Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagrm

Review

The bromodomain: From epigenome reader to druggable target☆

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ARTICLE INFO

Article history:
Received 20 February 2014
Received in revised form 15 March 2014
Accepted 23 March 2014
Available online xxxx

Keywords:
Bromodomain
Gene transcription
Small molecule inhibitors

ABSTRACT

Lysine acetylation is a fundamental post-translational modification that plays an important role in the control of gene transcription in chromatin in an ordered fashion. The bromodomain, the conserved structural module present in transcription-associated proteins, functions exclusively to recognize acetyl-lysine on histones and non-histone proteins. The structural analyses of bromodomains' recognition of lysine-acetylated peptides derived from histones and cellular proteins provide detailed insights into the differences and unifying features of biological ligand binding selectivity by the bromodomains. Newly developed small-molecule inhibitors targeting bromodomain proteins further highlight the functional importance of bromodomain/acetyl-lysine binding as a key mechanism in orchestrating molecular interactions and regulation in chromatin biology and gene transcription. These new studies argue that modulating bromodomain/acetyl-lysine interactions with small-molecule chemicals offer new opportunities to control gene expression in a wide array of human diseases including cancer and inflammation. This article is part of a Special Issue entitled: Molecular mechanisms of histone modification function.

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1. Introduction

Gene transcriptional activation or repression in the human genome is closely coupled to changes in the structure of chromatin comprising DNA and histone proteins. This complex and tightly coordinated relationship is made possible through the post-translational modifications of DNA-packing histones present in the chromatin. Chromatin contains the entire genomic DNA present in eukaryotic cells, and functions as the primary regulator that controls global dynamic changes in gene expression and silencing. Nucleosomes that function as the building blocks of chromatin pack 147-bp lengths of DNA in two super-helical turns around a histone octamer, which consists of a histone-3-histone-4 (H3–H4) tetramer and two H2A–H2B dimers. These nucleosome core particles are connected by short lengths of DNA between the linker histones H1 and H5 to form a nucleosomal filament, which then fold into the higher-order structure of the chromatin fiber. Within the chromatin structure, the structurally flexible N- and C-termini of the core histone octamers protrude out from the nucleosome particles and are subject to a wide array of post-translational modifications, including acetylation, methylation, phosphorylation, ubiquitination, ribosylation, biotinylation, citrullination, crotonylation, and SUMOylation [1–3]. These site- and state-specific modifications may act collectively in orchestrating genomic stability and gene expression or repression in the cell nucleus [4–6]. Lysine acetylation [7] is a highly dynamic modification that broadly impacts chromatin structure and function as well as gene transcription [8–10]. Further, lysine acetylation has been shown not to be limited to histones, but also takes place in different types of transcription-associated proteins, including histone modifying enzymes, transcription factors as well as chromatin regulators [11,12] suggesting that it may act as a more general regulator of protein function likely beyond transcriptional regulation, akin to phosphorylation [13]. Not surprisingly, changes in lysine acetylation among such transcription-associated proteins have been linked to different human diseases [14].

The dynamic role of lysine acetylation is, to some extent, attributed to the bromodomain (BrD), which is the only protein domain whose conserved activity is to function as an acetyl-lysine binding domain [15]. Some of BrD-containing proteins have been functionally implicated in disease processes, including cancer, inflammation and viral replication [16–19]. The development of small-molecule inhibitors of BrDs in recent years has enabled a number of chemical biology guided studies of BrD function and strongly suggests that they are *bona fide* druggable targets for various human diseases [19,20]. This review describes the current status of the description of the bromodomain family from a structural and chemical biology point of view.

1.1. The bromodomain fold and acetyl-lysine recognition

The available structures of BrDs reveal that they all share an evolutionary conserved structural fold of a left-handed four-helix bundle (α_Z, α_A, α_B and α_C), termed the 'BrD fold' [21–23]. The inter-helical α_Z-α_A (ZA) and α_B-α_C (BC) loops constitute a pocket that recognizes the acetyl-lysine modification (Fig. 1A). Despite the conserved BrD

☆ This article is part of a Special Issue entitled: Molecular mechanisms of histone modification function.

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http://dx.doi.org/10.1016/j.bbagrm.2014.03.011
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Please cite this article as: R. Sanchez, et al., The bromodomain: From epigenome reader to druggable target, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbagrm.2014.03.011

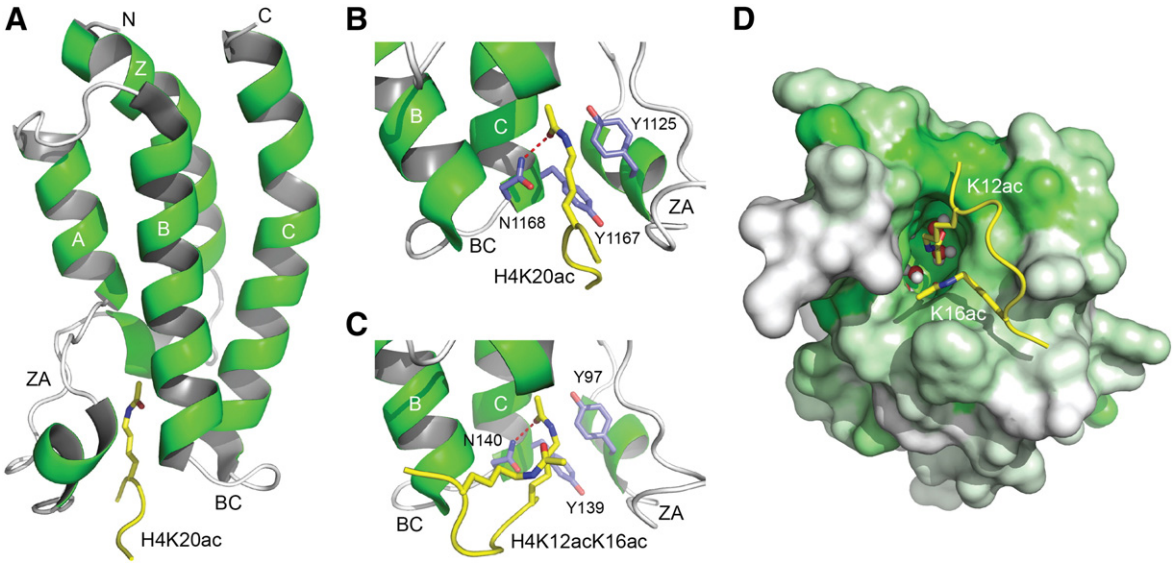

Fig. 1. The structural features of the bromodomain as the acetyl-lysine binding domain. (A) The BrD fold. Structure of the CBP BrD in complex with H4K20ac peptide (PDB 4n3w). (B) Close-up of the acetyl-lysine binding site in the CBP BrD. Key conserved interaction residues are shown. The hydrogen bond between Asn1168 and K20ac is shown in red. (C) Close-up of the di-acetylated lysine-binding site in the BRD4-BrD1. Key conserved interaction residues are shown. The hydrogen bond between Asn140 and K12ac is shown in red (PDB 3uvx). (D) Conservation of the acetyl-lysine binding site. The BRD4-BrD1 structure is shown with sequence conservation mapped on the surface. Green represents more conserved position, and white less conserved position. The conservation was computed from a multiple sequence alignment of all human BrDs. Conserved water molecules at the bottom of the K12ac binding pockets are shown as ball-and-stick models.

fold, the overall sequence similarity between members of the BrD family is not high, and there are significant variations in the sequences of the ZA and BC loops [24]. Nevertheless, the amino acid residues that are engaged in acetyl-lysine recognition are among the most conserved residues in the large BrD family, and correspond to Tyr^{1125}, Tyr^{1167} and Asn^{1168} in CREBBP (or CBP) (Fig. 1B) [25–27]. The acetyl-lysine residue forms a specific hydrogen bond between the oxygen of the acetyl carbonyl group and the side-chain amide nitrogen of the conserved asparagine residue (Asn^{1168} in CBP) [28] (Fig. 1B). However some BrDs, such as that of TRIM28 or the sixth BrD in the human Polybromo protein, contain a different residue (Tyr, Thr, or Glu) at the position of the conserved Asn [23]. The TRIM28 BrD does not bind to lysine-acetylated histones [29], whereas the BrD6 of Polybromo does, suggesting that there may be alternative modes of acetyl-lysine recognition by the BrD fold. The cooperative binding of two acetylation marks by a single BrD has also been described. This binding mode was first observed in BrD1 of BRDT [30] where both Kac residues of the H4K5acK8ac peptide occupy a single binding pocket. More recently BrD1 of BRD3 [31] and BrD1 of BRD4 [23] have been shown to also have the ability to recognize two acetylation marks with a single binding pocket. The recognition of di-acetylated peptides is also mediated by the conserved Asn residue, which interacts with one of the Kac residues, while the second Kac is bound at the edge of the canonical acetyl-lysine binding pocket, establishing hydrogen bonds with the peptide backbone (Fig. 1C) [30]. While BRDT, BRD3, and BRD4 all belong to the BET (bromodomain and extra-terminal) family of BrD-containing proteins, sequence and structural analysis suggests that BrDs outside of the BET family might also have the ability to recognize two acetylation marks [30,32]. An additional characteristic feature of the acetyl-lysine recognition pocket in BrDs is the presence of a network of water molecules that forms hydrogen bonds with carbonyl groups of the protein backbone at the base of the pocket [28]. These water molecules, which are an integral part of the acetyl-lysine binding pocket, and the residues in the deeper part of the acetyl-lysine binding pocket are relatively conserved over most of the BrD family (Fig. 1D). The selective recognition of acetyl-lysine in the context of different sequences is due to differences in key residues at the peptide-binding site [23,27,31,33,34]. For example, the residues participating in the recognition of H3K14ac by the second BrD of the human Polybromo protein are very different in the BrDs of PCAF and CBP explaining their different specificities for this specific mark [33].

1.2. The association of bromodomains with other chromatin modules

Most bromodomains are part of large multi-domain proteins with varying domain architectures [35,36], as such, BrDs are often found in tandem with other domains. More than 15 different domain types have been identified to occur within the same proteins as BrDs, including the PHD, PWWP, B-box type zinc finger, ring finger, SAND, FY Rich, SET, TAZ zinc Finger, helicase, ATPase, BAH (bromo adjacent homolog) domain, WD40 repeat and MBD (methyl-CpG binding domain) [37,38]. The most frequent association is that of a BrD with a PHD domain [37]. In many of these proteins the PHD and BrD are separated by a short amino acid sequence (<30 residues) and in some cases have been shown to form structurally interdependent tandem PHD/BrD arrangements such as that observed in TRIM28 [29] and TRIM33 [39]. The TRIM28 structure contains a distinct scaffold that unifies the two protein modules, in which the Z helix of the BrD forms a hydrophobic core that anchors the other three helices of the BrD on one side and the PHD finger on the other (Fig. 2A). A comprehensive analysis correlating transcriptional repression, UBC9 binding and SUMOylation showed that the PHD and BrD cooperate as a single functional unit to facilitate lysine SUMOylation [29,40]. This SUMO ligase activity is a divergent function for the BrD, which does not bind to lysine-acetylated histones in this form. The structure of the TRIM33 tandem PHD/BrD shows that the PHD finger binds to a methylated lysine, while the BrD bind to an acetylated lysine on the same peptide (H3K9me3K18ac), thus acting as a combinatorial reader of histone marks [39] (Fig. 2B). In contrast to TRIM28 and TRIM33, the structure of BPTF, which also contains a PHD finger and a BrD separated by a short linker [41], does not demonstrate any significant structural interactions between the two domains. In BPTF, the PHD domain recognizes the methylated lysine 4 residue of histone H3 (H3K4me3) [41,42].

Less is known about the functional consequences of tandem BrD/BrD combinations (the second most common domain association for the BrD). The structures of BrD1 of BRD4 with H4K8acK12ac [23] and of BrD2 of BRD2 with H4K5acK12ac [43], showed that two distinct BrDs can bind to the two marks simultaneously, suggesting the possibility

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