Bone marrow stromal cell antigen 2: Tumor biology, signaling pathway and therapeutic targeting (Review)

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Abstract. Bone marrow stromal cell antigen 2 (BST2) is a type II transmembrane protein that serves critical roles in antiretroviral defense in the innate immune response. In addition, it has been suggested that BST2 is highly expressed in various types of human cancer and high BST2 expression is related to different clinicopathological parameters in cancer. The molecular mechanism underlying BST2 as a potential tumor biomarker in human solid tumors has been reported on; however, to the best of our knowledge, there has been no review published on the molecular mechanism of BST2 in human solid tumors. The present review focuses on human BST2 expression, structure and functions; the molecular mechanisms of BST2 in breast cancer, hepatocellular carcinoma, gastrointestinal tumor and other solid tumors; the therapeutic potential of BST2; and the possibility of BST2 as a potential marker. BST2 is involved in cell membrane integrity and lipid raft formation, which can activate epidermal growth factor receptor signaling pathways, providing a potential mechanistic link between BST2 and tumorigenesis. Notably, BST2 may be considered a universal tumor biomarker and a potential therapeutical target.

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Abbreviations: BST2, bone marrow stromal cell antigen 2; HIV, human immunodeficiency virus 1; OSCC, oral squamous cell carcinoma; HCC, hepatocellular carcinoma; TGFβ, transforming growth factor-β; CBX, chromobox 6; IFNα, interferon α; EGFR, epidermal growth factor receptor; ILT7, immunoglobulin-like transcript 7; STAT3, signal transducer and activator of transcription 3; EZH2, enhancer of zeste homolog 2; GRB2, growth factor receptor bound protein 2; ERK, extracellular signal-regulated kinase; pDC, plasmacytoid dendritic cell; PI3K, phosphoinositide 3-kinase; AKT, serine/threonine kinase; NF-κB, nuclear factor κB; ER, estrogen receptor

Key words: BST2, molecular mechanism, therapeutic target, cancer, lipid raft, EGFR

Contents

1. Introduction

Bone marrow stromal cell antigen 2 (BST2), which was originally named HM1.24, is a cell transmembrane protein that was initially reported to exhibit increased expression in multiple myeloma in 1994 (1). Later, BST2 was renamed tetherin and CD317, and was known as a potent antiviral host factor, due to its ability to inhibit the release of human immunodeficiency virus 1 (HIV-1) viral particles, which could be antagonized by the viral membrane HIV viral protein U (2). BST2 can regulate the response of hosts to viral infection either by restraining the generation of new viral particles or by inhibiting viral dissemination across viral synapses and in a monocyte-to-endothelial cell model (3). A decade later, the gene was renamed BST2, due to its expression on the membrane of bone marrow stromal cells, and it was revealed to be associated with the growth of pre-B cells through promoting interactions between cells (4). BST2 consists of 180 amino acids and is located on

chromosome 19p13.2. The BST2 gene is widely expressed in numerous cells, including hepatocytes, plasma blast cells, early plasma cells, mature B cells, dendritic cells, pneumocytes, monocytes, pancreatic cells, kidney cells and vascular endothelial cells, suggesting that it plays vital roles in the innate immune response against viral infection and other physiological processes (2,5-7). An increasing number of studies have shown that BST2 upregulation is associated with numerous types of cancer, such as multiple myeloma (8,9), endometrial cancer (10), gastric cancer (11), glioblastoma multiforme (12), primary lung cancer (13), nasopharyngeal cancer (14), oral cavity cancer (15), oral squamous cell carcinoma (OSCC) (16), cervical cancer (17), breast cancer (18), pancreatic cancer (19), hepatocellular carcinoma (HCC) (20), colorectal cancer (21,22), head and neck squamous cell carcinoma (23), ovarian cancer (24), esophageal squamous cell carcinoma (22) and bladder cancer (25). The role and molecular mechanism of high BST2 expression have been investigated in several types of cancer; however, a review of the molecular mechanism of BST2 in these cancers not been reported.

The present review illuminates the structure and functions of the BST2 gene, and describes the association between high BST2 expression and clinicopathological parameters. Furthermore, the molecular mechanisms of high BST2 expression in breast cancer, HCC, gastrointestinal tumors and other solid tumors are considered, and whether BST2 could be used as a potential therapeutic target as a cell transmembrane protein is discussed.

2. Methods

Search strategy and study selection. The present review is a narrative review regarding the role of BST2 expression in cancer. To evaluate the clinical outcomes and prognostic significance of BST2 protein expression in cancer, eligible studies were searched for in the following databases: PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Knowledge (https://webofscience.clarivate.cn/wos/woscc/basic-search) and Cochrane Library (https://www.cochranelibrary.com/?contentLanguage=eng), between January 1970 and June 2023. The following key words were used for searching: 'BST2', 'HM1.24', 'CD317', 'tetherin', 'Bone marrow stromal cell antigen 2' and 'human cancer'.

The inclusion criteria for the primary studies, which are shown in Table I, were as follows: i) Studies that investigated the relationship between BST2 gene expression and clinical characteristics in human cancer; ii) studies that measured BST2 expression via immunohistochemistry (IHC) and reverse transcription-quantitative (q)PCR; iii) studies that were published as full-text articles and in English. Finally, eight studies were collected to analyze the relationship between clinicopathological parameters and BST2 upregulation.

An independent search was carried out by HY and QB with the same search method. Differences were discussed with other authors until a consensus was reached on each item.

3. Structure and function of BST2

Structurally, BST2, as a type II transmembrane protein, is composed of four different regions, as follows: N-terminal cytoplasmic region, accompanied by a transmembrane region (TM), coiled-coiled ectodomain and C-terminal glycosylphosphatidylinositol (GPI)-anchor site (26). The cytoplasmic region of BST2 contains two highly conserved tyrosine domains, which might activate other signaling pathways (27). The BST2 cytoplasmic tail could also induce tumor cell invasion (28). The BST2 gene is expressed as a monomeric structure. When the BST2 gene is located on the cell membrane, two parallel monomer BST2 proteins undergo dimerization by disulfide-linking of three cysteine residues (29). The cysteine residues of human BST2 are located at positions 53, 63 and 91 (30). Dimerized BST2 is in an activated state and is essential for its antiviral activity (29,31). The glycosylation of the BST2 ectodomain is modified at two asparagine residues, which are located at positions 65 and 92 (32). Dimerized BST2 is anchored into the cell membrane and is responsible for virus/exosome tethering (33), signaling potential (34) and organization of membrane microdomains (35). BST2 contains a lipid raft in the GPI anchor motif and the TM domain (32,36). The GPI site can affect the transduction of cellular activation or inhibition signals, resulting in Ca^{2+} fluxes, protein tyrosine phosphorylation or cytokine secretion (37,38). The highly conserved YxY motif in the cytoplasmic region is important in nuclear factor (NF)-κB activation and for association with the actin cytoskeleton (34,39). The structure of BST2 is shown in Fig. 1. BST2 may interact with membrane proteins and activate signaling pathways through lipid raft flux. In addition, BST2 is located mainly on the cell membrane and is vital for protecting membrane integrity by modulating the cytoskeleton and protecting cancer cells from natural killer cell-mediated cytolysis (26,27); BST2 can also be located in the membrane of trans-Golgi and endosomes (27). Notably, BST2 is involved in cell membrane integrity and lipid raft formation, and can activate Ca^{2+} and NF-κB signaling pathways, providing a potential mechanistic link between BST2 and tumorigenesis.

4. BST2 and viral defense

BST2 is a restriction factor that can assist the host immune system against invading pathogens. Notably, BST2 was originally shown to prevent the release of HIV particles (2). In addition, BST2 can bind to other envelope proteins, and inhibit the release of several other viruses, including hepatitis C virus (HCV), hepatitis B virus (HBV), measles virus (MV) (40) and severe acute respiratory syndrome coronavirus 2 (41). Viral infection often stimulates interferon (IFN), which in turn can lead to high BST2 expression (42). There are various inflammatory cytokine binding sites in the BST2 gene promoter region, suggesting that BST2 expression can be regulated by inflammatory cytokines (18). After viral infection, plasmacytoid dendritic cells (pDCs) can quickly produce numerous type I IFNs, upregulating BST2 expression. Subsequently, increased BST2 expression on the membrane of pDCs has a cis interaction with immunoglobulin-like transcript 7 (ILT7) to protect cells from viral infection (43). BST2 may also inhibit replication and transmission of influenza A virus by enhancing endoplasmic reticulum stress-induced apoptosis signals (44). These findings indicated that BST2 is an important innate immune molecule against viral infections.

Table I. Relationship between clinicopathological parameters and BST2 upregulation, as detected by immunohistochemistry.

	Association with high BST2 expression									
Type of cancer	Age	Sex	T stage	N stage	M stage	Lymphatic invasion	Vascular invasion	Tumor differentiation	Other outcomes	(Refs.)
Gastric cancer	-	NR	NR	+	+	+	NR	NR	Tumor size (-) Pathological grade (-) Lymph node metastasis (+)	(74)
	-	-	+	-	-	+	+	NR	Histological classification (+) HER2 expression (-)	(22)
Oral squamous cell carcinoma	-	-	-	NR	NR	NR	NR	-	Tumor depth (+) Perineural invasion (+) Bone invasion (-)	(15)
Renal cell carcinoma	+	-	+	+	+	NR	NR	NR	Overall survival (+) Histological classification (-)	(87)
HCC	-	-	-	-	-	NR	NR	-	Tumor number (+) Overall survival (+) Tumor size (+)	(20)
Bladder cancer	-	-	+	NR	NR	-	-	NR	Cellular atypia classification (-)	(25)
Colorectal cancer	-	-	+	+	+	-	-	NR	Histological classification (-)	(22)
	NR	NR	-	-	-	NR	NR	-	Microsatellite status (+) Histological type (-)	(79)
	-	-	+	+	+	NR	NR	NR	Overall survival (+) Pathological grade (-) Histological type (-)	(77)
Esophageal squamous cell carcinoma	-	-	-	-	NR	+	-	NR	Histological classification (-) Poor survival (+)	(22)

+, positive association; -, negative association; BST2, bone marrow stromal cell antigen 2; HCC, hepatocellular carcinoma; NR, not reported.

5. BST2: Roles in carcinogenesis

As well as the antiviral function of BST2, accumulating evidence has suggested that high BST2 expression is involved in several tumors, including hematological malignancies (such as multiple myeloma) (8), Down syndrome megakaryocytic leukemia (45) and solid tumors. The relationship between BST2 upregulation and clinicopathological characteristics is listed in Table I. The upstream factors and downstream signaling pathways of BST2 are summarized in Fig. 2. The present review focuses on the molecular mechanism of BST2 in human solid tumors.

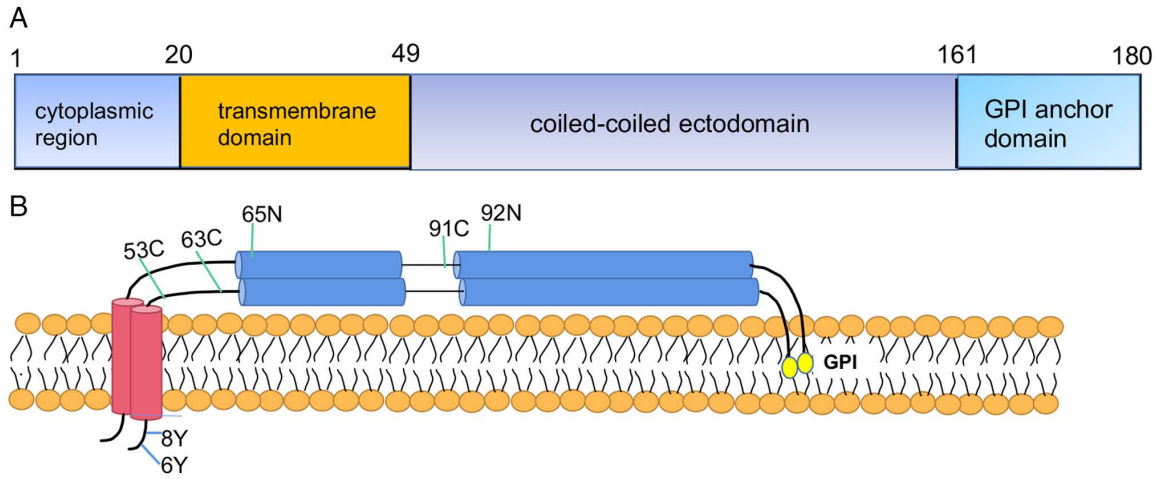

Figure 1. Schematic representation of human BST2 structure. (A) BST2 protein consists of four domains: N-terminal cytoplasmic region, transmembrane region, coiled-coiled ectodomain and C-terminal GPI-anchor domain. (B) Localization of BST2 on the cell membrane. Double tyrosine (Y) at positions 6 and 8 is vital for downstream factor activation. Cysteine (C) at positions 53, 63, and 91 is responsible for the formation of BST2 dimers. Asparagine (N) residues at positions 65 and 92 are glycosylation sites. The number represents the position of the amino acid. BST2, bone marrow stromal cell antigen 2; GPI, glycosylphosphatidylinositol.

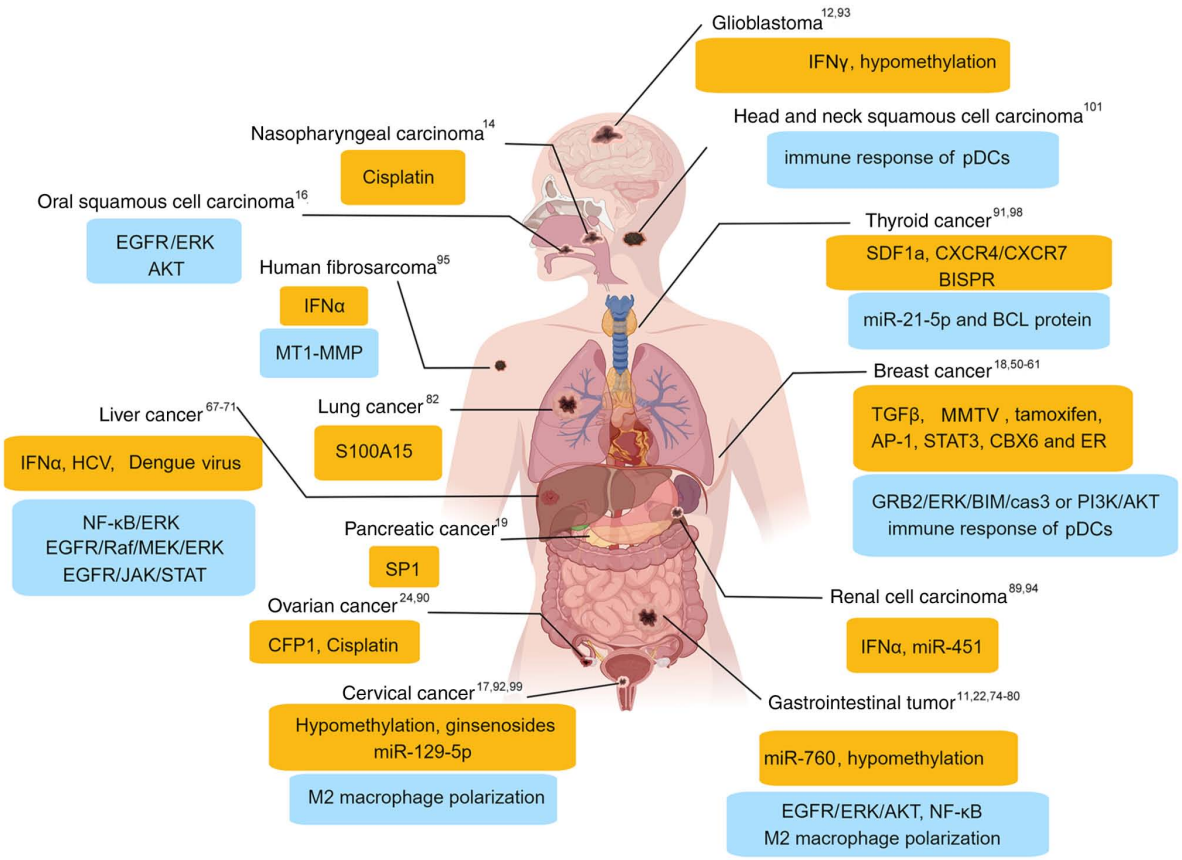

Figure 2. Schematic representation of molecular regulation of BST2. The upstream factors (yellow box) and downstream signaling factors or pathways (blue box) of BST2 in solid cancer are shown. The superscript numbers refer to the corresponding references. AKT, serine/threonine kinase; BISPR, BST2 IFN-stimulated positive regulator; BST2, bone marrow stromal cell antigen 2; cas3, caspase 3; CBX6, chromobox 6; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; GRB2, growth factor receptor bound protein 2; HCV, hepatitis C virus; IFN, interferon; JAK, Janus kinase; miR, microRNA; MMTV, mouse mammary tumor virus; pDCs, plasmacytoid dendritic cells; PI3K, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3; TGFβ, transforming growth factor-β.

BST2 and breast cancer. Breast carcinogenesis is generally accompanied by several genetic and epigenetic variations in normal or malignant cells. Over the last decade, therapy targeting specific biomolecules of breast cancer has been one of the directions of focus (46-48). Notably, the mRNA and protein expression levels of BST2 are elevated in breast cancer

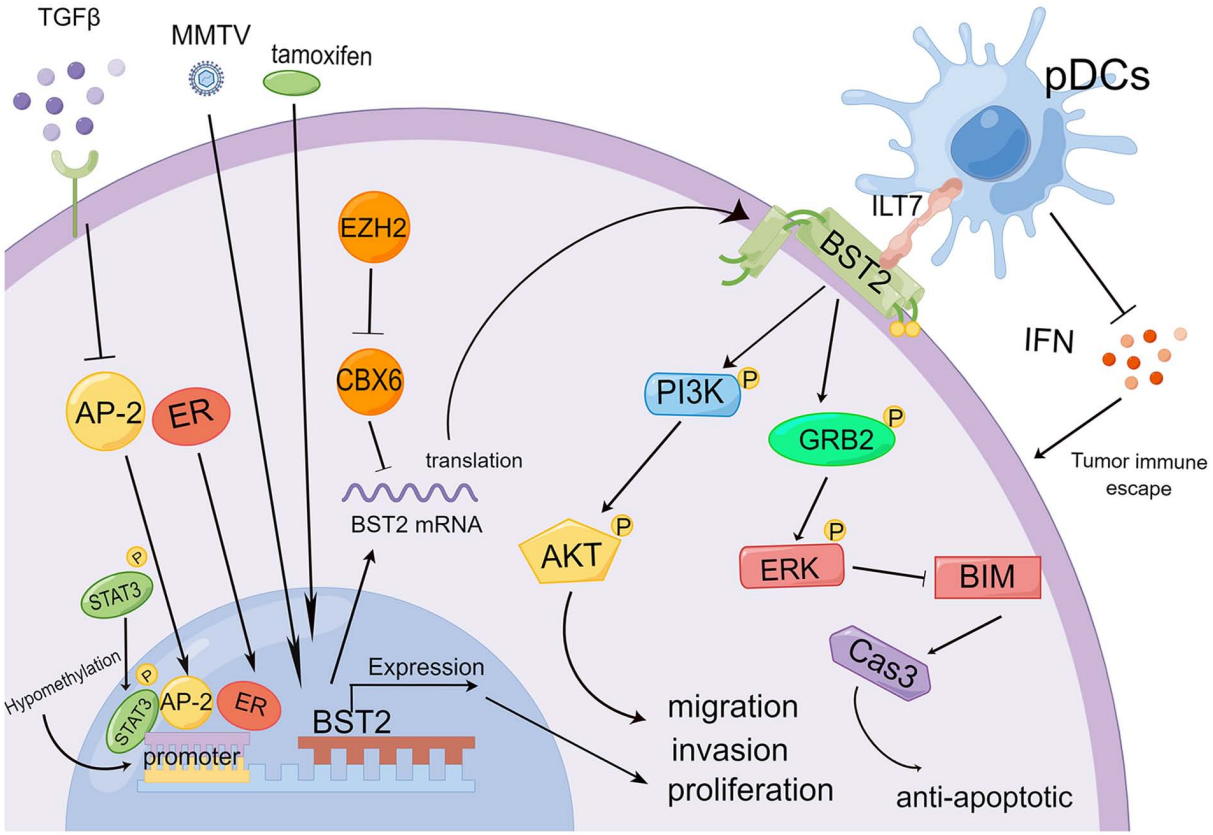

Figure 3. Molecular regulatory mechanism of high BST2 expression in breast cancer. Inflammatory microenvironment factors (TGFβ), viruses (MMTV) and drugs (tamoxifen) can regulate BST2 expression via activating transcription factors (AP-1, STAT3). Other factors (CBX6 and ER) can directly increase the expression of the BST2 gene. BST2 as a transmembrane protein can promote tumorigenesis, invasion and metastasis via the GRB2/ERK/BIM/cas3 or PI3K/AKT signaling pathways. BST2 upregulation can also inhibit the secretion of IFN in pDCs to enhance tumor escape. AKT, serine/threonine kinase; BST2, bone marrow stromal cell antigen 2; CBX6, chromobox 6; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste homolog 2; GRB2, growth factor receptor bound protein 2; IFN, interferon; ILT7, immunoglobulin-like transcript 7; MMTV, mouse mammary tumor virus; pDCs, plasmacytoid dendritic cells; PI3K, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3; TGFβ, transforming growth factor-β.

tissues and cells lines (4,18,28,42,46,49-60). In one study, the expression of BST2 was revealed to be significantly more increased than other known markers in breast cancer, such as human epidermal growth factor receptor (EGFR), estrogen receptor (ER), Myc or progesterone receptor (58).

Association between BST2 expression and clinical parameters in breast cancer. High BST2 expression is associated with some clinical parameters. BST2 has been shown to be significantly associated with tumor size in breast tumors and mammary cancer cells (54). BST2 can also increase cell proliferation, but is not associated with the percentage of apoptotic cells (4). BST2 has been reported to be highly expressed in grade 3 tumor cell lines (CCdl54, CCdl672 and CCdl675), as determined after analyzing 65 different breast cancer cells (18). Similar results have shown that BST2 mRNA expression is increased in high-grade luminal B tumors compared with that in low-grade luminal A tumors (54). BST2 also has a strong expression in preinvasive and invasive breast cancer cells (18) and tissues (49). Furthermore, BST2 upregulation increases the risk of bone metastasis. Another study confirmed that BST2 upregulation increases metastasis in a mouse model (54) and in bone metastatic breast tumor tissues (4). Moreover, Cox regression analysis has shown that increased BST2 expression is related to the prognosis of breast cancer (52). Notably, BST2 upregulation reduces survival and may be a predictor of distant metastasis (49,54). BST2 also promotes invadopodia formation and extracellular matrix degradation (49). These previous studies demonstrated that increased BST2 expression may be significantly associated with age, high grade, metastasis and survival rate.

Regulation of BST2 expression in breast cancer. The abnormal expression of BST2 has been summarized in previously published studies (Fig. 3). BST2 expression can be induced by several factors. Mouse mammary tumor virus infection can induce BST2 upregulation in mammary tumor tissues, and, as an adhesion molecule, BST2 can contribute to the metastasis and progression of cancer (57). The binding of transcription factor AP2 to the BST2 promoter is weakened by inhibiting the transforming growth factor-β (TGFβ) pathway, thereby increasing the expression of BST2 in tumor cells. High BST2 expression can inhibit the induction of apoptosis and enhance cell proliferation (18). Tamoxifen-induced BST2 expression has been reported to be involved in the invasion and migration of breast cancer (56). Active signal transducer and activator of transcription 3 (STAT3) is known to promote the malignancy of breast cancer, and can promote the transcription and expression of the BST2 gene (56,61). Chromobox 6 (CBX6), as an RNA-binding protein, can be

downregulated by enhancer of zeste homolog 2 (EZH2) and has decreased expression in breast cancer. Low expression of the CBX6 gene promotes BST2 expression, and enhances migration and invasion (51). Low expression of ER can also promote the expression of the BST2 gene, and high BST2 expression may be a potent predictor for poor patient survival and earlier activation of distant metastasis (50). Genome mutation analysis suggested that BST2 high mutation frequency is mainly induced by gene amplification, and increased BST2 expression is an independent prognostic indicator of breast cancer (52). Hypomethylation in the BST2 promoter region is correlated with high BST2 expression in breast cancer tissues and cell lines (55). Furthermore, increased BST2 expression can bind to the ILT7 ligand protein of pDCs and inhibit IFN release (42). Low levels of IFN further induce tumorigenesis through promoting tumor escape (62,63). Dimerization of BST2 may promote tumor cell proliferation via growth factor receptor bound protein 2 (GRB2)/extracellular signal-regulated kinase (ERK)/BIM/caspase 3 signaling pathway *in vivo* and *in vitro* (58). In addition, increased BST2 expression can activate phosphoinositide 3-kinase (PI3K)/serine/threonine kinase (AKT) in epithelial cells, gland cells and mammary tumors (57). These studies have suggested that BST2 gene expression is regulated by hypomethylation, viruses, and intracellular and extracellular factors (TGFβ, ER, AP2, STAT3, CBX6 and EZH2), and is involved in tumorigenesis via the GRB2/ERK/BIM/caspase 3 or PI3K/AKT signaling pathways in breast cancer.

BST2 and HCC. HCC is the most common type of primary liver cancer and the third most common cause of cancer-associated death worldwide (64). Numerous studies (65,66) have investigated the molecular biomarkers participating in HCC tumorigenesis; however, the intrinsic molecular mechanisms of the transmembrane protein BST2 in HCC are inadequately reported.

Expression and physiological functions of BST2 in HCC. Previous studies have shown that BST2 expression is significantly higher in HCC tissues than that in normal tissues (20,67,68). Similar results were confirmed in HCC cell lines, such as HepG2, Huh7, L02, HepAD38 and Huh7.5 (67,69,70). Xu *et al* (20) reported that BST2 upregulation is significantly associated with larger tumor size and overall survival, but is not related to sex, age, tumor differentiation, pathological grade and tumor-node-metastasis (TNM) stage, suggesting that BST2 could be an independent unfavorable prognosis factor (Table I). Another study revealed that high BST2 expression is also associated with HBV infection and overall survival (67). These studies have shown that higher expression of BST2 in patients with HCC is associated with a poorer prognosis.

Regulation of BST2 expression in HCC. The molecular mechanism of BST2 in HCC is shown in Fig. 4. First, IFNα can induce BST2 expression in HCV-infected or Dengue virus-infected HCC tissues or cell lines (69-71). HBV can also upregulate the expression of the BST2 gene in HCC tissues or cell lines (67). These studies suggested that BST2 may be an essential factor for the virus-induced tumorigenesis of HCC. Second, the endoplasmic reticulum degradation-enhancing α-mannosidase-like protein 3 protein is increased and is responsible for the trimming of BST2 in HCC cells. Non-N-glycosylation of BST2 at the N65 site is essential for BST2 function, and can promote the proliferation, migration, invasion and colony-forming ability of HCC cells through activating the NF-κB/ERK pathway. Non-N-glycosylation of BST2 may be a novel factor of BST2 in regulating HCC tumorigenesis (67). BST2 can also activate EGFR in a lipid raft-dependent manner, not mediated by EGFR ligands. Lipid rafts are known as cholesterol/sphingolipid-rich membrane domains, and exhibit higher levels in cancer cells than non-tumorigenic controls (72). The activation of EGFR further initiates the downstream signaling pathways, including the Janus kinase/STAT3 and Ras/Raf/MEK/ERK pathways. This mode of EGFR activation may be an interesting and potential therapeutic direction for targeting EGFR-driven malignancies (68). These studies have demonstrated that viral infection and IFNα may upregulate BST2 expression, and that high BST2 expression can activate the EGFR and NF-κB/ERK pathways in a lipid raft-dependent manner in HCC.

BST2 and gastrointestinal tumors. Both gastric cancer and colorectal cancer are types of gastrointestinal cancer, which is one of the most common malignant tumors in the world, with 4.8 million new cases and 3.4 million deaths reported in 2018 (73). Therefore, it is necessary to explore effective biomarkers for the diagnosis of gastrointestinal cancer.

Expression and physiological functions of BST2 in gastrointestinal cancer. Several studies have reported that increased BST2 expression is detected in gastric cancer (11,22,74,75). Similar results have also been found in colorectal cancer by whole exome sequencing data, gene array and IHC (21,22,76,77). Combining 606 patients from The Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus databases has shown that BST2 may be highly associated with prognosis (78). IHC and qPCR further confirmed that BST2 is mainly located in the cell membrane or cytoplasm, and high BST2 expression is detected in colorectal cancer compared with that in controls (78). The association between BST2 and clinical parameters in gastric and colorectal cancer has also been discussed in some previous studies. High BST2 expression has been shown to be significantly associated with histological classification, invasion, T classification and poor survival (Table I) (22). BST2 upregulation is also significantly related to lymph node metastasis and TNM stage (Table I) (74). In colorectal cancer, BST2 positive expression is closely associated with TNM stage and poorer survival (Table I) (22,77). However, high BST2 expression is not significantly linked to other clinicopathological parameters, including age, sex, histological grade, tumor location and distant metastasis (Table I) (77). These findings indicated that increased BST2 expression may be associated with the progression of gastric and colorectal cancer.

Regulation of BST2 expression in gastrointestinal cancer. The molecular mechanism of BST2 was summarized in this review according to the findings from previous studies (Fig. 5) (11,22,79,80). BST2 expression can be regulated by microRNAs (miRNAs/miRs) (11) and hypomethylation (79). BST2 has been reported to be regulated by miR-760, and to promote cell proliferation and migration by inducing NF-κB activation in gastric cancer (11). Upregulation of BST2 has

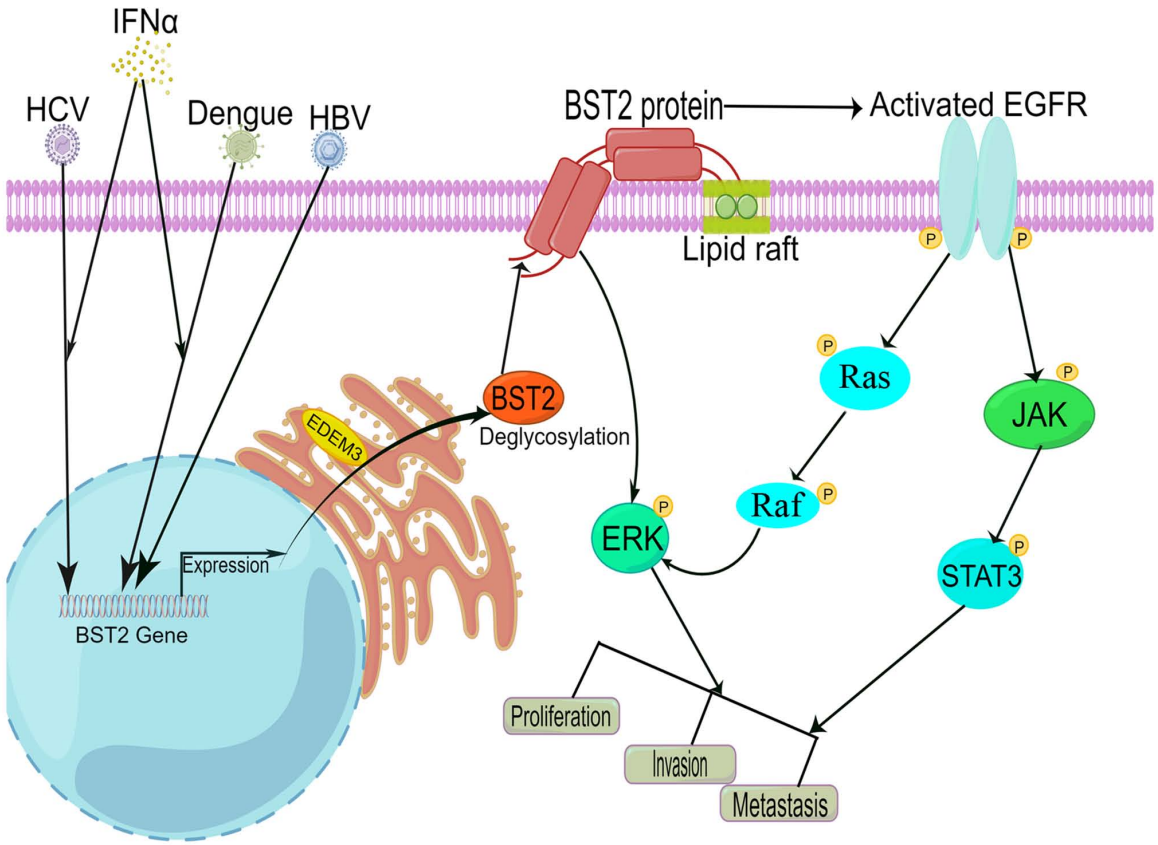

Figure 4. Molecular regulatory mechanism of high BST2 expression in HCC. IFNα can induce BST2 expression in HCV-infected or Dengue virus-infected HCC tissues or cell lines. HBV could upregulate the expression of the BST2 gene in HCC tissues or cell lines. Deglycosylation of BST2 enhances the proliferation, invasion and colony formation of hepatocytes *in vivo* via the NF-κB/ERK pathway. BST2 can activate EGFR via a lipid raft-dependent manner, not mediated by EGFR ligands. Subsequently, the activation of EGFR regulates downstream signaling pathways, including the Ras/Raf/MEK/ERK and JAK/STAT pathways. BST2, bone marrow stromal cell antigen 2; EDEM3, endoplasmic reticulum degradation-enhancing α-mannosidase-like protein 3; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; JAK, Janus kinase; NF-κB, nuclear factor-κB; STAT3, signal transducer and activator of transcription 3.

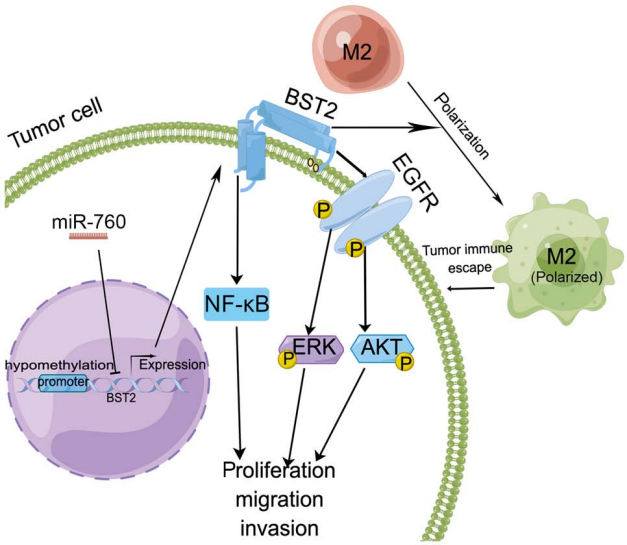

Figure 5. Molecular regulatory mechanism of high BST2 expression in gastrointestinal tumors. BST2 expression can be regulated by miRNAs and hypomethylation. BST2 induces macrophage M2 polarization to promote the progression of colorectal cancer to enhance tumor escape. BST2 may enhance proliferation, survival and migration via the EGFR/ERK/AKT or NF-κB signaling pathways. AKT, serine/threonine kinase; BST2, bone marrow stromal cell antigen 2; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; miR/miRNA, microRNA; NF-κB, nuclear factor-κB.

also been revealed to be significantly associated with worse survival in patients with colorectal cancer (79). BST2 may also enhance cell proliferation and survival by activating EGFR/ERK/AKT (22). In addition, BST2 can promote the progression of colorectal cancer via inducing macrophage M2 polarization (80). These studies indicated that BST2 may enhance proliferation, survival and migration by activating the EGFR/ERK/AKT or NF-κB signaling pathways, and reducing immune surveillance of M2 macrophages.

BST2 and lung cancer. Wang *et al* (13) reported that BST2 expression is positive in 42% of non-small cell lung cancer cell lines and 57% of small cell lung cancer cell lines, and that BST2 overexpression can promote tumor growth. Additionally, a higher expression of BST2 has been detected in neoadjuvant-treated non-small cell lung cancer (81). RNA sequencing analysis has revealed that BST2 can promote lung cancer progression via the induction of S100A15 (82). Bioinformatics analysis has demonstrated that BST2 is significantly associated with progression-free survival in 34 lung cancer database samples (83). For therapeutic targeting of BST2 in lung cancer, antibodies and cytokine factors have been examined. Modified anti-BST2 monoclonal antibodies, such as chimeric or humanized antibodies, have the potential to be new therapeutic targets in lung cancer; moreover, it could be more effective

to enhance antibody-dependent cell-mediated cytotoxicity when combining an anti-BST2 antibody with ILs/IFNs (84). Combination therapy with an anti-BST2 antibody and IFN-β has been shown to exhibit increased antitumor effects in lung cancer in a mouse model (13). Therefore, BST2 may promote cell proliferation and tumor progression in lung cancer, and combination therapy might be more effective than antibody therapy in lung cancer.

BST2 and other solid tumors. An increasing number of studies have shown that BST2 upregulation is associated with numerous types of cancer, including endometrial cancer (10), glioblastoma multiforme (12), nasopharyngeal cancer (14), oral cavity cancer (15), OSCC (16), cervical cancer (17), pancreatic cancer (19), head and neck squamous cell carcinoma (23), ovarian cancer (24), esophageal squamous cell carcinoma (22) and bladder cancer (25).

Expression and physiological functions of BST2 in other types of solid cancer. Abnormal BST2 expression is associated with different clinical parameters. In head and neck squamous cell carcinoma, Kaplan-Meier survival curve analysis has suggested that high BST2 expression is associated with a worse prognosis; however, tissue microarrays have shown that high BST2 expression is not significantly related with larger tumor size, higher histological grade and lymph node metastasis (23). In glioblastoma, BST2 exhibits high expression in high-grade tissues (85). Kong *et al* (12) reported that increased BST2 expression is associated with poor prognosis and higher grade gliomas. In esophageal squamous cell carcinoma, BST2 is associated with lymphatic invasion and significantly poorer survival, but is not significantly associated with age, sex, T classification, M classification, stage, histological classification and vascular invasion (Table I) (22). In bladder cancer, high BST2 expression is not significantly associated with age, sex, cellular atypia classification, lymphatic and vascular invasion, but is significantly related with T stage (Table I) (25). In endometrial cancer, authors have demonstrated that BST2 protein expression exhibits significantly positive staining in endometrial cancer compared with in the normal endometrium ($P<0.0001$); however, BST2 upregulation was not revealed to be associated with histological differentiation and pathological stage (86). In renal cell carcinoma, high BST2 expression is strongly related to age, TNM classification, stage and histological grade, but not to sex and histological classification (Table I) (87). An analysis of 530 patients with renal cell carcinoma from TCGA database has suggested that BST2 upregulation is closely associated with poor survival (88,89). These studies have suggested that BST2 upregulation could be associated with poor survival.

Regulation of BST2 expression in other types of solid cancer. BST2 is a transmembrane protein that can be regulated by viruses, antitumor drugs and cellular factors. First, drug resistance (such as to gefitinib, cisplatin and tamoxifen) can induce BST2 upregulation in OSCC cells (16), nasopharyngeal carcinoma cells (14) and in ovarian cancer cells (90). Second, FGD5 antisense RNA 1 downregulates miR-129-5p expression and further increases BST2 gene expression; BST2 can then promote cervical cancer progression via inducing M2 macrophage polarization (17). Notably, the expression levels of miR-451a have been shown to be strongly decreased in renal cell carcinoma. Notably, low miR-451a expression can induce the upregulation of BST2 expression, which is significantly associated with poor prognosis. Therefore, miRNAs may be a potential and effective target in the treatment of cancer (89). Third, the long non-coding RNA (lncRNA) BST2 IFN-stimulated positive regulator (BISPR) upregulates the expression of BST2 to promote the progression of thyroid papillary carcinoma (91). Fourth, hypomethylation is an important way to control BST2 expression in cervical cancer (92) and glioblastoma (93). The BST2 gene is significantly hypomethylated in cervical cancer tissue vs. in normal tissue (92). Fifth, type I IFN and MV infection can induce BST2 expression in neurons and mouse embryonic fibroblast cells (40). IFNα has also been reported to promote the expression of BST2 in a xenograft model of renal cell carcinoma (94), and BST2 is upregulated in human glioma and is associated with IFNγ response (12). In human fibrosarcoma cells, there is an opposite opinion that IFNα-induced BST2 could also interact with MT1-MMP to block cell proliferation and migration (95), thus suggesting that BST2 may be an inhibitor for cell proliferation and migration in human fibrosarcoma cells. IFNγ can strongly induce BST2 expression and BST upregulation can inhibit the adhesion of macrophages in tumor-draining lymph nodes and enhance tumor cell escape (96,97). Sixth, the transcription factor SP1 protein regulates the BST2 gene by binding to the BST2 promoter, and can promote cell proliferation and migration in pancreatic cancer (19). The CXXC zinc finger protein 1 can bind to the promoter of BST2 to directly regulate its transcription in ovarian cells (24). Seventh, the chemokine SDF1a interacts with CXCR4/CXCR7 to promote an invasive phenotype in the medullary thyroid by upregulating BST2 gene expression in thyroid cancer (98). These findings have suggested that BST2 expression can be regulated by viruses, antitumor drugs and cellular factors, and BST2 expression promotes the tumorigenesis of numerous types of cancer, with the exception of fibrosarcoma.

BST2 upregulation can induce cell proliferation and inhibit apoptosis. The BST2 gene promotes cell proliferation in OSCC (16), glioblastoma (12) and bladder cancer (25). BST2 elevates cell proliferation by upregulating the expression of cyclin A and cyclin D proteins, and by decreasing the expression of p21 in OSCC cells (16). By contrast, BST2 upregulation can inhibit cell apoptosis by inducing the anti-apoptotic BCL2 protein and decreasing the pro-apoptotic BAX protein (16). Furthermore, traditional medicinal plant ginsenosides can promote cell autophagy through decreasing the expression of BST2 in cervical cancer cells (99). BST2 small interfering RNA inhibits cell proliferation and invasive activities in renal cell carcinoma (87,88). By contrast, BST2 upregulation can contribute to the tumor migration of OSCC cells (15). BST2 may also promote the invasion of glioblastoma multiforme cells *in vitro* (12). The lncRNA BISPR upregulates BST2 and induces the progression of thyroid papillary carcinoma by regulating miR-21-5p and the anti-apoptotic BCL2 protein (91). Low BST2 expression induces calcium disorder, proteostasis breakdown and cell death (100). Thus, BST2 may promote cell proliferation and migration, and inhibit cell apoptosis in cancer.

BST2 upregulation has also been shown to promote tumor immune escape. BST2 upregulation is significantly associated

with the high expression of several immune checkpoints (PD-L1, B7-H3) in the microenvironment of head and neck squamous cell carcinoma. BST2 can also interact with pDCs and regulate their immune response (101). In addition, BST2 upregulation is related to two tumor-associated macrophage markers (CD163 and CD68) in head and neck squamous cell carcinoma (23). High BST2 expression can induce macrophage polarization to the M2-like phenotype, and these cells can contribute to immunodepression and further promote tumor progression (17). Thus, these studies have demonstrated that BST2 may be an important immune-related factor involved in tumor progression.

6. Treatment potential and future direction

Inhibitors, antibodies and combination therapy that target BST2 have been used for the treatment of cancer. In recent years, antibodies have been used extensively for immunotherapy by targeting specific immune checkpoint pathways (102,103). Immunotherapy with antibodies or inhibitors that target the immune checkpoint pathway has been used in the treatment of drug-resistant cancer, distant metastases and cancer recurrence (104). A BST2 inhibitor (B49Mod1) disrupts cysteine-linked BST2-mediated cell-cell interaction and inhibits the proliferation of breast cancer cells (46). Modified anti-BST2 antibodies (including chimeric and humanized antibodies) can have an antitumor effect on lung cancer cells (84). A single chain of BST2-specific antibody has been shown to induce the apoptosis of multiple myeloma cells in an immunodeficiency mouse xenograft model (105). BST2 amino acid 22-30 peptide can activate $CD8^+$ T cells to further kill multiple myeloma cells due to the highest probability of binding to HLA-A2 and may also be a suitable potential target for specific immunotherapy of multiple myeloma (106).

In addition, combination therapy with an antibody and cytokine/oligodeoxynucleotides may be more effective than using antibody alone. A combination of humanized anti-BST2 antibody with IFNα has been shown to exhibit a more effective antitumor ability in renal cell carcinoma xenograft models than antibody alone; thus, a humanized antibody accompanied by IFNα may be a potential therapy for renal cell carcinoma (94). CpG oligodeoxynucleotides are known to enhance tumor escape of macrophages and natural killer cells. In addition, combination therapy with an anti-BST2 antibody and oligodeoxynucleotides has been shown to exert an effective antitumor ability in a xenograft model (107). Therefore, combination therapy with an antibody and cytokine/oligodeoxynucleotides may be a future research direction for therapy.

7. Conclusions and limitations

Increased BST2 expression has been detected in various types of human cancer, including hematological tumors and solid tumors, especially in breast cancer, HCC, gastrointestinal cancer and lung cancer. In most types of cancer, high BST2 expression is associated with several tumor clinicopathological parameters, such as increased stage, invasion and overall survival. BST2 expression is regulated by viral infection, IFNs, transcription factors, miRNAs, lncRNAs, chemokines and methylation, and is involved in numerous types of cancer via activating signaling pathways, such as EGFR/AKT, NF-κB/ERK, GRB2/DIM/caspase 3. BST2 is also involved in cell membrane integrity and lipid raft formation, which can activate the EGFR signaling pathway via lipid rafts. Therefore, BST2 is considered a promising diagnostic marker and prognostic marker. The therapeutic effect of BST2 as an antitumor target has focused on inhibitors, antibodies or modified antibodies to BST2, and combination therapy with an antibody and cytokine/oligodeoxynucleotides. Notably, the aforementioned combination therapy may exhibit more profound antitumor activity.

To date, there is an abundance of *in vitro* evidence suggesting that high BST2 expression is significantly associated with tumorigenesis and progress. Further studies are still needed to investigate whether BST2 can be used as a novel biomarker in cancer. Finally, in combination with the structural, molecular functions and molecular mechanism of BST2 in various types of cancer, the present review may improve overall knowledge of tumorigenesis and progression in cancer types that exhibit BST2 upregulation induced by several factors, possibly leading to antibody therapeutic options for these types of cancer.

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Figs. 3-5 were generated using the Figdraw platform (https://www.figdraw.com/#/).

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Availability of data and materials

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Authors' contributions

BB, ZKZ and HLY contributed to the conception and design of the study. HLY wrote the first draft of the manuscript. QB, ZCW, XW, XZW and LHL wrote sections of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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