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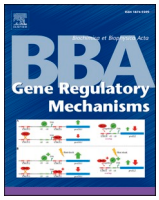

Research Paper

Catching BETs by viruses

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ABSTRACT

Viruses use diverse tactics to hijack host cellular machineries to evade innate immune responses and maintain their life cycles. Being critical transcriptional regulators, human BET proteins are prominent targets of a growing number of viruses. The BET proteins associate with chromatin through the interaction of their bromodomains with acetylated histones, whereas the carboxy-terminal domains of these proteins contain docking sites for various human co-transcriptional regulators. The same docking sites however can be occupied by viral proteins that exploit the BET proteins to anchor their genome components to chromatin in the infected host cell. In this review we highlight the pathological functions of the BET proteins upon viral infection, focusing on the mechanisms underlying their direct interactions with viral proteins, such as the envelope protein from SARS-CoV-2.

The BET (bromodomains and extra-terminal domain) family of transcriptional regulators contains four members, BRD2, BRD3, BRD4 and BRDT (BRDs). The BET proteins are involved in many vital biological processes, including cell proliferation and differentiation, gene expression, cell cycle progression and cellular responses to DNA damage [1]. One of the major functions of BRDs is to promote transcriptional elongation through interacting with p-TEFb (positive transcription elongation factor b) and releasing RNA polymerase II from promoter-proximal pause regions [2,3]. Aberrant activity of BRDs is linked to human diseases, particularly cancer, inflammation, obesity, and neurological, autoimmune and cardiovascular disorders [4]. The most characterized BET protein BRD4 forms chromosomal translocations in squamous carcinoma and NUT midline carcinoma and is directly implicated in the progression of acute myeloid leukemia and breast cancer [5]. In the past few years numerous BET inhibitors have been developed, and some show promising therapeutic effects in cancer models for NUT midline carcinoma, hematological malignancies and neuroblastoma [5–9].

All human BRDs contain two acetyllysine-recognizing bromodomains (BDs) and extra-terminal (ET) domains, and additionally, a C-terminal domain (CTD) is present in BRD4 and BRDT (Fig. 1a). First bromodomain (BD1) and second bromodomain (BD2) of BRD4 select for distinct acetyllysine substrates [10]. While BD1 recognizes primarily acetylated lysine residues in histone tails, BD2 interacts with acetylated non-histone proteins [11]. Acetyllysine binding activities of both BDs are important for the tethering and stabilization of the BRD4-harboring transcription complexes at specific genomic loci and for activation of gene expression [12]. The ET domain of BRD4 binds to a hKhK motif of the human proteins NSD3, CHD4, ATAD5 and JMJD6 recruiting them to chromatin [13], whereas CTD associates with p-TEFb [2,3,14].

A growing number of viruses have the ability to bind human BET proteins and exploit them in various stages of the viral life cycle, such as viral replication, genome maintenance and transcription. The Karposi's sarcoma-associated herpesvirus latent nuclear antigen (LANA) sequence harbors a motif that is recognized by the ET domains of BRD2 and BRD4. The formation of the LANA-ET complex enables the integration of the herpesvirus episome into host chromatin, leading to a decrease in BRD4-mediated gene activation and altering the cell cycle [15–18]. The structure of the ET domain of BRD4 in complex with the LANA peptide shows that the viral peptide pairs with the linker connecting two α-helices of the protein to form a double-stranded antiparallel β-sheet [13] (Fig. 1b). The binding mode of LANA described in Zhang et al. is highly reminiscent of the binding mode of non-viral human protein ligands of the BRD4 ET domain. Likewise, the C-terminal region of murine leukemia virus (MLV) integrase adopts a β-hairpin fold and forms a three stranded antiparallel β-sheet, pairing with the linker of the ET domains

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of BRD4 and BRD3 [19,20]. This interaction stimulates the catalytic activity of MLV and its integration into the host cell DNA near transcription start sites [21].

The genomes of human papillomavirus (HPV) and bovine papillomavirus 1 (BPV-1) replicate in the host cell as autonomous episomes through a process controlled by the viral proteins E1 and E2. To facilitate the viral genome segregation in mitosis, the E2 protein anchors the viral genome to host mitotic chromosomes via binding to Brd4 [22]. The engagement with BRD4 also enables transcriptional activation of E2 target genes and repression of oncogenic viral genes [23–27]. Functional studies have shown that the N-terminal activation domain (AD) of E2 recognizes CTD of BRD4, whereas the C-terminal DNA-binding domain of E2 is responsible for the anchoring to the viral DNA. The AD-CTD binding mechanism was elucidated from the crystal structure of AD of the E2 protein from HPV-16 bound to the Brd4 CTD peptide [28] (Fig. 1c). In the complex, the CTD peptide forms a single α-helix that binds almost perpendicularly to the three α-helices of AD, making contacts with each of them. Abbate et al. report that there is essentially no difference between the structures of AD in the CTD-bound state and the apo-state, suggesting that AD has a rigid fold and a pre-made site

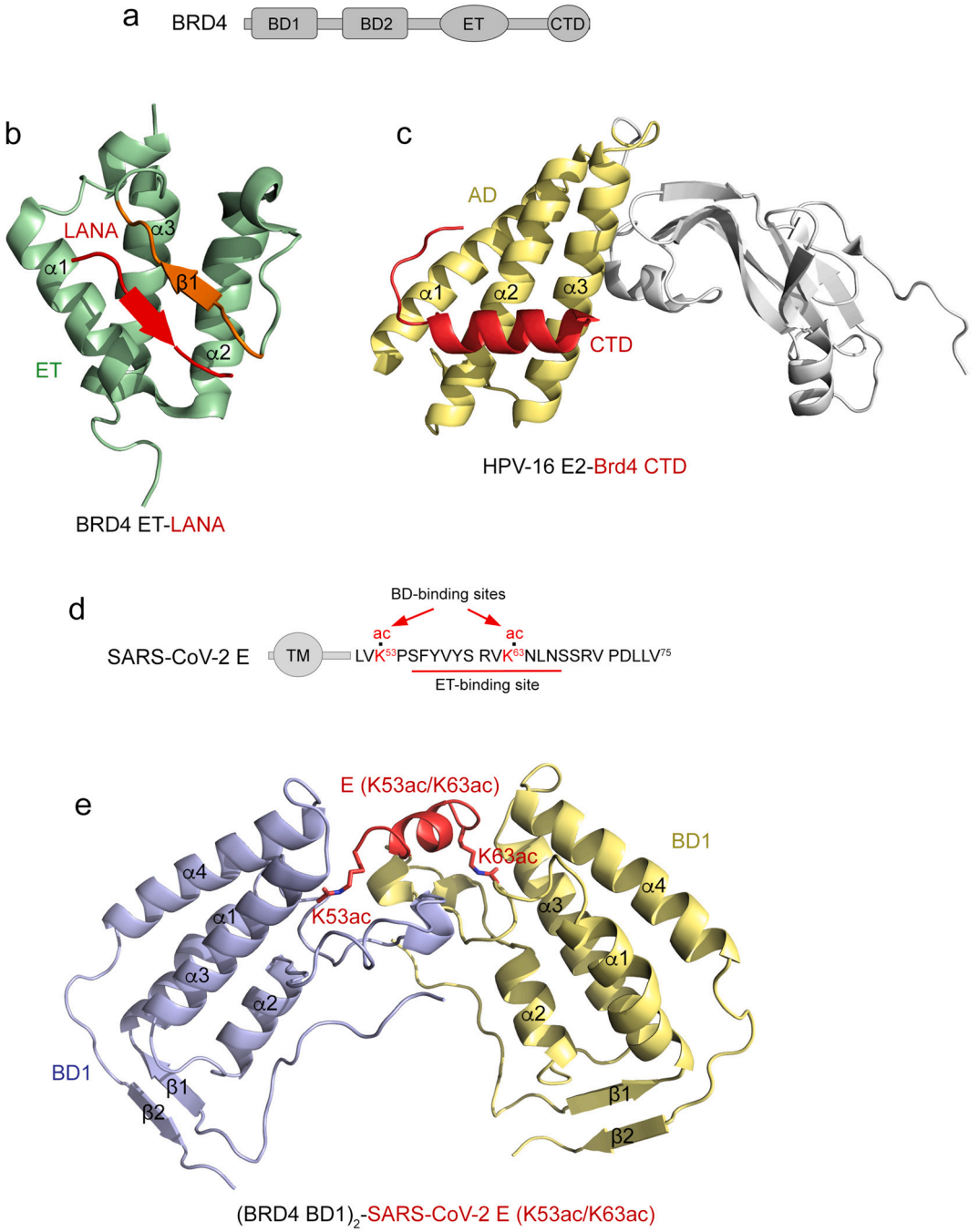

Fig. 1. Diverse mechanisms by which viruses capture BRD4. (a) Domain architecture of BRD4: BD1, first bromodomain; BD2, second bromodomain; ET, extra-terminal; CTD, C-terminal domain. (b) A ribbon diagram of the NMR structure of the BRD4 ET domain in complex with the LANA peptide (PDB ID: 2nd0) [13]. LANA is colored red. (c) A ribbon diagram of the crystal structure of the E2 protein from HPV-16 in complex with the Brd4 CTD peptide (PDB ID: 2nnu) [28]. AD of the E2 protein is colored yellow, and CTD of Brd4 is red. (d) Domain architecture and the sequence of the SARS-CoV-2 E protein: TM, transmembrane domain. The BD-binding sites (acetylated lysine residues) and the ET-binding site are highlighted in red. (e) A ribbon diagram of the crystal structure of BRD4 BD1 (blue and yellow) in complex with the SARS-CoV-2 E peptide diacetylated at K53 and K63 (red) (PDB ID: 7TV0) [30].

available for the engagement with diverse binding partners [28].

In 2020, BRD2 and BRD4 were identified as potential interactors of the envelope (E) protein from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) [29]. Two years later the direct interaction between human BRD4 and the E protein of SARS-CoV-2 has been confirmed experimentally [30,31]. The SARS-CoV-2 E protein contains only two lysine residues, K53 and K63, located in the C-terminus of the protein (Fig. 1d). In their recent work, Vann et al. demonstrate that human histone acetyltransferase (HAT) p300 and to a lesser degree the MYST-family HAT complexes can acetylate the SARS-CoV-2 E peptide and that full-length SARS-CoV-2 E protein expressed in 293 T cells is acetylated and forms complex with BRD4 [30]. Both BD1 and BD2 of BRD4 interact with diacetylated K53ac/K63ac E peptide, exhibiting a 30–40 μM binding affinity, but bind weaker to mono-acetylated E peptides.

The crystal structure of BRD4 BD1 in complex with the diacetylated K53ac/K63ac E peptide reveals that two molecules of BD1 capture one E peptide [30] (Fig. 1e). Each acetylated lysine of E occupies a canonical binding pocket at the top of a four-helix bundle of BD1 and utilizes a common mechanism for acetyllysine recognition by forming the hydrogen bond with N140 of BD1. The E peptide folds into an α-helix, which positions K53ac and K63ac for the coinciding interaction with two BDs. Interestingly, the same region of the homologous E protein from SARS-CoV exists in an α-helical conformation even in an apo-state of the protein [32]. In addition to the acetyllysine-dependent association with BRD4, the SFYVYSRVK(63)NLN region of the SARS-CoV-2 E protein was found to interact with the ET domain of BRD4 in an acetyllysine independent manner [30].

BETs are known to mediate inflammatory and immune responses to viral infection in general [4] and regulate COVID-19 mediated cytokine storm and cardiac damage [33]. Multiple studies have described the reduction in SARS-CoV-2 replication and infection when the acetyllysine binding activity of BET BDs is blocked by the BET inhibitors, including JQ1, OTX015, ABBV-744, INCB054329, SF2523 and Apabetalone (RVX-208), but only when these inhibitors were used hours or days before the virus is introduced [30,33–38]. BRD2, and to a lesser extent BRD4, is an important positive transcriptional regulator of the SARS-CoV-2 entry receptors, such as angiotensin-converting enzyme 2 (ACE2) [31]. Qiao et al. first reported the downregulation of ACE2 in the prostate and lung cell lines and lungs of C57BL/6 mice treated with the BET inhibitor JQ1 [35]. An unbiased CRISPRi screen later identified BRD2 to be indispensable for the expression of ACE2 in Calu3 lung epithelial cells [34]. Treatment of cells up to 72 h with BET inhibitors reduced both ACE2 RNA and protein levels without affecting cell viability. Similar to the effect of BRD2 or ACE2 knockdown during infection, the prophylactic treatment of cells with BET inhibitors for 72 h reduced SARS-CoV-2 infection ~100-fold in cells.

The role of BETs in regulating innate immunity is well documented and involves primarily the recruitment of p-TEFb and transcription factors, including RELA, the STAT family and the IRF family, to chromatin for transcription elongation [2,3]. Importantly, investigating pre- and post-entry effects of the BET inhibition on SARS-CoV-2 infection Chen et al. found that the BET proteins can play proviral and antiviral roles depending on when the host cell is treated with the BET inhibitors [31]. When BET inhibitors were applied to cells at the time of infection and not before, JQ1 and dBET6 significantly increased SARS-CoV-2 replication and infectious particle production [31]. The expression of important interferon-stimulated genes and proinflammatory cytokines for mounting a robust antiviral response to the virus, including IFNB1, ISG15, and IL6, were reduced in the presence of BET inhibitors. Moreover, the expression of SARS-CoV-2 E protein alone, which the authors show is reversibly acetylated in cells, was sufficient to suppress BET protein-mediated antiviral gene expression. These data together with the observation that depletion of BRD2, BRD3, or BRD4 by CRISPR Cas9 in cells constitutively overexpressing the ACE2 receptor enhances viral replication implicate BET proteins in acting as post-entry antagonists of SARS-CoV-2 infection [31]. These studies also suggest that the SARS-CoV-2 E protein interferes with the antiviral role of BET proteins. We note that the ability of BET inhibitors to suppress proinflammatory cytokine expression may be desirable later in infection as Mills et al. found that treatment with the BET inhibitor INCB054329 in mice blocked the expression of proinflammatory cytokines during LPS challenge associated with SARS-CoV-2 induced cardiac dysfunction [33]. Another BRD4 inhibitor, SF2523, combined with antiviral entry inhibitors required minimal doses to block SARS-CoV-2 replication and infection, highlighting a benefit of combinatorial inhibition approaches [37,38].

1. Concluding remarks

Recent advances in high-throughput sequencing and genetic-based screening have greatly enhanced our understanding of how viruses hijack and subvert host cell signaling pathways and alter immune responses. Viruses rely on the host transcriptional and translational machineries for their survival and replication, and as critical components of transcriptional programs, especially related to immunological defense and inflammatory responses, the BET proteins are direct targets of various viruses. The studies discussed above reveal diverse strategies by which viral proteins utilize functions of BRDs for their own benefit. Continue deciphering the virus-host BRDs interactions at the atomic resolution level is imperative to the development of antiviral therapeutic strategies and treatment regiments directed at BETs. Currently, a first generation of BET inhibitors is at the center of an intense clinical evaluation for the treatment of some viral infections.

The finding that the E protein of SARS-CoV-2 is acetylated in cells by human HATs and therefore is capable of binding to bromodomains of BRD4 raises the question of whether other viruses, once acetylated by host acetyltransferases, target bromodomains of BETs. Intriguingly, the E2 protein of BPV-1 is acetylated by p300, particularly at K111 in the transactivation domain, and this acetylation activates E2-dependent transcription [39]. The HPV-31 E2 protein, in which K111 is mutated to arginine and thus acetylation is eliminated, lost its ability to stimulate transcription and E1-mediated DNA replication [40,41]. Overexpression of p300 increases replication of HPV-31 E2 but not its K111R mutant, indicating that p300-dependent acetylation of K111 is required for active viral replication [41]. It has further been shown that the counterpart of p300, the deacetylase SIRT1, represses HPV-16 replication, and knockout of SIRT1 increases HPV-16 E2 acetylation [42]. Accumulating evidence suggests that targeting of bromodomains of BRDs by acetylated viral proteins could be a potentially more common process that needs to be explored in future studies.

Author contributions

All authors contributed to writing and editing the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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