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Review

BST-2/tetherin: Structural biology, viral antagonism, and immunobiology of a potent host antiviral factor

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ABSTRACT

BST-2 (also known as tetherin, CD317, or HM1.24) was first described as a potent interferon-inducible host antiviral factor nearly five years ago. Since that time, numerous reports have been published regarding the antiviral activity and immunological properties of this protein. BST-2 blocks viral replication by inhibiting enveloped virus budding from the surface of infected cells. To counteract this, most viruses have developed strategies to antagonize BST-2, each employing a unique mechanism. In this review, we summarize the antiviral function, structural biology and immunobiology of BST-2. Taken together, our current understanding of BST-2 suggests potential avenues as well as challenges to exploiting its action in the development of broad spectrum antiviral treatments.

1. Introduction

The process of viral replication within infected host cells requires complex interplay between viral and host factors. To control viral infections, humans and other mammals have evolved innate immune mechanisms in the form of interferon-inducible host factors that interfere with various steps in the viral replication cycle. Some examples are the APOBEC3 family of cytidine deaminases (Sheehy et al., 2002), viperin (Seo et al., 2011), ISG15 (Skaug and Chen, 2010), TRIM5α (Nakayama and Shioda, 2010), SAMHD1 (Laguette and Benkirane, 2012), and bone marrow stromal antigen 2 (BST-2). BST-2 is unique among these antiviral factors in that it possesses molecular and structural features that allow it to restrict a broad range of enveloped viruses.

2. Antiviral function of BST-2

BST-2 was first reported to be a potent host antiviral factor in 2008, when it was demonstrated that it inhibited release of HIV-1 viral particles deficient in the viral membrane protein Vpu (Neil et al., 2008; Van Damme et al., 2008). BST-2 blocks viral replication by trapping enveloped viral progeny on the surface of infected cells, leading to their internalization and degradation (Evans et al., 2010; Sauter et al., 2010). It has been demonstrated that BST-2 can inhibit viral budding for a number of enveloped viruses (summarized in Table 1). Most viruses have developed strategies to counteract BST-2 functions. Accordingly, several reports have demonstrated BST-2-mediated restriction of virus release using either mutant viruses deficient in their BST-2-antagonizing proteins or virus-like particles (VLPs). As mentioned above, BST-2 antiviral activity was first demonstrated for Vpu-deficient HIV-1 (Jouvenet et al., 2009; Van Damme et al., 2008). Subsequent studies using either VLPs or antagonist-deficient viruses have demonstrated BST-2-mediated restriction of several modified retroviruses (alpha-, beta-, delta-, lenti-, and spuma-) (Jouvenet et al., 2009), arenaviruses (Lassa and Machupo) (Radoshitzky et al., 2010; Sakuma et al., 2009), herpesviruses (KSHV) (Mansouri et al., 2009), filoviruses (Ebola and Marburg) (Jouvenet et al., 2009; Sakuma et al., 2009), rhabdoviruses (vesicular stomatitis) (Weidner et al., 2010), paramyxoviruses (Sendai, Nipah) (Radoshitzky et al., 2010), orthomyxoviruses (influenza A) (Watanabe et al., 2011; Yondola et al., 2011), and flaviviruses (Hepatitis C) (Dafa-Berger et al., 2012). BST-2 has also been shown to effectively inhibit budding of intact infectious viruses, including arenaviruses (Lassa and Machupo) (Radoshitzky et al., 2010) and rhabdovirus (vesicular stomatitis virus) (Weidner et al., 2010). However, BST-2 does not restrict other infectious viruses such

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Table 1
Summary of experimental observations for virus release inhibited by BST-2.

Virus	Family	Inhibits VLP or ADV[a]	Inhibits infectious virus
HIV-1	Retrovirus	Yes (Neil et al., 2008; Van Damme et al., 2008)	No
HIV-2	Retrovirus	Yes (Jia et al., 2009; Le Tortorec and Neil, 2009)	
SIV	Retrovirus	Yes (Jouvenet et al., 2009)	
FIV	Retrovirus	Yes (Jouvenet et al., 2009)	
Mason-Pfizer monkey virus	Retrovirus	Yes (Jouvenet et al., 2009)	
Prototypic Foamy virus	Retrovirus	Yes (Jouvenet et al., 2009)	Yes (Xu et al., 2011)
Rous Sarcoma virus	Retrovirus	Yes (Jouvenet et al., 2009)	
Murine Leukemia virus	Retrovirus	Yes (Jouvenet et al., 2009)	
Human Endogenous retrovirus	Retrovirus	Yes (Jouvenet et al., 2009)	
Human T-Lymphocytic virus	Retrovirus	Yes (Jouvenet et al., 2009)	
Equine Infection Anemia virus	Retrovirus	Yes (Jouvenet et al., 2009)	
Ebola	Filovirus	Yes (Kaletsky et al., 2009; Radoshitzky et al., 2010)	No (Radoshitzky et al., 2010)
Marburg	Filovirus	Yes (Radoshitzky et al., 2010; Sakuma et al., 2009)	No (Radoshitzky et al., 2010)
Lassa	Arenavirus	Yes (Radoshitzky et al., 2010; Sakuma et al., 2009)	Yes (Radoshitzky et al., 2010)
Machupo	Arenavirus	Yes (Radoshitzky et al., 2010)	Yes (Radoshitzky et al., 2010)
KSHV	Herpesvirus	Yes (Mansouri et al., 2009)	
Cowpox	Poxvirus		No (Radoshitzky et al., 2010)
Vesicular Stomatitis virus	Rhabdovirus		Yes (Weidner et al., 2010)
Rift Valley Fever virus	Bunyavirus		No (Radoshitzky et al., 2010)
Hepatitis C virus	Flavivirus		Moderate (Dafa-Berger et al., 2012)
Mumps	Paramyxovirus	No (Kong et al., 2012)	
Sendai	Paramyxovirus	Yes (Kong et al., 2012)	
Nipah	Paramyxovirus	Yes (Kong et al., 2012; Radoshitzky et al., 2010)	
Influenza A	Orthomyxovirus	Yes (Watanabe et al., 2011; Yondola et al., 2011)	Yes (Mangeat et al., 2012) No (Bruce et al., 2012; Watanabe et al., 2011)

[a] Antagonist-deficient virus.

as filoviruses (Ebola and Marburg), poxviruses (cowpox), or bunyaviruses (Rift Valley fever virus) (Radoshitzky et al., 2010). Taken together, these findings suggest BST-2 exhibits a broad, but not universal, spectrum of activity targeting enveloped virus release. Likewise, enveloped viruses appear to variably encode antagonists to BST-2 or alternatively may utilize budding pathways that circumvent BST-2 activity. Nevertheless, BST-2 appears to have an evolutionarily conserved function, as the homolog from humans, several species of primates (Jia et al., 2009; Lim and Emerman, 2009; McNatt et al., 2009), mouse (Goffinet et al., 2009; Radoshitzky et al., 2010), and rat (Goffinet et al., 2009) have all been shown to restrict HIV-1 and several other enveloped viruses (Radoshitzky et al., 2010).

3. Structural and molecular features of BST-2

BST-2 is a type II transmembrane protein with a unique topology consisting of a short N-terminal cytoplasmic tail (CT), a single transmembrane region (TM), an ectodomain (ED), and a second membrane anchor, a C-terminal glycosylphosphatidylinositol (GPI) (Fig. 1A). Analysis suggests this double-anchor topology is only shared in the human genome with an isoform of the prion protein (Moore et al., 1999). Accumulating experimental evidence has demonstrated that each of these structural features plays a vital role in BST-2 antiviral activity. For example, deletion of either one of the membrane anchors (i.e., the TM or GPI) renders BST-2 non-functional for restricting viral budding (Iwabu et al., 2009; Neil et al., 2008; Perez-Caballero et al., 2009; Van Damme et al., 2008). Deletion of the transmembrane domain or GPI anchor abolish antiviral activity and retains BST-2 at the plasma membrane, suggesting these anchors play a direct functional role exclusive from proper localization (Perez-Caballero et al., 2009). The ectodomain is primarily involved in antiviral activity as well (as mentioned below), however, it should be noted that construction of a BST-2-like protein containing heterologous protein domains was shown to confer partial antiviral activity (Perez-Caballero et al., 2009), suggesting that antiviral activity is at least partially mediated by the protein's structural configuration, and not its primary sequence.

BST-2 is localized within lipid rafts on the cell surface, in the trans-Golgi network, and/or within recycling endosomes (Kupzig et al., 2003; Masuyama et al., 2009). Unlike other GPI-anchored proteins, BST-2 is internalized from lipid rafts on the cell surface through clathrin-mediated endocytosis, which is facilitated by a non-canonical tyrosine-based motif on the N-terminal cytoplasmic tail (Masuyama et al., 2009). Although localization to lipid rafts is hypothesized to be dictated by the GPI-anchor, a recent study suggests that determinants in the ectodomain also contribute to proper localization in lipid raft microdomains (Hammonds et al., 2012). The ectodomain contains two main sequence-invariant features: three cysteines and two N-linked glycosylation sites (Fig. 1A). Three invariant cysteine residues (C53, C63, and C91 in human) within the domain stabilize homodimerization of BST-2 through intermolecular disulfide linkages (Hinz et al., 2010; Swiecki et al., 2011); at least one cross-linked cystine must be present for dimer stabilization (Andrew et al., 2009; Perez-Caballero et al., 2009). Conversely, the N-linked glycosylation sites appear to be dispensible for function. Mutation of invariant N-linked glycosylation sites at amino acid residues N65 and N92 revealed that these residues are required for anterograde transport and possibly for proper folding of BST-2, but are not necessary for antiviral activity (Perez-Caballero et al., 2009).

The BST-2 ectodomain is of particular structural interest as it is necessary for maximal antiviral activity (Andrew et al., 2009; Perez-Caballero et al., 2009). Recent crystal structures of the BST-2 ectodomain reveal that it forms a parallel homodimer (Hinz et al., 2010; Schubert et al., 2010; Swiecki et al., 2011; Yang et al., 2010), and solution studies of the transmembrane domain in lipid environments lend supportive evidence that dimers are anchored in membranes in the same orientation (Cole et al., 2012). Structural and biochemical analysis of the BST-2 ectodomain reveal that it serves as a molecular bridge to connect the plasma membrane to a budding virion through a distance of about 170 Å. The ectodomain further displays conformational plasticity which likely aids in the dynamic process of trapping budding viruses (Hammonds et al., 2010; Hinz et al., 2010; Swiecki et al., 2011). The full structure of the coiled-coil ectodomain from mouse BST-2 allowed for analysis of the coiled-coil interface across known BST-2 homologs (Swiecki et al., 2011). Sequence analysis revealed that all species conserve a unique