Beyond Tethering the Viral Particles: Immunomodulatory Functions of Tetherin (*BST-2*)

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Host response to viral infection is a highly regulated process involving engagement of various host factors, cytokines, chemokines, and stimulatory signals that pave the way for an antiviral immune response. The response is manifested in terms of viral sequestration, phagocytosis, and inhibition of genome replication, and, finally, if required, lymphocyte-mediated clearance of virally infected cells. During this process, cross-talk between viral and host factors can shape disease outcomes and immunopathology. Bone marrow stromal antigen 2 (*BST-2*), also known as tetherin, is induced by type I interferon produced in response to viral infections, as well as in certain cancers. *BST-2* has been shown to be a host restriction factor of virus multiplication through its ability to physically tether budding virions and restrict viral spread. However, *BST-2* has other roles in the host antiviral response. This review focuses on the diverse functions of *BST-2* and its downstream signaling pathways in regulating host immune responses.

Keywords: tetherin, immunomodulatory, antiviral, cancer

History and Molecular Characterization

INITIALLY DISCOVERED AS A SURFACE MARKER for terminally differentiated and neoplastic B cells, bone marrow stromal antigen-2 (*BST-2*) was later reported to have diverse cellular functions (Goto *et al.*, 1994; Ishikawa *et al.*, 1995). *BST-2* is widely expressed but its levels vary from cell to cell (Erikson *et al.*, 2011; Hanagata and Li, 2011; Jones *et al.*, 2012). *BST-2* is a type II transmembrane protein and contains ~180 amino acids (aas). The mature protein adopts a unique topology comprising a short *N*-terminal cytoplasmic tail (1–20 aas) followed by an α -helical transmembrane domain (21–48 aas), an ectodomain (49–161 aas), and a C-terminal glycosylphosphatidylinositol (GPI) domain (162–180 aas) (Kupzig *et al.*, 2003; Hinz *et al.*, 2010).

The cytoplasmic tail of *BST-2* has a highly conserved YXY tyrosine motif known to play a role in NF- κ B-mediated signaling and clathrin-mediated endocytosis (Masuyama *et al.*, 2009; Tokarev *et al.*, 2009; Galao *et al.*, 2012), whereas its ectodomain contains three cysteine residues and two glycosylation sites that are highly conserved during evolution (Andrew *et al.*, 2009). These conserved cysteine residues covalently link monomers to form dimeric or tetrameric forms of *BST-2* (Swiecki *et al.*, 2011). Two *N*-linked glycosylation sites (at N65 and N92) are required for the proper folding of *BST-2*, and the GPI domain anchors

BST-2 to cell surface lipid rafts. *BST-2* expression is present at the plasma membrane, as well as in the trans-Golgi network and within recycling endosomes (Hammonds *et al.*, 2010).

Antiviral Activity of *BST-2*

In 2008, Bieniasz and Guatelli groups independently reported that *BST-2* restricted the release of human immunodeficiency virus-1 (HIV-1). *BST-2* inhibited virion release of a recombinant HIV-1 lacking the *Vpu* gene by tethering the nascent virion to the host cell plasma membrane (Neil *et al.*, 2008; Van Damme *et al.*, 2008). This prompted the name “tetherin” for *BST-2*. Subsequently, *BST-2* was shown to tether a broad range of enveloped viruses, but its tethering activity against enveloped viruses is not a universal phenomenon. The antiviral activity of *BST-2* is related to its membrane anchoring topology (Andrew *et al.*, 2009). The two anchoring domains of *BST-2* form a bridge between the budding virion and the host plasma membrane, thereby physically restricting virion release (Neil *et al.*, 2008; Van Damme *et al.*, 2008). Perez Caballero *et al.* (2009) demonstrated that the membrane anchoring domains are necessary and sufficient for viral tethering. The antiviral activity of tetherin is independent of other host factors. *BST-2* transmembrane domain, dimeric ectodomain,

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and GPI anchor domains are critical for *BST-2* antiviral activities. Tethered virions are either retained at the cell surface or mobilized for endocytic internalization and subsequent ubiquitin-based degradation (Neil *et al.*, 2006; Miyakawa *et al.*, 2009). *BST-2* antiviral activities against a variety of enveloped viruses, including retroviruses, alphaviruses, rhabdoviruses, and mammarenaviruses, have been recently discussed in several excellent review articles (Tokarev *et al.*, 2009; Evans *et al.*, 2010; Arias *et al.*, 2011; Sarojini *et al.*, 2011; Swiecki *et al.*, 2013; Mahauad-Fernandez and Okeoma, 2016). This review highlights other aspects of *BST-2* biology, including cell signaling, immunomodulatory functions, and immunity.

***BST-2* and Cell Signaling Pathways**

BST-2 expression is induced by type I and type II interferons (IFNs) in response to viral infection. The role of *BST-2* in cell biology was first illustrated by its potent induction of *NF-κB* (Matsuda *et al.*, 2003). More recent studies confirmed a role for *BST-2* in regulating *NF-κB* signaling (Cocka and Bates, 2012; Galao *et al.*, 2012; Tokarev *et al.*, 2013). *BST-2* induction of *NF-κB* is dependent upon its multimerization or viral sensing actions (Tokarev *et al.*, 2013). Earlier studies identified TGF beta-activated kinase 1 (*TAK1*) as being critical for *BST-2*-induced *NF-κB*-mediated signal transduction (Galao *et al.*, 2012; Tokarev *et al.*, 2013). However, subsequent studies identified additional intermediate signaling molecules with roles in activation of the *NF-κB* signaling pathway by *BST-2*. Thus, knockdown of TNF receptor associated factor 6 (*TRAF6*) or TNF receptor associated factor 2 (*TRAF2*)/ubiquitin-conjugating enzyme E2N (*Ubc13*) gene expression blocked *BST-2*-mediated *NF-κB* activation (Galao *et al.*, 2012). In contrast, myeloid differentiation primary response protein *MyD88*, *TRAF2*, *TAK1*, *TAK1*-binding protein 1 (*TAB1*), and *TAK1*-binding protein 2 (*TAB2*) were found dispensable for *BST-2*-induced activation of the *NF-κB* signaling pathway (Tokarev *et al.*, 2013). These findings revealed that *BST-2*, through induction of *NF-κB* signaling, can influence the host inflammatory response to a virus (Moynagh, 2005; Liu *et al.*, 2017b), but the underlying mechanisms remain to be elucidated.

Immunomodulatory Role of *BST-2* After Infection

IFNs and innate immunity

Upon pathogen encounter, pattern recognition receptors including Toll-like receptors (TLRs), Nod-like receptors (NLRs), and RIG-I-like receptors (RLRs) (Goubau *et al.*, 2013; Cao, 2015; Chan and Gack, 2016; Liu *et al.*, 2017a) can initiate antiviral responses, including IFN-I and proinflammatory cytokine production (Takeuchi and Akira, 2010). IFN-I signaling through the IFN receptor and JAK/STAT pathway induces expression of hundreds of IFN-stimulated genes that contribute to the establishment of an antiviral state that limits virus propagation within the infected host (Schneider *et al.*, 2014). IFN-I responses are highly controlled and short lived, but if unchecked, excessive expression of IFNs may harm the host (Gota and Calabrese, 2003) and negatively affect hematopoiesis (Lin *et al.*, 1998).

Plasmacytoid dendritic cells (pDCs) are among the highest producers of IFNs and inflammatory cytokines upon sensing bacterial or viral nucleic acids through *TLR7* and *TLR9* receptors (Colonna *et al.*, 2004; Honda and Taniguchi, 2006). *BST-2* negatively regulates the IFN-I response in pDCs (Cao *et al.*, 2009). *BST-2* is a biological ligand for the human pDC-specific receptor immunoglobulin-like transcript 7 (*ILT7*), and binding of *BST-2* to *ILT7* can initiate signaling through the *ILT7*-*FcεRIγ* (a high-affinity IgE receptor) complex. *FcεRIγ* contains an immunoreceptor tyrosine-based activation motif in its cytoplasmic tail that mediates a calcium-dependent signaling cascade that inhibits the production of IFNs and inflammatory cytokines by pDCs (Cho *et al.*, 2008; Cao *et al.*, 2009). However, the detailed mechanisms underlying this negative feedback loop are largely unknown. Coculture of pDCs with *BST-2*-expressing cells reduced IFN-I production by pDCs after stimulation by the oligodeoxynucleotide, CpG-A (Janovec *et al.*, 2018). Moreover, treatment with a MEK1/2 inhibitor significantly increased IFN production (Janovec *et al.*, 2018), suggesting that the *BST-2*-*ILT7*-mediated downregulation of IFN-I is at least partially associated with MEK1/2 signaling. This pathway is highly specific for human pDCs, as *ILT7* is only present in human and primate pDCs (Brown *et al.*, 2004).

BST-2-mediated downregulation of the IFN-I response was also linked to the ability of this protein to counteract the RLR-mediated IFN-I signaling pathway (Jin *et al.*, 2017). Specifically, *BST-2* recruits the E3 ubiquitin ligase, *MARCH 8*, which catalyzes the lysine (K27) linked poly-ubiquitin chains on the mitochondrial antiviral-signaling protein (*MAVS*) (Jin *et al.*, 2017), which targets *MAVS* for autophagic degradation through nuclear domain 10 protein 52 (*NDP52*) receptor. As *MAVS* is an essential host signaling adaptor protein for IFN-I production, its degradation negatively affected the IFN response (Jin *et al.*, 2017) (Fig. 1). Interestingly, murine *NDP52* lacks the ubiquitin-binding domain LIM-L (Thurston *et al.*, 2009; Inomata *et al.*, 2012; Deretic *et al.*, 2013), which should prevent *BST-2*-mediated degradation of *MAVS*. In fact, pDCs from *BST-2* knockout mice showed reduced IFN-I secretion in response to viral challenges (Swiecki *et al.*, 2012). These results suggest that evolutionary selection of the LIM-L domain in *NDP52* and *ILT7* expression by human pDCs cells influences how *BST-2* regulates IFN-I production in these cells relative to mouse pDCs. Additional research is required to determine how *BST-2* affects the innate antiviral immune response in different species.

Adaptive immunity

Although *BST-2* has conserved coding regions, polymorphic forms do exist across species. Thus, NZW/LacJ (NZW) mice contain *BST-2* alleles lacking the endosomal-sorting motif (YxY) and show higher *BST-2* cell surface expression than C57BL/6 mice, whose *BST-2* contains the YxY motif. Consistent with its higher cell surface expression, *BST-2* from NZW mice exhibited a more potent antiviral activity against Friend murine leukemia retrovirus (F-MuLV) than *BST-2* from C57BL/6 mice (Barrett *et al.*, 2012). However, the endocytosis-competent version of *BST-2* in C57BL/6 mice showed a greater ability to control viremia, suggesting a role for immune modulatory functions

FIG. 1. *BST-2* regulation of the IFN-I response. (1) Virion interacts with cell surface receptors to enter the cell. (2) Viral genome (RNA) is recognized by the RLRs. RIG-I signals are transduced to the transcription factors through stimulation of *MAVS* at the mitochondrion-associated membrane. Activation of *MAVS* leads to phosphorylation of *IRF3*. Phosphorylated dimers of *IRF3* then translocate to the nucleus where they bind and activate specific promoters triggering expression of IFNs. (3) Type-I IFNs interact with IFNAR, recruit, and phosphorylate the *STAT1* and *STAT2*. *STAT1* and *STAT2* form a heterodimer that, in turn, recruits the *IRF9* to make a complex. This complex translocates to the nucleus and induces expression of genes (e.g., *BST-2*) regulated by IFN-stimulated response elements. (4) *BST-2* recruits the E3 ubiquitin ligase *MARCH 8*. (5) *MARCH 8* then catalyzes the K27-linked polyubiquitin chains on *MAVS* at K7 position. (6) Cargo receptor *NDP52* recognizes ubiquitinated *MAVS*. (7) *NDP52* delivers *MAVS* to autophagosome for degradation. (8) *BST-2*-mediated autophagosome degradation of *MAVS* and terminal of *RIG-I*, *MAVS*-mediated *IFN-I* production via a negative feedback manner. *BST-2*, bone marrow stromal antigen 2; IFN, interferon; *IRF3*, IFN response factor 3; IFNAR, IFN- α/β receptor; *MAVS*, mitochondrial antiviral-signaling protein; RLR, *RIG-I*-like receptor; *STAT*, signal transducers and activators of transcription.

linked to *BST-2* (Li *et al.*, 2014). Consistent with this hypothesis, enhanced restriction of F-MuLV in C57BL/6 mice was associated with a stronger IFN γ response in NK cells, CD4 $^{+}$ T cells, and CD8 $^{+}$ T cells (Li *et al.*, 2014). Increased endocytosis of virions by pDCs in C57BL/6 mice could trigger *TLR3*-mediated IFN-I production, leading to augmented NK function, as these cells are highly responsive to *TLR3*- and *TLR7*-dependent cytokine stimuli (Swiecki *et al.*, 2012; Gibbert *et al.*, 2014; Li *et al.*, 2014, 2016) (Fig. 2A). This might account for lower IFN-I production

observed in *BST-2*-deficient pDCs (Swiecki *et al.*, 2012). Because *BST-2* can influence IFN-I levels, it has the potential to modulate host defense during both the early and late phases of viral infection. Accordingly, using the mouse model of chronic infection by lymphocytic choriomeningitis virus (LCMV), we showed that the early confinement and sequestration of virions in the splenic marginal zone were compromised in the absence of *BST-2* (Urata and Kenyon, 2018). This resulted in alterations in antiviral T cell priming, leading to reduced T cell proliferation and effector functions

FIG. 2. Antiviral and immunomodulatory functions of *BST-2*. (A) (1) *BST-2* interacts with viral envelope and restricts cellular egress of nascent virion that, in turn, internalizes the virion through endocytosis. (2) In addition, endosomally expressed *BST-2* halts virion trafficking and likely allows more time for endosomal proteases to act upon and degrade the virions. (3) Endosomal degradation of viral envelope facilitates release of genomic RNA that activates *TLR3* and *TLR7*-mediated innate immune pathways. (4, 5) Activation of *TLR3* and *TLR7* along with other costimulatory molecules can further enhance expression of ISGs and cytokines in antigen presenting cells. (6) Cytokines such as *IL-15* can promote NK cell activation and function. (7) Proteolytically degraded viral proteins generate a plethora of viral peptides that are often cross-presented by MHC I and can stimulate CD8 T cells. (8) Similarly, peptides loaded into MHC II can promote CD4 T cell activation. (B) In HIV-1-infected cells, the interaction between *BST-2* and viral Env protein can increase accumulation of Env at the surface of the cell. This can facilitate interactions with circulating antibodies against HIV-1 and stimulate ADCC-mediated elimination of the infected cell. (C) *BST-2* can tether exosomes like viral envelopes restricting their movement. Exosomes often carry signaling molecules such as DAMPs and activated EGFR. DAMP-carrying exosomes can activate antiviral immunity, whereas EGFR-carrying exosomes can suppress it. ADCC, antibody-dependent cellular cytotoxicity; DAMPs, damage-associated molecular patterns; EGFR, epidermal growth factor receptor; HIV-1, human immunodeficiency virus-1; IL, interleukin; ISGs, IFN-stimulated genes; TLR, Toll-like receptor.

(e.g., *IFN γ* and *TNF α*). Peripheral control of a chronic LCMV infection was also compromised in *BST-2*-deficient mice, and the virus established long-term persistence in the brain (Urata and Kenyon, 2018). These findings illustrated how *BST-2* can influence both innate and adaptive immune responses to viral infections. Further studies are required to understand the direct versus indirect contributions of *BST-2* to antiviral immunity, and how the functionality of this protein can be enhanced to help fight infections.

The relationship between *BST-2* and antibody-dependent cellular cytotoxicity (ADCC) in HIV-1-infected cells is well established (Arias *et al.*, 2014). Higher surface expression of Env in infected cells could facilitate ADCC. HIV-1 mutants with impaired *Vpu*-mediated *BST-2* counteracting activity show increased surface accumulation of Env protein in infected cells, which can facilitate ADCC. Thus *BST-2* increases the susceptibility of *Vpu*-mutated HIV-infected cells

to ADCC and knockdown of *BST-2* decreases the sensitivity of HIV-infected cells to ADCC (Arias *et al.*, 2014). Notably, overexpression of *BST-2* in response to type I IFN, interleukin (IL)-27 or by other means, upregulates surface expression of Env protein and further stimulates HIV-1-infected cells for ADCC-mediated elimination (Pham *et al.*, 2016; Richard *et al.*, 2017) (Fig. 2B). These studies demonstrate an indirect connection of *BST-2* and ADCC phenomena in HIV-1-infected cells, although this phenomenon is not yet reported in other viral infection models. Therefore, *BST-2* could modulate interplay between innate and adaptive immune response to control viral replication.

Other immunomodulation roles of *BST-2*

Various other immunomodulation functions of *BST-2* have also been reported. For example, in addition to tethering of

viral envelope, it also reported to tether exosomes and could influence its cellular target and interactions (Edgar *et al.*, 2016). Exosomes are involved in host immune responses and linked with various diseases such as cancer and neurodegenerative disorders (Soria *et al.*, 2017; Tai *et al.*, 2018). In case of cancer, exosome carries damage-associated molecular patterns (DAMPs) in myeloid cells that stimulate inflammatory cytokine productions and could promote cancer progression (Hoshino *et al.*, 2015; Nabat *et al.*, 2017). Alternatively, tumor exosomes could also suppress innate antiviral immune response by transferring the activated epidermal growth factor receptor (EGFR) to the dendritic cells (Gao *et al.*, 2018) (Fig. 2C). Thus *BST-2*'s tethering action on exosome could influence outcome of host immune response to tumor. In a different model, Sally James *et al.* identified a new subset of nondifferentiating bone marrow stromal cells (BMSCs), which exclusively expresses higher *BST-2* and IL-7, although specific functional roles of *BST-2* in these BMSCs are yet to be defined (James *et al.*, 2015). A similar observation was made wherein higher cells surface expression of *BST-2* was noticed in cancellous bone fragments resident cells (El-Sherbiny *et al.*,

2018). However, relevance of *BST-2* expression and its mechanistic role is yet to be elucidated.

BST-2 and Cancer

Increased *BST-2* expression has been documented in different cancer tissues, including ovarian, lung, head and neck, cervical, thyroid, breast, endometrial, pancreatic glioblastoma, and myeloma (Wang *et al.*, 2009; Wainwright *et al.*, 2011; Tai *et al.*, 2012; Yokoyama *et al.*, 2013; Fang *et al.*, 2014; Mahauad-Fernandez *et al.*, 2014, 2015; Milutin Gasperov *et al.*, 2014). *BST-2* overexpression at the early stage of multiple myeloma suggested that *BST-2* might be a suitable target for cancer immune therapy. However, not all cancer types exhibit increased *BST-2* expression. *BST-2* expression is unchanged in thyroid and lung adenocarcinomas and is downregulated in liver, kidney, lung squamous, and prostate cancer relative to normal cells (Mahauad-Fernandez *et al.*, 2015). Almost all breast tumors express *BST-2* to a certain level, and a higher expression level of *BST-2* is associated with aggressive and progressive malignancy

FIG. 3. The influence of *BST-2* on tumor cell survival, invasion, and migration. **(A)** The dimeric form of *BST-2* can facilitate cell-to-cell interactions or extracellular matrix interactions. *BST-2* activation leads to phosphorylation of its cytoplasmic tail (most likely in the tyrosine-6 and tyrosine-8 positions). Phosphorylated *BST-2* recruits GRB-2 and activates a kinase (unknown) that phosphorylates ERK (pERK), which, in turn, phosphorylates BIM, resulting in subsequent proteasomal degradation of BIM. In the absence of BIM, procaspase-3 is neither cleaved nor activated. This results in cancer cell survival. In a monomeric form, cytoplasmic domain of *BST-2* is not phosphorylated, which can promote apoptosis of cancer cells. **(B)** The YXY motif of *BST-2* is responsible for cancer cell migration and invasion. In the absence of the YXY motif, cancer cells exhibit a reduced migration rate.

(Mahauad-Fernandez *et al.*, 2014). The functional significance of *BST-2* expression levels in malignancy remains to be elucidated, but *BST-2* homodimers appear critical in certain instances for the promotion of cancer cell adhesion (Mahauad-Fernandez and Okeoma, 2017). In addition, *BST-2* enhances cancer cell survival and growth by promoting proteosomal degradation of proapoptotic proteins, such as *BIM*—a member of the *Bcl-2* protein family (Mahauad-Fernandez and Okeoma, 2017) (Fig. 3A). Evidence indicates that the cytoplasmic tail of *BST-2* is responsible for cell migration and invasion, but the mechanisms underlying such functions are largely unknown (Naushad *et al.*, 2017) (Fig. 3B). Studying the role of *BST-2* in different cancers is a very active area of research, and in future we expect that novel insights will emerge regarding the relationship between *BST-2* and malignancy.

Conclusion

Cells have an array of factors that play precise roles in maintaining normal physiology and responding to diverse challenges (infections, tumors, etc.). A plethora of factors have been discovered that contribute to host defense against pathogens and the maintenance of immune homeostasis. *BST-2* is one such factor, and studies have highlighted multifaceted biological roles for *BST-2* in antiviral responses, cell signaling, immune modulation, and even malignancy. Because the immune system has the potential to cause pathology, it is important that responses are precisely regulated. A role for *BST-2* in immune modulation is supported by its ability to alter IFN- γ , *NF- κ B*, and T cell effector functions. The detailed mechanisms by which *BST-2* executes these functions remain to be elucidated, but future studies are likely to uncover a broader role for *BST-2* in shaping host responses to infection and cancer. This knowledge may facilitate the development of therapeutics based on regulating *BST-2* functionality.

Authors' Contributions

R.T. and D.N. structured the article and gave their inputs toward shaping the article. J.C.d.I.T. and D.B.M. made critical suggestions and editing the article.

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