^+$ infiltrating cells was negatively correlated with B7-H3 expression on tumor cells, whereas the density of $CD68^+$ infiltrating cells was positively correlated with B7-H3 expression in tumor-infiltrating immune cells. This may suggest that B7-H3 has a negative impact on $CD8^+$ lymphocytes that could lead to evasion of the immune system. Moreover, considering B7-H3 is involved in gastric carcinogenesis, we may assume that one of the molecular mechanisms of GC progression is accomplished through the interaction of B7-H3 with $CD68^+$ cells. This is in accordance with previous findings that tumor-associated macrophages are involved with enhanced tumor progression, and their infiltration is strongly associated with poor survival in patients with various solid tumors[59].

H. pylori and B7-H3 in GC

The effect of *H. pylori* on the carcinogenesis process has been described by two main mechanisms. First, *H. pylori* infection mounts a chronic inflammatory response resulting in an increased cell turnover that over several decades may result in an accumulation of mitotic errors. In addition, oncogenesis stimulated by *H. pylori* is also a result of the toxic action of virulence factors such as cytotoxin-associated gene A (CagA), Cag pathogenicity island, and vacuolating cytotoxin A[115]. CagA is the main oncogenic molecule, and it is delivered into the cytoplasm of the host cells *via* a bacterial type 4 secretion system (T4SS). Upon entering the gastric epithelial cell, a part of CagA becomes phosphorylated. Both phosphorylated and nonphosphorylated CagA interact with multiple host signaling proteins, further leading to the impairment of cytoskeletal and tissue structure and causing disorders of cell proliferation and apoptosis[116]. Moreover, *H. pylori* also translocates its cell wall peptidoglycan fragments into a host cell *via* the T4SS. Peptidoglycan is recognized by an intracellular pattern recognition receptor, NOD1, further leading to the activation of the MAPK and NF-kB pathways[117,118]. Lina *et al*[119] investigated the relationship between *H. pylori* infection, immune response, and B7-H3 protein. They quantified gene expression level of *B7-H3* in tissue samples by reverse transcription-polymerase chain reaction (PCR) and showed a strong upregulation of *B7-H3* expression in the *H. pylori*-positive biopsies compared to uninfected samples. In their *in vitro* study, they observed a strong positive correlation between *H. pylori* CagA/T4SS/peptidoglycan and expression levels of B7-H3 in the N87 gastric epithelial cell line. Also, their results revealed that *H. pylori*-mediated upregulation of B7-H3 in gastric epithelial cells is p38/MAPK mediated. Additionally, they showed that *H. pylori* upregulated B7-H3 expression both directly *via* CagA and peptidoglycan and indirectly by manipulating the host T cell response and inducing chronic inflammation[119].

B7-H3 promotes progression in GC

Invasion and metastasis are two of many biological capabilities of cancer cells, which enable the cell to enter the vessels as well as to extravasate and invade into a distant organ[36,120]. Researchers have implicated various proteins involved in these processes in GC. Moreover, several studies reported that B7-H3 is overexpressed in GC, but the functional role of B7-H3 in the progression of GC is still controversial. Accordingly, Dai *et al*[111] confirmed that B7-H3 is aberrantly expressed in GC. In their study, they showed significantly higher B7-H3 immunohistochemical staining and relative mRNA expression in the tumor tissues in the GC group compared to the

healthy control group. To explore the role of B7-H3 in GC tumorigenesis, they transfected the GC cell line SGC-7901 with short hairpin RNA (shRNA) against B7-H3. After confirmation of transfection efficiency, their results revealed that B7-H3 has a pivotal role in tumor migration and invasion, indicating that higher aggressiveness and a poor clinical outcome correlate with B7-H3 expression levels. Also, in their *in vivo* experiment, which considered the orthotropic transplantation GC model, they found that decreased B7-H3 expression reduced tumor metastasis.

Li *et al*[120] also tested the involvement of B7-H3 in promotion of GC progression. They transfected the human GC line, N87, with shRNA for B7-H3. shRNA-mediated silencing decreased membrane and cytoplasm levels of B7-H3, and this was confirmed by immunoblot analysis. Moreover, they reported that B7-H3 silencing reduced N87 cell migration and invasion, and inhibited N87 cell lung metastasis in nude mice. They found that B7-H3 silencing downregulated the expression of metastasis-associated molecule, C-X-C chemokine receptor type 4 (CXCR4) in N87 cells and confirmed these findings by flow cytometry, immunoblotting and real-time PCR. CXCR4 is a stromal cell-derived factor-1 receptor and initiates various downstream signaling pathways, such as PI3K/Akt, MAPK, NF-κB, and JAK2/STAT3. Activation of these signaling pathways increases intracellular calcium levels, gene transcription, chemotaxis, cell survival, and proliferation[121]. It was reported that CXCR4 is involved in tumor growth, migration, and invasion, and the increase in CXCR4 expression in primary GC positively correlated with lymph node metastasis[121,122]. Further, they analyzed 120 samples of GC patients by immunohistochemistry and found that B7-H3 overexpression correlated with CXCR4 expression. Also, they reported that there is a direct interaction between B7-H3 and CXCR4 in N87 cells by coimmunoprecipitating these two proteins. Because the AKT, ERK, and JAK2/STAT3 signaling pathway aberrations could promote metastasis, they further investigated the interplay between these pathways and B7-H3. Results obtained in this study suggested that B7-H3 silencing suppressed GC cell migration and invasion by reducing AKT, ERK, and JAK2/STAT3 pathway activation[120].

Cancer-associated fibroblasts (CAFs) represent an important component of the tumor microenvironment. These cells modulate cancer metastasis by synthesizing and remodeling the extracellular matrix and production of growth factors. Also, they have a strong influence on angiogenesis, tumor mechanics, drug access, and therapy responses. Some evidence shows that CAFs could modulate the immune system[123]. Alpha-smooth muscle actin (α-SMA) is one of the cytokines secreted by CAFs that is associated with the progression of various malignancies, such as osteosarcoma, head and neck squamous cell carcinoma, and lung adenocarcinoma. Zhan *et al*[31] found that in stromal cells of GA patients, B7-H3 is mainly expressed in α-SMA-positive fibroblasts. In addition, high stromal B7-H3 expression and high α-SMA expression were associated with significantly poorer OS, whereas B7-H3 depletion led to reduced CAF migration, invasion, and cytokine secretion abilities.

B7-H3 antiapoptotic activity in GC

Radiotherapy plays a significant role in the treatment of GC. However, radioresistance in GC cells remains a serious concern. A primary reason for this is the cancer cells' capacity to evade radiation-induced cell death[109,124]. B7-H3 can increase the radioresistance of GC cancer cells by modulating apoptosis, cell cycle progression, and DNA double-strand breaks. Li *et al*[109] used two different GC cell lines: SGC-7901 cells constructed to overexpress B7-H3 by lentiviral transfection and MGC-803 for the shRNA knockdown of B7-H3. After irradiation, they assessed cell viability by using crystal violet staining and reported that B7-H3 silencing enhanced radiosensitivity and cell death, while the B7-H3 overexpression increased the radioresistance of GC cells. The proportion of apoptotic cells was determined by flow cytometry and confirmed previous results that B7-H3 inhibited radiation-induced apoptosis in GC cells. Moreover, they found that B7-H3 overexpression increased the radioresistance of GC cells by modulating DNA double-strand breaks by decreased formation of nuclear γH2AX (form of the histone variant H2AX that is phosphorylated at the Ser-139 residue) foci after irradiation. Formation of γH2AX by phosphorylation of the Ser-139 residue of H2AX is an early cellular response to the induction of DNA double-strand breaks, and it is often used as a highly specific and sensitive molecular marker for monitoring DNA damage and repair in the context of ionizing radiation[125]. In addition, B7-H3 overexpression increased the radioresistance by modulating cell cycle arrest. It was also found that B7-H3 overexpression downregulated autophagy in GC cell lines, which was demonstrated by diminished levels of microtubule-associated protein 1A/1B-light chain 3 in B7-H3-overexpressing cells. Finally, transmission electron microscopy and immunohistochemical analysis performed on patient tissue

samples confirmed that B7-H3 increased the radioresistance of GC cells through regulating baseline levels of cell autophagy[109].

B7-H3 IN EC

EC is the eighth most common cancer worldwide, with 572000 new cases *per* year[2]. Causing about 509000 deaths annually, it continues to be a largely fatal malignancy with overall 5-year survival ranging from 15% to 20%[2,126]. Histologically, most ECs are divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). EAC represents the most common pathological type of EC in Western countries, whereas the main type in Asia is ESCC[126,127]. Approximately 70% of patients with EC are men, and male predominance is even more marked in the EAC histological subtype[2,126]. Significant risk factors for ESCC include smoking, alcohol use, and achalasia, whereas major risk factors for EAC are gastroesophageal reflux disease, Barrett's esophagus, obesity, and smoking[128,129].

Currently, EC treatment requires a multimodal approach. In some early-stage EC cases that have minimal local involvement (stage T1a and sometimes T1b) and no lymph node involvement and metastasis, endoscopic management could be an option. Locally advanced, nonmetastatic EAC and ESCC (stage T1b–T4, N1–N3, M0) require surgical resection in most cases. Survival of EC patients with ≥ T2 tumors or lymph node involvement that are treated only surgically, is poor, so the additional treatment, including neoadjuvant or perioperative chemotherapy, radiotherapy, or chemoradiotherapy, represents the standard for patients with ≥ T2 EAC and ESCC[130]. Nevertheless, the limited efficacy and severe adverse effects of conventional treatments demanded the development of new therapeutic approaches, which are primarily based on targeted therapy.

Epidermal growth factor receptor (EGFR) inhibitors, such as cetuximab, improve progression-free survival and OS in patients with resectable ESCC without increasing toxicity or postoperative morbidity. However, therapy success is reduced due to drug resistance caused by mutations in EGFR-related genes. Inhibitors of PD-L1 (pembrolizumab), VEGFR-2 (ramucirumab), and HER-2 (trastuzumab) have been verified to improve survival and prognosis in advanced ESCC and EAC[131]. Despite the use of all currently available strategies, the 5-year survival rate is still far from satisfactory [126]. Contrary to CRC and GC, there are just a few studies regarding B7-H3 involvement in the pathogenesis of EC.

B7-H3 in tumor cells of EC and immunity

B7-H3 is observed on the membrane and in the cytoplasm of EC cells, whereas the expression of B7-H3 on healthy esophageal tissue is quite rare[26,127,132]. Chen *et al*[26] estimated the correlation between patient clinical parameters and tumor cell B7-H3 expression, and reported that the lower B7-H3 expression correlated with better OS rate.

The B7-H3-related prognosis of the patients with EC is described by various molecular mechanisms. As we mentioned before, B7-H3 has a crucial role in immune regulation, EMT promotion, invasion, and metastasis in different gastrointestinal cancers[11]. Accordingly, Chen *et al*[26] investigated the relationship between B7-H3 and $CD3^+$ T cell infiltration in EC patients. They observed that B7-H3 expression negatively correlated with the density of infiltrating $CD3^+$ T cells in EC patients' tissues. These results suggested that B7-H3 might be involved in the suppression of a T cell-mediated antitumor response.

Similar results were shown by Wang *et al*[132], indicating an underlying role of B7-H3 in the evasion of immunity in ESCC. First, high B7-H3 expression levels were associated with lymph node metastasis, and patients with B7-H3 highly expressed tumors had poor prognosis. It was discovered that the number of infiltrating $CD8^+$ T cells was significantly lower in B7-H3-high-expressing tumor tissue, indicating that B7-H3 expression in ESCC may play an important role in overcoming $CD8^+$ T cell antitumor activity. This is in accordance with the result obtained by Guo *et al*[113] regarding the lower density of $CD8^+$ cells in GC tissues with B7-H3 overexpression.

Regulatory T cells (Tregs) are essential controllers of peripheral immune tolerance, preventing autoimmune diseases and limiting chronic inflammatory diseases[133]. Tregs influence metabolic inflammation and tissue repair[134]. However, these cells have also been found to inhibit antitumor immunity, and their infiltration correlates significantly with a worse outcome in advanced EC patients[133,135]. In the study by Wang *et al*[132], a positive correlation between Tregs infiltration and B7-H3 expression

in ESCC tissue was noted. This result illustrates that coinhibitory molecules such as B7-H3 could play immunosuppressive roles by recruiting and activating the number of suppressor T cells to mediate tumor immune escape and accelerate cancer development. Similarly, the density of $CD68^+$ tumor-associated macrophages was also increased in high B7-H3 expressing ESCC tissue, and it is well known that in various types of cancer tumor-associated macrophages are able to promote EMT, tumor cell invasion, migration, and angiogenesis[54,58,132,136].

B7-H3 promotes progression in EC

The involvement of B7-H3 protein in EC progression was examined in the study by Chen *et al*[26]. They performed the transfection of Eca-109 human EC cell line with shRNA for B7-H3. Results indicated that the knockdown expression of B7-H3 could inhibit the proliferation, colony formation ability, migration and invasion of the human EC cell line, suggesting that the B7-H3 expressed by tumor cells could significantly promote progression in this malignancy. The B7-H3 knockdown in the Eca-109 EC cell line was also performed by Wang *et al*[132]. Their *in vitro* study also revealed that B7-H3 downregulation reduced the invasive and migratory ability of Eca-109 cells, but did not suppress their proliferation. In addition, their *in vivo* study examined B7-H3 expression in various stages of ESCC carcinogenesis induced by 4-nitroquinoline 1-oxide in mice. It was observed that B7-H3 was weakly expressed or absent in normal esophageal tissues and esophageal tissues in the stage of dysplasia, but highly expressed in the carcinoma stage. These findings confirm the role of B7-H3 in esophageal carcinogenesis.

The same study[132] also revealed that ESCC patients with lower expression of B7-H3 and B7-H4 had significantly longer OS. Concomitantly, patients with both B7-H3 and B7-H4 high-expressing tumors had the poorest prognosis, whereas those with low coexpression of these molecules had the best survival. Similar results were obtained by Chen *et al*[137]. They showed that the high expression of both B7-H3 and B7-H4 was associated with increased invasion as well as high TNM stage in patients with ESCC. A combination of B7-H3 and B7-H4 expression could be used as a valuable risk factor for predicting the prognosis of patients with ESCC[132,137].

Finally, Song *et al*[127] detected high expression of B7-H3 and EGFR in most patients with ESCC. The high expression of both B7-H3 and EGFR was associated with more advanced tumor infiltration and clinical staging. Patients with higher expression of B7-H3 or EGFR had worse OS and progression-free survival.

B7-H3 AS A POTENTIAL THERAPEUTIC TARGET IN GASTROINTESTINAL TUMORS

Targeted therapy represents a new promising therapeutic approach for several cancers and has the specific advantage of more efficacy and less side effects compared to traditional chemotherapy[7,138]. Recent scientific data have provided strong evidence that B7-H3 is a valuable target protein for immune-based antitumor therapy due to its overexpression across several different types of cancer but seldom in normal cells[7,16]. B7-H3 was also found to be overexpressed in the most common tumors of the GIT, CRC, GC, and EC, while minimal expression of this molecule was found in healthy colorectal, gastric and esophageal tissues[26,38,61,111]. Moreover, this molecule was shown to be expressed in tumor stroma and vasculature of GIT tumors, making it a potential target to disrupt the tumor microenvironment and inhibit angiogenesis[31,50]. Furthermore, the involvement of B7-H3 in various processes of tumorigenesis in these cancers was confirmed by many studies. *In vitro* and *in vivo* studies showed that experimental depletion or blocking of B7-H3 in gastrointestinal cancers may enhance the antitumor immune response[22], inhibit tumor progression, invasion, and metastasis[26,28,38,111,120], and decrease resistance to anticancer therapy[62,71,74]. Also, it was shown that B7-H3 knockdown could influence cancer cell metabolism[27,94] and may reduce the carcinogenic activity of tumor stromal cells such as CAF[123].

Regarding the molecular mechanisms of carcinogenesis mentioned in this review, targeting B7-H3 could be a potential therapeutic modality to impair GIT tumor development and progression. Different agents could be used to target the tumor-specific molecules: mAbs, bispecific antibodies, and chimeric antigen receptor T cell (CAR-T) therapy.

Monoclonal antibodies: Monoclonal antibodies are monovalent laboratory-produced antibodies derived from a single B cell clone and predetermined to target the same

epitope[139]. Their development made a significant advancement in the treatment of various malignant tumors[140]. Therapeutic functions of mAbs could be exerted through multiple molecular mechanisms, including enhancement of the antitumor immune response, inhibition of tumor signaling pathways, inhibition of angiogenesis, induction of apoptosis, and delivery of payloads (*i.e.*, cytotoxic agents, toxins, or radioisotopes) to the targeted tumor site[141].

Recent studies showed that targeting immune checkpoints, such as PD-1, PD-L1 and CTLA-4, with blocking mAbs is very effective in treating patients with different kinds of tumors[142]. However, the treatment of B7-H3 expressing gastrointestinal tumors with blocking mAbs has been examined in only a few preclinical studies. Lu *et al*[22] demonstrated that MIH35, a blocking B7-H3 mAb, significantly enhanced the cytotoxic effect of Vδ2 T cells on colon cancer cells *in vitro* and in mice models. Furthermore, B7-H3 blockade by 3E8, a specific B7-H3 antibody, significantly sensitized CRC cells to irradiation in the xenografts of nude mice[74].

Despite the satisfying results obtained from *in vitro* studies and animal models, the development of cancer treatment strategies in humans by using a blocking B7-H3 mAb is difficult because the B7-H3 receptor still remains unknown[143]. However, the other antibody-based strategies utilizing different effector mechanisms to target B7-H3-expressing cancer cells have been tested in clinical trials[143]. In preclinical studies, enoblituzumab (MGA271), a mAb reactive to cancer-associated B7-H3, demonstrated enhanced antitumor activity through potent antibody-dependent cell-mediated cytotoxicity against a broad range of tumor cell types[7,15].

A phase I clinical study of enoblituzumab had been conducted in patients with refractory tumors that overexpress B7-H3: Prostate cancer, renal cell carcinoma, head and neck cancer, triple-negative breast cancer, bladder cancer, non-small lung cancer, and melanoma (Trial NCT01391143)[144]. Another B7-H3 mAb, 8H9, radiolabeled with ^{131}I was used to treat relapsed neuroblastoma involving the central nervous system. The intrathecal administration of ^{131}I-8H9 improved the survival of patients with relapsed central nervous system neuroblastoma[145]. A further investigation on MGA271 and 8H9 mAbs in CRC, GC, and EC treatment is necessary as well as the precise determination of the B7-H3 receptor and development of blocking B7-H3 mAbs that will be used in GIT tumors.

Antibody-drug conjugates are mAbs specifically linked to anticancer cytotoxic payloads. This way a cytotoxic agent could be selectively delivered to cancer cells [146]. In a preclinical study, monomethyl auristatin E-linked anti-B7-H3 antibody-drug conjugates displayed a dose-dependent antitumor activity against B7-H3-expressing tumor cells in CRC cell lines HCT-116, KM12, and HT29. Also, pyrrolobenzodiazepine-conjugated B7-H3 antibody-drug conjugates destroyed both colon cancer cells and endothelial cells of the tumor vasculature, eradicating established tumors and metastases and improving long-term OS in mice[11,50].

Bispecific antibodies: Bispecific antibodies are antibodies containing two different antigen-binding sites[147]. Dual specificity provides diversity in treatment strategies, including redirecting immune cells to cancer cells, inhibition of the two different signaling pathways at the same time, delivering payloads to tumor sites, and dual targeting of various disease mediators[148]. Targeting of two antigenic determinants enables bridging of cytotoxicity-triggering receptors on an effector cell (such as CD3 on T cells) with selected surface molecules on tumor cells[149]. This kind of immune synapse-like interaction was shown to be sufficient for the activation of T cells and killing of the tumor cells, even in the absence of the additional costimulatory signal [150]. This ability was tested by Ma *et al*[151]. Anti-CD3-anti-B7-H3 bispecific antibodies were used to direct activated T cells to kill B7-H3 expressing tumor targets. It was discovered that activated T cells armed with anti-CD3-anti-B7-H3 bispecific antibody secreted more IFN-γ, TNF-α, and IL-2 than unarmed activated T cells and had enhanced cytotoxic activity against a wide range of B7-H3-expressing tumors, including CRC, pancreatic cancer, lung cancer, breast cancer, prostate cancer, cervix cancer, and glioblastoma. B7-H3 bispecific-armed activated T cells also mediated higher levels of specific cytotoxicity against B7-H3-positive tumor cells compared with B7-H3 mAb alone. Because B7-H3 is negatively correlated with $CD3^+$ infiltration in CRC and EC tissue, anti-CD3-anti-B7-H3 bispecific antibody may potentially be used to recruit immune cells in the tumor nest and stimulate their antitumor effects[26,61].

The safety and tolerability of orlotamab (MGD009), a humanized, bispecific dual-affinity re-targeting molecule that recognizes both B7-H3 and CD3 has been examined in a phase I clinical trial (NCT02628535). The study included patients with B7-H3-expressing tumors such as colon cancer, mesothelioma, bladder cancer, melanoma,

squamous cell carcinoma of the head and neck, non-small lung cancer, clear cell renal cell carcinoma, ovarian cancer, thyroid cancer, triple-negative breast cancer, pancreatic cancer, soft tissue sarcoma, and prostate cancer. The aim of this study was to also evaluate pharmacokinetics, pharmacodynamics, and potential antitumor activity of MGD009[152].

CAR-T cell: CARs are fusion proteins that consist of a single-chain mAb fragment and one or more intracellular signaling domains of the T cell receptor. CAR-T therapy starts with an *ex vivo* genetic modification of a patient's autologous T cells. This modification provides the T cells with a tumor antigen-specific CAR. After cell expansion, CAR-T cells are reinfused back into the patient[153]. Many clinical trials had focused on CAR-T therapy in hematological malignancies, and certain advances were made. However, solid tumors are less susceptible to this kind of therapy because of the lack of adequate cancer-specific antigens that can be targeted by CAR-T cells [154]. It has been shown that the density of target antigen may be a crucial factor for successful recognition and killing by CAR-T cells[16].

The number of B7-H3 positive samples in CRC[18,51,61], GC[31,112,120], and EC[26, 132,137] patient tissues as well as the number of B7-H3-high-expressing tumors among B7-H3 positive samples varies according to the results of different studies. This heterogeneous expression of B7-H3 in tumors of the GIT indicates that it may be necessary to examine the B7-H3 expression status in surgical specimens before starting a targeted therapy. Targeting various tumor antigens of CRC, GC, and EC have been examined in CAR-T cell-related clinical trials. However, there has still not been a study testing a B7-H3 CAR-T in these tumors[154]. Yang *et al*[155] constructed a preclinical model of human lung cancer and melanoma, which was treated by a tandem CAR molecule targeting two tumor-associated antigens: B7-H3 and CD70. This bivalent targeting CAR-T cell induced a superior antitumor effect and tumor regression in a lower dose than unspecific CAR-T cells. This study also showed that B7-H3 and CD70 were coexpressed on multiple solid tumors, including colon, esophageal, liver, kidney, breast and brain cancer, whereas their expression in normal tissues was not detected. This is a promising fact for a therapy with good selective toxicity. The results of this study indicate that colon cancer and EC may be adequate candidates for tandem CAR-T cell therapy targeting B7-H3 and CD70. The coexpression B7-H3 and EGFR in most patients with ESCC could potentially be used to create tandem CAR-T targeting these two tumor antigens[127].

CONCLUSION

B7-H3 is significantly expressed among the most common cancers of the GIT, including CRC, GC, and EC, whereas its expression in normal healthy tissue of these organs was shown to be absent or minimal. The influence of B7-H3 on progression, metastasis, and resistance to anticancer therapy of these tumors is remarkable (Figure 1). The results of the studies analyzed in this review suggest that B7-H3 can modify the immune response and provide tumor immune evasion *via* reducing T lymphocyte infiltration and inhibiting their effector/cytotoxic activity as well as by modifying the activity of memory T cells and Tregs. Furthermore, B7-H3 is involved in GIT cancer progression and metastasis through various nonimmunological mechanisms. This molecule can promote migration of gastrointestinal cancer cells, invasion, and angiogenesis. In addition, resisting cell death and resistance to chemotherapy and radiotherapy of GIT tumors seem to be associated with the overexpression of B7-H3, which can modify the expression of pro- and antiapoptotic genes, the activity of the cell cycle controlling proteins, and DNA repair mechanisms. Many of the abovementioned tumorigenesis stimulating molecular mechanisms result from B7-H3-related induction of signal transduction pathways, such as JAK2/STAT3, PI3K/Akt, ERK, and NF-κB. B7-H3 influence on nonimmunological cells of the tumor microenvironment, such as macrophages and fibroblasts, also takes part in the cancer-promoting action of this molecule. Finally, as an essential hallmark of cancer, reprograming cancer cell metabolism was also shown to be related to the expression of B7-H3.

Most available data show that the overexpression of B7-H3 is associated with worse prognosis in CRC, GC and EC, making it a valuable prognostic marker. High levels of the soluble isoform detected in the sera of patients with CRC suggest that sB7-H3 may be a potential non-invasive biomarker for this tumor.

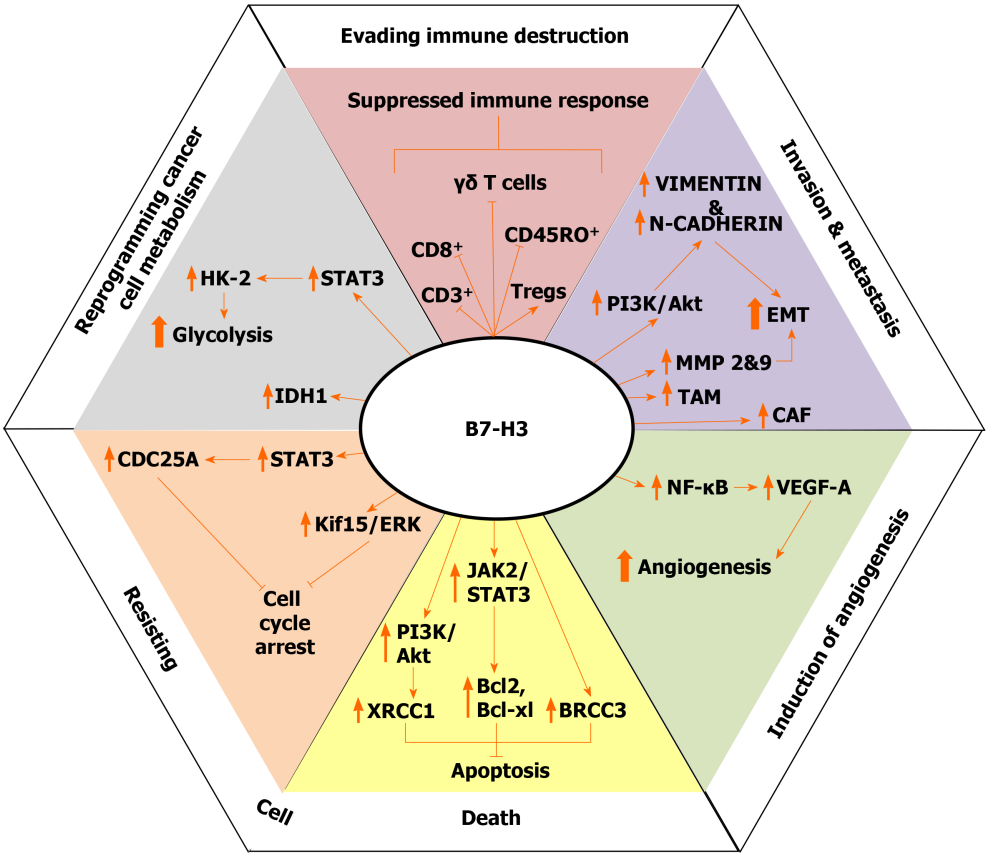

Figure 1 Potential roles of the B7 homologue 3 protein in gastrointestinal tumors described through the "hallmarks of cancer". In this schematic overview, we summarized the published findings of the B7 homologue 3 (B7-H3) effects on the biological behavior of gastrointestinal tract tumors. Some of these molecular mechanisms are presented as the result of B7-H3-related induction of several signaling pathways involved in the coordination of gene expression, reprogramming of cancer cell metabolism, resisting cell death, and promotion of angiogenesis, invasion, and metastasis. The arrow-headed lines represent induction, while the bar-headed lines denote inhibition. AKT: Protein kinase B; B7-H3: B7 homologue 3; Bcl-2: B cell lymphoma 2; Bcl-xl: B cell lymphoma-extra-large; BRCC3: BRCA1/BRCA2-containing complex 3; CAF: Cancer-associated fibroblasts; CDC25A: Cell division cycle 25A protein; EMT: Epithelial–mesenchymal transition; ERK: Extracellular-signal-regulated kinase; HK2: Hexokinase 2; IDH1: Isocitrate dehydrogenase 1; JAK2: Janus kinase 2; KIF15: Kinesin family member 15; MMP: Matrix metalloproteinase; NF-κB: Nuclear factor-kappa B; PI3K: Phosphatidylinositol 3-kinase; STAT3: Signal transducer and activator of transcription 3; TAM: Tumor-associated macrophage; Tregs: Regulatory T cells; VEGFA: Vascular endothelial growth factor A; XRCC1: X-ray repair cross complementing group 1.

Finally, all the summarized, established data imply that B7-H3 could be a promising therapeutic target for anticancer therapy in GIT tumors. *In vitro* and *in vivo* studies confirmed that experimental depletion or inhibition of B7-H3 in gastrointestinal cancers improved antitumor immune response, impaired tumor progression, invasion, angiogenesis, and metastasis, and decreased resistance to anticancer therapy. Unfortunately, there are just a few clinical studies that involve B7-H3 targeting in GIT tumors.

We assume that the determination of the B7-H3 receptor is one of the first steps to the successful use of B7-H3 blocking agents in therapy. Furthermore, future research should reveal the precise molecular mechanism of immunological and nonimmunological roles of B7-H3, with the aim of creating the effective and selective anticancer drugs. The heterogeneity of B7-H3 expression in GIT cancers demands a thorough detection of B7-H3 in tumor tissue before the use of targeted therapy. In the end, the perspective of B7-H3 as a prognostic biomarker and potential therapeutic target should be examined in the other, less frequent, tumors of the GIT, such as carcinoid tumors, gastrointestinal stromal tumors, lymphomas, sarcomas, and desmoid tumors.

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