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Bromodomains as therapeutic targets

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Acetylation of lysine residues is a post-translational modification with broad relevance to cellular signalling and disease biology. Enzymes that 'write' (histone acetyltransferases, HATs) and 'erase' (histone deacetylases, HDACs) acetylation sites are an area of extensive research in current drug development, but very few potent inhibitors that modulate the 'reading process' mediated by acetyl lysines have been described. The principal readers of ε-*N*-acetyl lysine (K_{ac}) marks are bromodomains (BRDs), which are a diverse family of evolutionary conserved protein-interaction modules. The conserved BRD fold contains a deep, largely hydrophobic acetyl lysine binding site, which represents an attractive pocket for the development of small, pharmaceutically active molecules. Proteins that contain BRDs have been implicated in the development of a large variety of diseases. Recently, two highly potent and selective inhibitors that target BRDs of the BET (bromodomains and extra-terminal) family provided compelling data supporting targeting of these BRDs in inflammation and in an aggressive type of squamous cell carcinoma. It is likely that BRDs will emerge alongside HATs and HDACs as interesting targets for drug development for the large number of diseases that are caused by aberrant acetylation of lysine residues.

Lysine acetylation is similar to protein phosphorylation in its prevalence as a post-translational modification and also has a large effect on the physicochemical property of the modified residue. The addition of an acetyl moiety to the side-chain nitrogen of lysine leads to neutralisation of charge, which can significantly influence protein conformation and protein–protein interactions, thus resulting in the modulation of enzyme activities and protein assembly (Ref. 1). The central role of ε-*N*-acetylation of lysine residues (K_{ac}) is reflected by the large number of acetylation sites that have been identified in proteins (Ref. 2). Acetylation is particularly abundant in large macromolecular complexes that are present in the cell nucleus, suggesting a key role of acetylation in the regulation of chromatin and transcriptional control. In particular, the unstructured tails of histones are hotspots of acetyl lysine modification. Histone acetylation levels have been associated with an open chromatin architecture and transcriptional activation, but specific marks have also been linked to chromatin condensation (e.g. H4K16) (Refs 3, 4), regulation of metabolism (Ref. 5) and DNA repair (Ref. 6). Acetylation of transcription factors can either stimulate or silence gene

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transcription, and inappropriate acetylation levels have been associated with aberrant transcription of disease-promoting genes in cancer and inflammation, instigating the development of inhibitors for histone deacetylases (HDACs) (Ref. 7) and histone acetyltransferases (HATs) (Ref. 8).

Recruitment of proteins to macromolecular complexes by acetylated lysine residues is mediated by bromodomains (BRDs), which are evolutionarily highly conserved protein-interaction modules that recognise ε-*N*-lysine acetylation motifs (Ref. 9). However, BRDs in BRD4 have recently been shown to bind propionylated and butyrylated lysine residues (Ref. 10). BRDs are named after the *Drosophila* gene *brahma* where the BRD sequence motif was first reported (Refs 11, 12). Since then, BRDs have been identified in a number of nuclear proteins such as HATs (Ref. 13), ATP-dependent chromatin-remodelling complexes (Ref. 14), methyltransferases (Refs 15, 16) and transcriptional coactivators (Refs 17, 18, 19) (Table 1).

Role of BRD proteins in chromatin biology

BRDs have an important role in the targeting of chromatin-modifying enzymes to specific sites. Often they act with other protein-interaction modules to guarantee a high level of targeting specificity for these essential enzymes. For example, the methyltransferase ASH1L contains a combination of one BRD and one plant homology domain (PHD), as well as a bromo-adjacent homology domain (BAH) (Ref. 20). ASH1L is a member of the trithorax group of transcriptional activators. In *Drosophila*, ASH1L activates ultrabithorax expression, and mammalian homologues have been associated with actively transcribed genes. Another example of a multidomain methyltransferase containing a BRD is the mixed lineage leukaemia (MLL) gene product (Ref. 21), which is an essential gene and acts as a key regulator of the expression of many genes. MLL is required for proper segment identity in mammals, it displays haplo-insufficiency and regulates self-renewal of haematopoietic stem cells by controlling HOX (homeobox) gene expression (Refs 22, 23, 24).

In addition, the HATs CREBBP and EP300 contain several protein-interaction modules, including one BRD, and zinc finger and KIX domains (Ref. 25). Both proteins share a high degree of sequence similarity and act as transcriptional coactivators that control a large variety of biological processes, including cell growth, genomic stability, development, neuronal plasticity and memory formation, as well as energy homeostasis (Ref. 26). CREBBP is a coactivator of the cAMP response element-binding CREB transcription factor. The fundamental role of CREBBP is reflected by the severe phenotype of homozygous knockout mice, which die in utero with signs of defective blood vessel formation in the central nervous system, developmental retardation, and delays in both primitive and definitive haematopoiesis (Ref. 27). Similarly, homozygous deletion of *Ep300* results in mice that die between days 9 and 11.5 of gestation as a result of defects in neurulation, cell proliferation and heart development (Ref. 28). Two additional HAT-containing BRDs have been reported and these interact with EP300 and CREBBP: PCAF [also known as K(lysine) acetyltransferase 2B (KAT2B)] and the related GCN5. Both proteins acetylate histones and transcription factors, and act as transcriptional coactivators. *Gcn5*-knockout mice die during embryogenesis because of severe growth retardation, failure in the development of dorsal mesoderm lineages and anterior neural tube closure (Refs 29, 30). By contrast, homozygous deletion of the closely related *Pcaf* gene does not show gross abnormalities, but leads to short-term memory deficits and an exaggerated response to acute stress and conditioned fear, associated with increased plasma corticosterone levels (Ref. 31).

Recent data identified evolutionarily conserved AAA ATPase ANCCA (AAA nuclear coregulator cancer-associated protein)/ATAD2 as a protein required for recruitment of transcription factors of the E2F family to their target sites, and as a transcriptional coregulator of Myc, oestrogen and androgen receptors (ARs). ATAD2 associates through its BRD with histone H3 acetylated at Lys 14 during late mitosis, regulating the expression of genes required for cell cycle progression (Refs 32, 33, 34).

Dual BRD proteins of the BET (bromodomain and extra-terminal) family also have a pivotal role regulating the transcription of growth-promoting genes and cell cycle regulators. The BET family is represented by four members in humans (BRD2, BRD3, BRD4 and the testis-specific isoform BRDT), with each containing two N-terminal

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Table 1. Bromodomain-containing proteins and their functions

Protein	Name	Function	BRDs
ASH1L	Absent, small or homeotic-like	Methyltransferase	1
ATAD2A/B	AAA domain-containing protein 2	ATPase, coactivator	1
BAZ1A/B	BRD adjacent to zinc finger domain protein 1A	Chromatin assembly and remodelling	1
BAZ2A/B	BRD adjacent to zinc finger domain protein 2A/B	Unknown	1
BRD1	BRD-containing 1	Transcription factor	1
BRD2	BRD-containing 2	Transcription factor	2
BRD3	BRD-containing 3	Transcription factor	2
BRD4	BRD-containing 4	Transcription factor	2
BRDT	BRD-containing protein testis specific	Transcription factor	2
BRD7	BRD-containing 7	Transcriptional repressor	1
BRD8A/B	BRD-containing 8A/B	TRRAP/TIP60 complex	2
BRD9	BRD-containing 9	Unknown	1
BRPF1A/B	Peregrin	MOZ complex subunit	1
BRPF3A	BRD and PHD-finger-containing protein 3	Unknown	1
BRWD3	BRD and WD-repeat-containing protein 3	JAK/STAT signalling	2
CECR2	Cat eye syndrome critical region 2	Chromatin remodelling	1
CREBBP	CREB-binding protein	HAT	1
EP300	HAT p300	HAT	1
FALZ	Fetal Alzheimer antigene	Chromatin remodelling	1
GCN5L2	General control of amino acid synthesis protein 5-like 2	HAT	1
MLL	Mixed lineage leukaemia	Histone methyltransferase	1
PB1	Polybromo	SWI/SNF PBAF subunit	6
PCAF	P300/CBP-associated factor	HAT	1
PHIP	PH-interacting protein	Insulin signalling	2
PRKCBP1	Protein kinase C-binding protein 1	Transcriptional regulator	1
SMARCA2A/B	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin	SWI/SNF ATPase	1
SMARCA4	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin	SWI/SNF ATPase	1
SP100/SP110/SP140	Nuclear body protein	Transcriptional regulator	
TAF1/TAF1L	Transcription initiation TFIID-associated factor	Transcription initiation	2
TRIM24/TRIM28/TRIM33/TRIM66	Transcription intermediary factor	Transcriptional silencer	1
WDR9	BRD and WD-repeat-containing protein 1	Chromatin remodelling	2
ZMYND11	Zinc finger MYND-domain-containing protein 11	Corepressor	1

BRD, bromodomain; HAT, histone acetyltransferase; MOZ, monocytic leukaemia zinc finger protein; PHD, plant homology domain; SNF, sucrose nonfermenting.

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BRDs. BRD4 and BRD2 are key mediators of transcriptional elongation by recruiting the positive transcription elongation factor complex (P-TEFb). The P-TEFb core complex is composed of cyclin-dependent kinase-9 (CDK9) and its activator cyclin T. CDK9 phosphorylates the RNA polymerase II (RNAPII) C-terminal domain, a region that contains 52 heptad repeats. RNAPII undergoes sequential phosphorylation at Ser5 during promoter clearance and at Ser2 by P-TEFb at the start of elongation. It has been shown that BRD4 couples P-TEFb to acetylated chromatin through its BRDs. Interestingly, in contrast to other BRD-containing proteins and transcription factors, BET proteins remain associated with condensed and hypoacetylated mitotic chromosomes (Ref. 35), suggesting a role in epigenetic memory (Refs 36, 37). Homeostasis of BET expression levels is important for cell cycle control because both inhibition of BRD4 by microinjected specific antibodies and overexpression of BRD4 lead to cell cycle arrest in the G2M and G1S phases, respectively (Refs 38, 39), and genetic knockdown of BRD4 in cultured human cells significantly reduces cell growth (Ref. 40). BRD2 associates with the E2F transcription factors and with the SWI/SNF (switch mating type/sucrose nonfermenting) complex to regulate the expression of diverse genes (Ref. 41) such as cyclin D1 (CCND1) (Ref. 42). BRD2 can function as a transcriptional coactivator or corepressor in a promoter-specific or tissue-specific manner. Deletion of either BRD2 or BRD4 in mice is lethal, and *Brd4*$^{+/-}$ mice also show severe developmental defects (Refs 43, 44, 45). Mutagenesis of the *Brd2* promoter region resulted in mice that expressed reduced levels of BRD2 without causing gross developmental abnormalities. However, these mice are extremely obese without developing glucose intolerance (Ref. 46). The testis-specific BET family member BRDT is essential for normal spermatogenesis, and specific deletion of the first BRD in mice results in abnormal spermatids and sterility (Ref. 47). In agreement with studies in mice, altered histone modifications have been observed in the *BRDT* promoter region of subfertile patients (Ref. 48), and genome-wide association studies linked polymorphism in *BRDT* to sterility in European men (Ref. 49).

Tandem BRDs are also present in TAF1 [RNAPII, TATA box binding protein (TBP)-associated factor, 250 kDa formerly called TAFII250], the largest subunit of the general transcription factor TFIID. TAF1 binds to the core promoter sequence encompassing the transcriptional start site, and also interacts with other transcriptional regulators, thereby modulating the rate of transcription initiation (Ref. 50). It acts as a general transcriptional activator and as such regulates a variety of essential biological processes, including myogenesis, DNA-damage response, the cell cycle and apoptosis (Refs 51, 52, 53, 54). The C-terminal tandem BRDs have been shown to specifically recognise the diacetylated histone H4 tail at K5/K12 or K8/K16, as well as diacetylated P53 at K373/K382 at the p21 promoter (Refs 55, 56). TAF1L is a testis-specific homologue of TAF1. TAF1L is X-linked and might act as a functional substitute for TAF1 during male meiosis, when sex chromosomes are transcriptionally silenced. Similarly to TAF1, TAF1L can bind to the TATA-binding protein (TBP) and can functionally substitute for TAF1 in a temperature-sensitive hamster cell line (Ref. 57).

The WD repeat proteins BRWD1 (WDR9) and BRWD3 also contain tandem BRDs. Members of this family are involved in a variety of cellular processes, including cell cycle progression, signal transduction, apoptosis and gene regulation (Refs 58, 59). Mutations in mice revealed a role for BRWD1 in spermiogenesis and the oocyte–embryo transition (Ref. 60). Despite the specific phenotype in germ-cell maturation, BRWD1 is widely expressed, and its expression levels are dynamic during mouse development. It associates with the SWI/SNF complex component and functions as a transcriptional regulator involved in chromatin remodelling (Ref. 61). Little is known about the biological function of BRWD3. However, in *Drosophila*, BRWD3 function has been genetically linked to the JAK–STAT pathway (Ref. 62).

Single BRD modules are present in some members of the tripartite motif (TRIM) family of transcriptional regulators (Ref. 63). TRIM proteins are characterised by the presence of a RING finger, one or two zinc-binding motifs named B-boxes, and an associated coiled-coil region (Ref. 64). TRIM24 (Tif1α), for instance, contains an N-terminal TRIM domain, a nuclear receptor (LxxLL) interaction motif and a C-terminal PHD-BRD (Ref. 65). TRIM24 associates with chromatin (Ref. 66) and mediates

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ligand-dependent activation of AR and the retinoic acid receptor (RAR), and has been shown to interact with other nuclear receptors such as thyroid, vitamin D_3 and oestrogen receptors (Ref. 67). TRIM28 (TIF1β) is a corepressor for Krüppel-associated box-domain-containing zinc finger proteins (Ref. 68), which have a crucial role in early embryogenesis. TRIM28 associates with heterochromatin-associated factors HP1α, HP1β and HP1γ to promote the silencing of euchromatic genes (Ref. 69), and recruitment of TRIM28 to centromeres is required for induction of the parietal and visceral endoderm differentiation pathways (Refs 70, 71, 72). Interestingly, the PHD domain of the TRIM28 corepressor functions as an intramolecular E3 ligase, leading to sumoylation of the adjacent BRD. Sumoylation is required for TRIM28-mediated gene silencing, suggesting that the tightly linked PHD-BRD module functions as an intramolecular ubiquitin-like modifier (SUMO) E3 ligase (Refs 73, 74).

TRIM33 (Tif1γ) is a ubiquitin ligase that targets SMAD4 (Ref. 75). Formation of transcription regulatory complexes of SMAD4 with receptor-phosphorylated SMAD2 and SMAD3 is a key event in canonical TGFβ signalling. Consequently, depletion of TRIM33 in human cell lines inhibits SMAD4-dependent cell proliferation by competing with SMAD4 for selective binding to receptor-phosphorylated SMAD2 and SMAD3 (Ref. 76). Mice deficient in Trim33 die in utero, demonstrating that TRIM33 has an important role in development (Ref. 77). The relatively poorly studied TRIM66 (Tif1δ) is mainly expressed in testis and, similarly to TRIM24/33, associates with heterochromatin-associated factors (HPs) but not with nuclear receptors, and functions as a transcriptional silencer (Ref. 78).

The TRIM family member PML (promyelocytic leukaemia protein TRIM19) has no BRD itself but associates with SP proteins, a family of three proteins in humans (SP100, SP110 and SP140) that all contain a PHD-BRD tandem module N-terminally flanked by a SAND DNA-binding domain. The complex of PML and SP100 is found in nuclear bodies, which are nuclear structures that have been associated with the pathogenesis of acute promyelocytic leukaemia (Ref. 79). Nuclear bodies are implicated in the regulation of many cellular functions, including chromatin organisation (Ref. 80), DNA repair and genome stability (Refs 81, 82), as well as regulation of transcription (Refs 83, 84, 85). In addition, the nuclear body is a target of autoantibodies in patients with primary biliary cirrhosis (Ref. 86) and is involved in viral response (Ref. 87). However, little is known about the precise mechanisms whereby nuclear body proteins exert their functions.

BRDs have an essential role in the assembly and correct targeting of SWI/SNF complexes, which are particularly rich in BRD interaction modules. SWI/SNF complexes, also called Brahma-associated factors (BAFs), remodel chromatin structure, contributing to either transcriptional activation or repression of target genes, depending on the composition of the various complexes. The components of SWI/SNF complexes were originally identified in screens for mutants that result in defects in mating-type switching in yeast or that were unable to grow on sucrose (Refs 88, 89, 90). Microarray studies later showed that SWI/SNF functions as a transcriptional regulator that affects about 5% of all genes in yeast (Ref. 91). Mammalian SWI/SNF complexes have a key role in cell differentiation and proliferation, and represent an essential component of the embryonic stem cell core pluripotency transcriptional network (Refs 92, 93). All SWI/SNF complexes contain a core subunit, which alters chromatin structure in an ATP-dependent manner, resulting in an open and accessible conformation with increased affinity for transcription factors (Ref. 94). In humans, two related SWI/SNF ATPase components are expressed. These two proteins are mutually exclusive in SWI/SNF complexes and have been named after the *Drosophila* homologue Brahma as BRG1 (Brahma-related gene-1, SMARCA4) and the related protein BRM (SMARCA2). BRG1 and BRM contain a C-terminal BRD that has been implicated in the recognition of acetylated lysines within histone H3 and H4 tails (Ref. 95). Several SWI/SNF complexes have been shown to mediate critical interactions between a number of hormone and other nuclear receptors (Refs 96, 97, 98, 99). In addition, BRG1 has been shown to associate with Rb proteins, inducing cell cycle arrest and transcriptional repression in an HDAC-dependent manner. BRG1/HDAC-containing complexes have been shown to repress expression of genes involved in cell cycle

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regulation (Refs 100, 101). The chromatin-remodelling activity of BRG1 has also been shown to be important for traversal of the nucleosome by RNAPII (Ref. 102). The SWI/SNF complex PBAF (polybromo-associated BRG1-associated factor) is characterised by the presence of the polybromo protein (PB1) (also called BAF180) (Refs 103, 104). PB1 is required for ligand-dependent transactivation by nuclear hormone receptors and contains six BRDs, two bromo-associated domains (BAH) and a homeobox DNA-binding domain. PBAF complexes, but not BAF, activate vitamin-D-receptor-dependent transcription in response to vitamin D, and mice lacking Pb1 have defects in heart development (Ref. 105) because of impaired epithelial-to-mesenchymal transition and arrested maturation of the epicardium as a result of the downregulation of FGF, TGF and VEGF signalling (Ref. 106). PB1 also has a role in cell cycle regulation and is a key regulator of senescence (Ref. 107).

BRDs are present in chromatin-remodelling complexes of the ISWI (imitation SWI) family that assemble into at least seven different complexes containing a central core ATPase of the two SNF2-like mammalian homologues SNF2L and SNF2H of yeast ISWI. ISWI complexes are key regulators of transcription, heterochromatin replication and chromatin structure. The ISWI complex NURF (nucleosome remodelling factor) contains the BRD PHD finger transcription factor BPTF. BPTF contains a C-terminal PHD-BRD and was identified as a highly expressed protein in patients with Alzheimer disease as fetal Alz-50 reactive clone 1, and in fetal brain in patients with neurodegenerative diseases (fetal Alzheimer antigen, FALZ) (Refs 108, 109). The PHD domain in BPTF associates with trimethylated histone H3 Lys4, an interaction that is required for the recruitment of SNF2L1 to promoters (Ref. 110). The ISWI complex ACF/WCRF (ATP-utilising chromatin remodelling and assembly factor/Williams syndrome transcription factor) contains BAZ1 (also called WCRF or ACF1), a protein of the BAZ (BRD adjacent zinc finger) family, which is represented by four related genes in humans (BAZ1A, BAZ1B, BAZ2A and BAZ2B), with similar domain organisation, including a PHD-BRD interaction module. BAZ1A was first identified in HeLa cell nuclear extract as a factor associating with SNF2H forming a complex with ATP-dependent chromatin-remodelling activity (Ref. 111). Later, the SNF2H/BAZ1A remodelling activity was shown to be required for the DNA-replication machinery to penetrate condensed chromatin structures. SNF2H/BAZ1A is particularly enriched in replicating pericentromeric heterochromatin, and knockdown of BAZ1A by RNAi impairs replication of condensed chromatin (Refs 112, 113).

BAZ2A (TIP5, TTF-1-interacting protein 5) is a key subunit of the NoRC (nucleolar remodelling complex), which mediates transcriptional silencing of ribosomal RNA (Ref. 114). Interestingly, mutation of a tyrosine residue in the BAZ2A BRD in yeast impairs interaction with acetylated histones (Ref. 115) and the mutation Y1775F represses NoRC interaction with chromatin and RNA polymerase I transcription (Ref. 116). A table containing all human BRD proteins identified to date and a phylogenetic tree of this protein family is shown in Table 1 and Figure 1a, respectively.

BRD substrates

Given the central role of BRDs in epigenetic gene regulation, it is surprising that only a few substrates have been reported and mapped to specific sites. Reported affinities range from low micromolar to millimolar K_D values, raising questions regarding the physiological relevance of described weak in vitro substrate interactions, as well as which additional factors contribute to binding specificity (Table 2). BRDs are often associated with other protein-interaction modules, a mechanism that is thought to generate high target selectivity and increased binding affinity with substrates owing to avidity that is generated on simultaneous binding of several interaction domains. This property led to the suggestion that epigenetic regulation recognises patterns of post-translational modifications (words) rather than single modifications (letters) (Ref. 130). In addition, the reading process might require combinations of several modifications for high-affinity interaction with a single BRD. Recently, Moriniere and coworkers showed that the testis-specific BET isoform BRDT requires the presence of several acetylation sites for high-affinity binding to histone tails (Ref. 118). Interestingly, both acetylated lysines interact with the same binding pocket in BRDT (Fig. 1b). It is also

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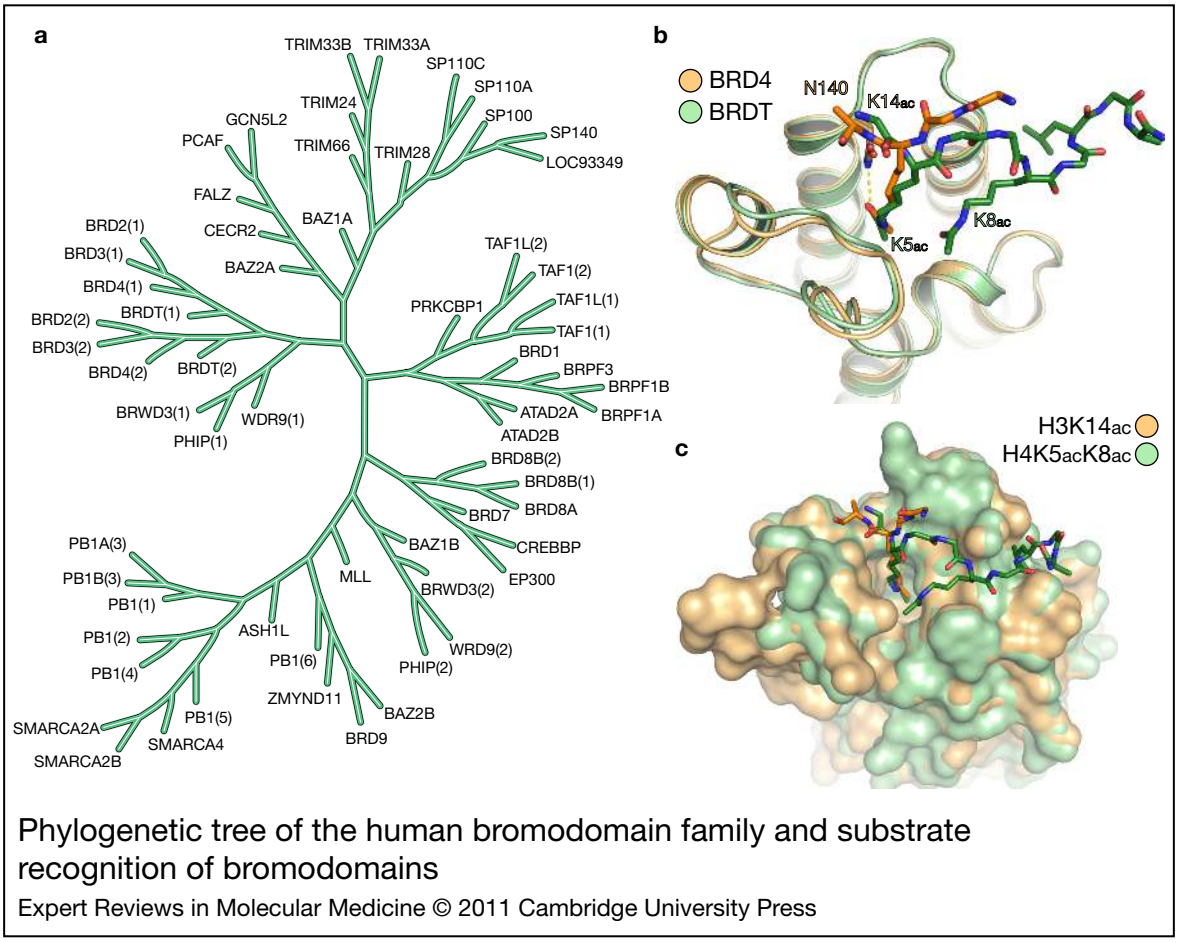

Phylogenetic tree of the human bromodomain family and substrate recognition of bromodomains

Figure 1. Phylogenetic tree of the human bromodomain family and substrate recognition of bromodomains. (a) Phylogenetic tree based on sequence alignments of predicted BRDs. For targets with multiple BRDs, the domains have been numbered starting from the N-terminus and the number is shown in parentheses. (b) Interaction of mouse BRD4 (Ref. 117) and mouse BRDT (Ref. 118) with monoacetylated Lys14 in histone H3 and a diacetylated H4 peptide monoacetylated on both Lys5 and Lys8. (c) Surface representation in similar orientation. See Table 1 for an explanation of protein symbols.

likely that other post-translational modifications, such as phosphorylation and methylation, influence substrate recognition, providing the basis for crosstalk of transcription control and cellular signalling. Similarly, the related BRD protein BRD3 also requires two adjacent acetylation sites for tight interaction with the transcription factor GATA1 (Ref. 131).

BRDs as therapeutic targets in cancer

Many proteins that use BRDs for their recruitment to specific regulatory complexes have been implicated in the development of cancer. BRD-containing proteins are usually multicomponent, and often the reported disease association has not been directly linked to defects in the BRD module itself. However, a number of dominant oncogenic rearrangements and correlation of overexpression of BRD proteins with patient survival provide a strong case for targeting BRDs in cancer.

Genetic rearrangements of BRD-containing proteins have been linked to the development of a number of extremely aggressive tumours. A very aggressive poorly differentiated carcinoma that originates mainly from midline locations such as the head, neck or mediastinum is NUT (nuclear protein in testis) midline carcinoma (NMC) (Ref. 132). NMCs are genetically characterised by translocations that involve the NUT protein with BRD4, BRD3 or an unknown partner gene. BRD4–NUT rearrangements are

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Table 2. Bromodomain substrates with known affinity

BRD	Sequence	Affinty (μM)[a]	Refs
BRD2	H4K12	2900 (NMR)	119
	H4K5/12	140 (SPR)	120
BRD4(1)	H3K14	118 ± 28 (ITC)	10
	H3K14-propyl	337 ± 76 (ITC)	
	H3K23-propyl	380 ± 105 (ITC)	
	H4K5	325 ± 72 (ITC)	117
	H4K5	810 (NMR)	121
	H4K12	650 (NMR)	
	H4K5/K8	38 ± 3.7 (ITC)	10
BRD4(2)	H3K14	327 ± 75 (ITC)	10
	H3K14-propyl	213 ± 15 (ITC)	
	H3K23-propyl	208 ± 16 (ITC)	
	H4K5	107 ± 23 (ITC)	117
	H4K5	1000 (NMR)	121
	H4K12	1350 (NMR)	
	H4K5/K8	212 ± 32 (ITC)	10
BRDT(1)	H2BK12/15	157 ± 15 (ITC)	118
	H3K9/14/18/23	390 ± 36 (ITC)	
	H4K5/8	21.9 ± 1.7 (ITC)	
	H4K8/12	193 ± 22 (ITC)	
	H4K12/16	117 ± 22 (ITC)	
	H4K5/12	340 ± 67 (ITC)	
	H4K5/8/12/16	28.0 ± 6.1 (ITC)	
BRDT(2)	H3K9/14/18/23	214 ± 48 (ITC)	
	H3K14/18	217 ± 28 (ITC)	
	H3K18/23	176 ± 52 (ITC)	
	H3K9/18	360 ± 140 (ITC)	
	H3K18	251 ± 62 (ITC)	
BRD7	H3K9	3960 (NMR)	122
	H3K14	1190 (NMR)	
	H4K8	1790 (NMR)	
	H4K12	3420 (NMR)	
	H4K16	2560 (NMR)	
CREBBP	H4K20	218 (NMR)	123
	H3K36	122 (NMR)	
	p53K382	187 (NMR), 155 (FP)	
GCN5L2	H4K8	900 (NMR)	124
	H4K16	900 (NMR)	
PB1	H3[b]	1.1 - 34 (FA)	125
PB1(1)	H3K4	390 (FP)	126
PB1(2)	H3K9	360 (FP)	
PB1(4)	H3K23	120 (FP)	
PCAF	H4K8	346 ± 54 (NMR)	127
	H3K9	1051 (NMR)	123
	H3K14	128 (NMR)	
	H3K36	402 (NMR)	
	H4K16	365 (NMR)	
	H4K20	247 (NMR)	
	TATK50	84 (NMR), 212 (FP)	
SMARCA4	H3K9/14	500 (NMR)	128
	H3K14	1200 (NMR)	95
	H4K8	4000 (NMR)	
	H4K12	3600 (NMR)	
TAF1 (BRD-BRD)	H4K16	39 ± 7 (ITC)	55
	H4K8/16	5.6 ± 0.2 (ITC)	
	H4K5/12	1.4 ± 0.3 (ITC)	
	H4K5/8/12/16	5.3 ± 0.2 (ITC)	
TRIM24 (PHD-BRD)	H3K9	232 ± 33 (ITC)	129
	H3K14	229 ± 32 (ITC)	
	H4K16	26 ± 2 (ITC)	
	H3K23	0.07 ± 0.01 (ITC)	

[a]Method of affinity experiments are in parentheses. [b]Histone H3 residues 1-25 with single acetylations on K4, K9, K14, K18 or K23.
Abbreviations: FA, stopped-flow fluorescence anisotropy; FP, fluorescent polarization; ITC, isothermal titration calorimetry; NMR, nuclear magnetic resonance; SPR, surface plasmon resonance.

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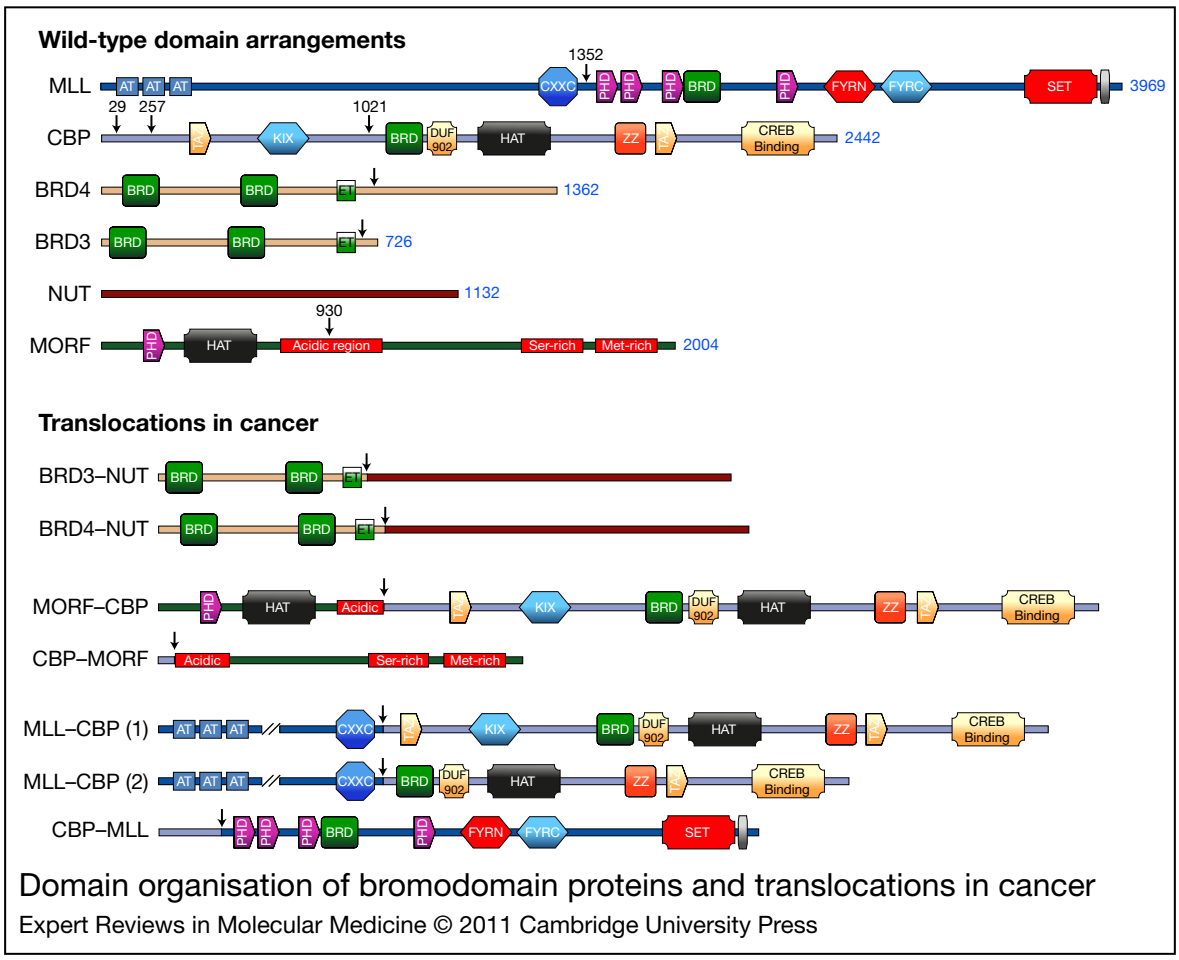

Figure 2. Domain organisation of bromodomain proteins and translocations in cancer. BRD modules are shown in green (labelled BRD). Other domain types are labelled directly in the figure and breakpoints are indicated by arrows. Wild-type domain arrangements are shown in the upper panel. See Table 1 for an explanation of protein symbols.

most frequent, occurring in two-thirds of cases. Both BRD4–NUT and BRD3–NUT fusion genes encode proteins composed of the N-terminal tandem BRDs and almost the entire NUT gene (Fig. 2). BRD–NUT blocks cellular differentiation, and depletion of this oncogene by RNAi results in squamous differentiation and cell cycle arrest (Refs 133, 134). BRD4–NUT specifically recruits CBP/p300, leading to stimulation of CBP/p300 HAT activity, formation of nuclear foci and inactivation of p53 (Ref. 135). Selective inhibition of BRD4–NUT by recently developed acetyl lysine competitive inhibitors results in epithelial differentiation, tumour shrinkage and survival in BRD4–NUT xenograft mice (Ref. 136).

Chromosomal translocations of CREBBP with the MLL protein and the monocytic leukaemia zinc finger protein (MOZ) have been described in myeloid and lymphoid acute leukaemia and myelodysplasia secondary to therapy with drugs targeting DNA topoisomerase II (Refs 137, 138) (Fig. 2). CREBBP also contributes to tumourigenesis of NUP98–HoxA9 and MOZ–TIF2 fusion proteins by activating transcription (Refs 139, 140). In addition, CREBBP mutations have been identified in relapsed acute lymphoblastic leukaemia (Ref. 140) and are very common in diffuse large B-cell lymphoma and follicular lymphoma, constituting the major pathogenetic mechanism shared by common forms of B-cell non-Hodgkin's lymphoma (Ref. 141). CREBBP and the related HAT EP300 are also highly expressed in advanced prostate cancer, and expression

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levels have been linked with cancer patient survival (Ref. 142).

Overexpression of several BRD proteins has been reported in cancer and has been linked to patient survival. For instance, a recent study showed that ATAD2 is overexpressed in more than 70% of breast tumours and that higher protein levels correlate with tumour histological grades, poor overall survival and disease recurrence (Ref. 33). Revenko and coworkers showed that ATAD2 is required for recruitment of specific E2F transcription factors and for chromatin assembly of the host cell factor 1–MLL histone methyltransferase complex. As a result of its association with the MLL methyltransferase, depletion of ATAD2 results in a marked decrease of trimethylation of Lys4 in histone H3, which has been linked to transcriptional activation. BRD mutations disable ATAD2 function as an E2F coactivator and its ability to promote cancer cell proliferation (Ref. 32). The closely related protein ATAD2B has recently been shown to be highly expressed in glioblastoma and oligodendroglioma, as well as in breast carcinoma (Ref. 143).

Aberrant expression has also been reported for TRIM24 in breast cancer, and high expression levels have been shown to negatively correlate with survival of breast cancer patients (Ref. 129). In liver, however, TRIM24 seems to function as a liver-specific tumour suppressor (Ref. 144). TRIM24 also interacts with AR and enhances transcriptional activity of the AR by dihydrotestosterone in prostate cancer cells (Ref. 145). These data suggest that TRIM24 function and its role in tumourigenesis might be highly context dependent.

The testis-specific BET family member BRDT is frequently overexpressed in non-small-cell lung cancer (Ref. 146) and several other cancers (Ref. 147), but the functional consequences of BRDT overexpression have not been investigated so far. The role of BRD4 in cancer is better understood. BRD4 has been shown to be a key regulator of cell cycle control and transcriptional elongation of growth-promoting genes. In particular, the key role of BRD4 in the recruitment of P-TEFb (CDK9/cyclinT) to transcriptional start sites provides an alternative strategy to targeting CDK9, which emerged as a validated target in chronic lymphocytic leukaemia (Ref. 148). In breast cancer, however, *BRD4* has been identified as an inherited susceptibility gene for disease progression and its expression levels have been associated with patient survival (Ref. 149). BRD4 and BRD2 also have a key role for the transmission of tumour viruses during mitosis by providing a chromatin anchor to viral episomes. For instance, during latent viral infection of herpes viruses associated with development of Kaposi sarcoma, the transmission of viral genomes to daughter cells during mitosis is mediated by the episome's latency-associated nuclear antigen 1, which is tethered to chromatin through its interaction with BRD4 (Ref. 150). Also, papilloma viruses that have been linked to the development of cervical cancers and Epstein–Barr viruses associate with BRD4 in order to anchor their viral genomes to mitotic chromosomes (Refs 151, 152).

BRDs as therapeutic targets for the treatment of inflammation

Transcriptional control of proinflammatory cytokines is the central mechanism in the aetiology of inflammatory disease, and given the success of HDAC inhibitors in this area, it is likely that selective BRD inhibitors will modulate these processes. A first example has been provided by the recent pan-BET inhibitor iBET, which leads to the disruption of chromatin complexes responsible for the expression of inflammatory genes and conferred protection against lipopolysaccharide-induced endotoxic shock and bacteria-induced sepsis (Ref. 153). Three sites of polymorphism in *BRD2* have recently been linked to rheumatoid arthritis (Ref. 154) and *Brd2*-hypomorphic mice are severely obese and have reduced inflammation in fat tissue (Ref. 46).

The BRD-containing HATs EP300/CREBBP have been proposed as therapeutic targets in inflammatory diseases such as lung inflammation and asthma (Ref. 155). Activation of proinflammatory genes is intimately linked to activation of nuclear factor κB (NFκB). The activated p65 subunit translocates to the nucleus, where its affinity to its target genes and transcriptional activity is regulated by acetylation by EP300/CREBBP. Compounds that inhibit NFκB acetylation such as the natural product gallic acid have anti-inflammatory properties (Refs 156, 157). EP300 and PCAF also regulate inflammatory responses through their

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regulation of cyclooxygenase-2 (COX2) expression. COX2 is a key enzyme of prostaglandin biosynthesis that is well established as a major player in inflammatory response and a clinically successful target for the development of anti-inflammatory drugs. Stimulation by bacterial lipopolysaccharides and other cytokines leads to increased binding of PCAF and EP300 to the *COX2* promoter, and its activation. Conversely, inhibitors of EP300 have been shown to reduce COX2 protein levels and promoter activities (Ref. 158).

The concerted activation of several proinflammatory genes is regulated by the SWI/SNF class of ATP-dependent remodelling complexes, which make the promoters of inflammatory genes permissive for transcriptional induction. The presence of the catalytic ATPase subunit BRG1 at the promoter of proinflammatory genes such as *IL6* has been shown to be necessary for activation of these genes, and termination of transcriptional activation is regulated by proteasomal degradation of BRG1, ensuring a timely and adequate immune response (Ref. 159). Although experimental data are still missing, it is intriguing to speculate that removal of BRG1 from promoter regions might have an effect on inflammatory conditions.

BRDs as therapeutic targets for the treatment of neurological diseases

Increasing evidence points to the fact that epigenetic targets have a role in the molecular manifestation of stress and related disorders. Because BRD inhibitors have only just been discovered, no study has addressed the role of BRD inhibition in neurological disorders so far. However, several studies report important functions of BRD-containing proteins in several diseases. TRIM28, for instance, is highly expressed in the mouse hippocampus and cerebellum. Inducible deletion of *Trim28* in the forebrain of adult mice resulted in stress-related behaviour and cognitive impairment of these mice similar to effects observed in behavioural disorders such as borderline personality or bipolar disorder. Chromatin immunoprecipitation experiments confirmed changes in histone methylation and acetylation patterns in the promoter regions of TRIM28 target genes such as *Mkrn3* and *Pcdhb6* (Refs 160, 161).

Two other BRD-containing proteins, SMARCA2 (BRM) and BRD1, have been identified in genome-wide association studies as susceptibility genes for schizophrenia and bipolar disorder in several independent studies, but the molecular mechanisms are still unclear (Refs 162, 163). In addition, low levels of SMARCA2 have been found in the post-mortem prefrontal brains of schizophrenic patients, and the gene expression profiles in the diseased brains match those after downregulation of SMARCA2 in cells and in SMARCA2-knockout mice, which show impaired social interaction and prepulse inhibition. Interestingly, SMARCA2 expression can be increased in the mouse brain on application of antipsychotic drugs, providing further evidence of the potential of this protein as a target for the treatment of schizophrenia (Refs 164, 165).

Mutations in *CREBBP*, and less frequently in *EP300*, are the genetic background for Rubinstein–Taybi syndrome (RTS), a rare human genetic disorder characterised by mental retardation and physical abnormalities; many patients with RTS have either breakpoints or microdeletions in chromosome 16p13.3 where the *CREBBP* gene is located, but also heterozygous point mutations can lead to RTS (Refs 166, 167, 168). Several of the pathological features can be mirrored by heterozygous *Crebbp*-deficient mice strains (Refs 169, 170, 171). Although the precise mechanisms underlying the disease are not yet understood, it is thought that the HAT activity of CREBBP and reduced transcriptional activity result in altered synaptic plasticity, which ultimately influences long-term memory, leading to mental retardation (Ref. 172). EP300 also has a role in the aetiology of amyotrophic lateral sclerosis, Alzheimer disease and Huntington disease. Huntington disease is a polyQ disease in which polyglutamine repeats are added to the Huntingtin protein, causing its translocation to the nucleus and formation of aggregates. CREBBP and PCAF interact directly with Huntingtin aggregates, resulting in their depletion (Refs 173, 174). Indeed, HDAC inhibitors have long been used as mood stabilisers and are studied for the treatment of Huntington and Alzheimer diseases (Ref. 175).

Development of BRD inhibitors

BRDs share a conserved fold that comprises a left-handed bundle of four alpha helices (α_Z, α_A, α_B,

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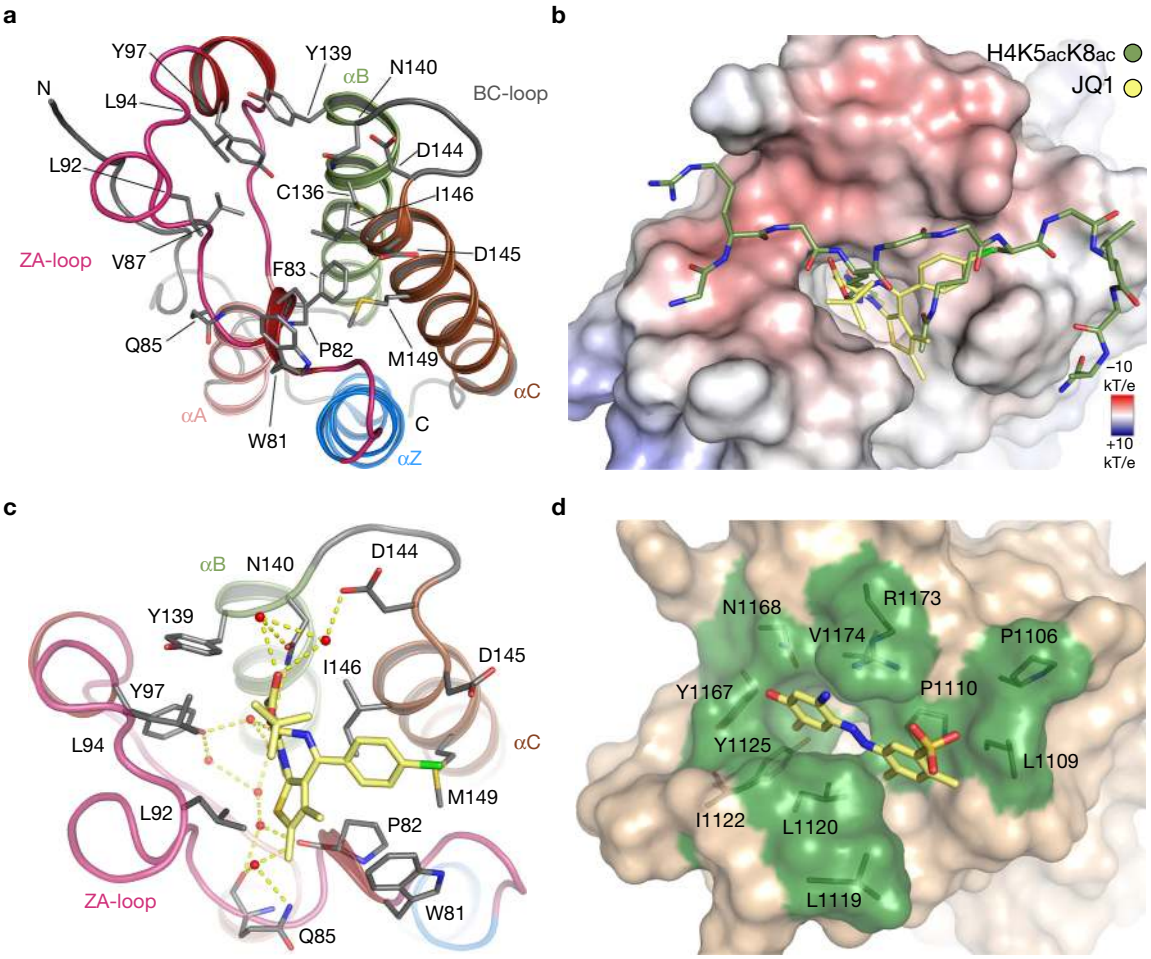

Structural overview of a bromodomain and binding mode of bromodomain inhibitors

Figure 3. Structural overview of a bromodomain and binding mode of bromodomain inhibitors. (a) Ribbon diagram of the first BRD of BRD4. The main structural elements as well as the acetyl lysine binding site residues are labelled. (b) Superimposition of a diacetylated BET substrate peptide and the inhibitor JQ1. Inhibitor and peptide molecules are shown in stick representation and are coloured according to atom types. (c) Binding of JQ1 to the bromodomain of BRD4. Conserved water molecules in the active site are highlighted and hydrogen bonds are shown as dashed lines. (d) Complex of ischemin with CREBBP (Ref. 176).

α_C), linked by highly variable loop regions (ZA and BC loops), which form the rim of the substrate-binding pocket and determine substrate recognition (Refs 55, 127) (Fig. 3a). Despite the conservation of the overall BRD fold, the surface and loop regions of BRDs are highly diverse, suggesting that inhibitors with high specificity can be designed. Cocrystal structures with peptidic substrates have demonstrated that the acetyl lysine is recognised by a central deep hydrophobic cavity, where it is anchored by a hydrogen bond to an asparagine residue present in most BRDs (Ref. 177). Acetylation of lysine residues neutralises the charge of the ε-amino group. As a consequence, the central cavity of acetyl lysine binding sites in BRDs is quite hydrophobic and particularly rich in aromatic residues; it also has sufficient size to accommodate potent acetyl lysine competitive ligands. These properties make BRDs attractive targets for the design of pharmacologically active molecules that compete with protein interactions mediated by these modules.

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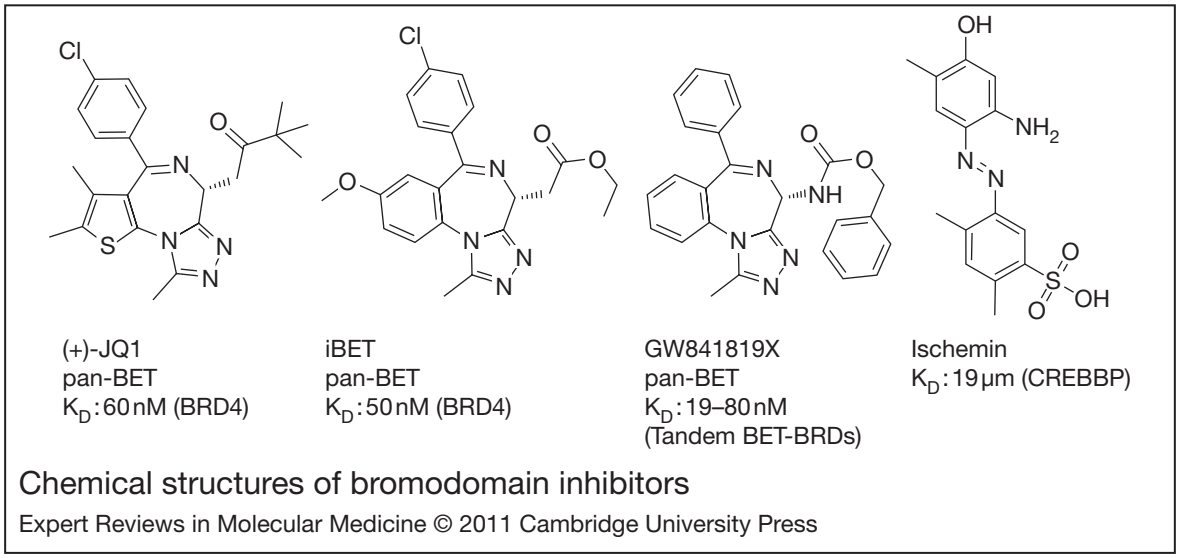

Figure 4. Chemical structures of bromodomain inhibitors. Specificity and dissociation constants are also indicated.

Potent and very selective inhibitors have recently been published for BET BRDs (Refs 136, 153, 178). All inhibitors that have been published so far are based on a triazolo-diazepine scaffold that successfully mimics interactions observed in BET peptide complexes (Fig. 3b). Interestingly, a number of tightly bound and conserved water molecules remain in cocrystal structures of BET triazolo-diazepine complexes, which interact with the inhibitor through a network of hydrogen bonds (Fig. 3c). Two BET inhibitors have been studied in two different disease models, providing compelling support of BET BRDs as targets in drug discovery. The inhibitor JQ1 has been studied in midline carcinoma where inhibition of BRD4–NUT led to terminal differentiation, cell cycle arrest and apoptosis of carcinoma cells, and significant reduction of tumour growth in patient-cell-line-derived xenograft models (Ref. 136). The inhibitor iBET led to significant reduction of the expression of proinflammatory genes in activated macrophages, and conferred protection against lipopolysaccharide-induced endotoxic shock and bacteria-induced sepsis, supporting inhibition of BET BRDs as a strategy for the generation of immunomodulatory drugs (Ref. 153).

Acetyl lysine mimetic inhibitors have also been reported in the case of CREBBP, competing for its interaction with p53. These inhibitors were identified by NMR screening using a library of compounds that consists of one aromatic ring connected to an $-NHCOCH_3$ group by different types of linkers (Ref. 179). The same laboratory also reported a series of cyclic peptides with improved binding affinities over natural substrates (Ref. 179) and azobenzene-based inhibitors such as 4-hydroxyphenylazo-benzenesulfonic acid (MS456) and ischemin. Ischemin binds to the BRDs of CREBBP with a dissociation constant (K_D) of 19 μM and shows at least fivefold selectivity over other human BRDs. The binding mode of ischemin in CREBBP is shown in Figure 3d. In cellular assays ischemin alters post-translational modifications of p53 and histones, inhibits p53 interaction with CBP and transcriptional activity in cells, and prevents apoptosis in ischaemic cardiomyocytes (Ref. 179). Early lead compounds such as *N*1-aryl-propane-1,3-diamine have also been identified for PCAF (Ref. 180). A summary of the chemical structures of the currently most advanced BRD inhibitors is shown in Figure 4.

Research in progress and outstanding research questions

Targeting BRDs for the development of protein-interaction inhibitors has recently emerged as a strategy for the design of pharmacologically active reagents. The relatively weak interaction

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of BRDs with their substrates, the diversity and physicochemical properties of the acetyl lysine binding site, and the large number of available crystal structures will facilitate the rational design of such inhibitors. However, BRDs usually constitute only one of the interaction domains found in BRD-containing proteins, and whether selective inhibition of the acetyl lysine interaction alone will result in the desired phenotype needs to be investigated in future research projects. The large number of diseases that have been linked to BRD-containing proteins and the success of particular HDAC inhibitors indicate that BRD inhibitors will find a large number of applications in pharmaceutical sciences and basic research.

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Further reading, resources and contacts

Websites

Bromodomain structures solved by the Structural Genomics Consortium:
http://www.sgc.ox.ac.uk/structures/BRO.html

Chemical probe resource for epigenetic targets:

http://www.thesgc.org/chemical_probes/epigenetics/

Disease-annotated chromatin epigenetic resource:

http://wodaklab.org/dancer/

The chromatin database:

http://www.chromdb.org/

Human Histone Modification Database (HHMD):

http://bioinfo.hrbmu.edu.cn/hhmd/

Features associated with this article

Figures

Figure 1. Phylogenetic tree of the human bromodomain family and substrate recognition of bromodomains.
Figure 2. Domain organisation of bromodomain proteins and translocations in cancer.
Figure 3. Structural overview of a bromodomain and binding mode of bromodomain inhibitors.
Figure 4. Chemical structures of bromodomain inhibitors.

Tables

Table 1. Bromodomain-containing proteins and their functions.
Table 2. Bromodomain substrates with known affinity.

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