Brd4 and BET Family Proteins

Bromodomain-containing protein 4 (Brd4) is a member of the BET family that in yeast and animals contains two tandem bromodomains (BDI and BDII) and an extraterminal (ET) domain (1). The bromodomain is a conserved region of ~110 amino acids that structurally forms 4 α-helices (αv, αA, αw, and αC) and 2 loops, linking αv and αA (ZA loop) and αw and αC (BC loop), capable of binding acetyl-lysine residues in histones and many other proteins (2). In humans, four BET proteins (Brd2, Brd3, Brd4, and Brdt) exhibit similar gene arrangements, domain organizations, and some functional properties. Brd2, formerly named RING3 (really interesting new gene 3) or Fshr1 (female sterile homeotic related gene 1), is a nuclear serine/threonine kinase possessing chromatin binding activity with preference for acetylated lysine 12 on histone H4 and transcription activity via its association with transcriptional regulators such as E2F1 (3, 4). Brd3 (also called ORFX or Fshr2) and Brdt (for bromodomain, testis-specific) are less well characterized although mouse Brdt has been reported to induce global chromatin reorganization in an acetylation-dependent manner (5). Brd4, originally named MCAP (mitotic chromosome-associated protein; Ref. 6) but also called Fshr4 or Hunk1, is a chromatin binding factor with preference for acetylated Lys-14 on histone H3 and Lys-5/12 on H4 (7). Except for Brdt, which is expressed specifically in testis and ovary, Brd2, Brd3, and Brd4 are widely distributed (8, 9). Interestingly, the chromosomal locations of these Brd genes are adjacent to the four Notch genes found in the human genome with Brd2 and Notch4 on chromosome 6, Brd3 and Notch1 on chromosome 9, Brd4 and Notch3 on chromosome 19, and Brdt and Notch2 on chromosome 1 (10, 11), indicating a likely functional relationship between human Brd and Notch gene families.

The domain organization of mammalian Brd proteins is conserved and extends to homologues in other species, including Drosophila Fsh and Saccharomyces cerevisiae Bdf1 and Bdf2 proteins (Fig. 1A). Although BDI, BDII, and the ET domain are characteristic of the BET family proteins, other domains, such as motifs B and SEED (Ser/Glu/Asp-rich region), are also highly conserved (9). The C-terminal motif (CTM) (12) and motif A (9), however, are not present in every protein. The sequence feature and alignment of each domain across different species are presented in supplemental Figs. 1 and 2. Other than the gene paralogues, many of the BET proteins exist in two (i.e. long and short) isoforms generated by alternatively spliced transcripts differing at their 3’ ends (Fig. 1B). The long form of human and mouse Brd4 is often the only isoform detected (6, 8) and accounts for the majority of the biological activity. The function of the short form (also known as Hunk1 in humans), if expressed (13), remains undefined. Interestingly, a fusion protein, containing the N-terminal 719 amino acids of human Brd4 linked to the nearly complete Nut (nuclear protein in testis) protein (spanning amino acids 6–1132, missing only the first 5 residues) caused by t(15;19)(q13,p13.1) chromosomal translocation, has been reported in some epithelial carcinomas (13).

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MINIREVIEW: Chromatin Adaptor Brd4

FIGURE 1. Domain organization of Brd4 family proteins. A, human (h), Drosophila (d), and yeast (y) BET proteins. Numbers indicate the amino acid boundaries of each domain or the corresponding amino acid residues of individual proteins. Identification of amino acid sequences is conducted with ClustalW software based on published information (1, 9, 12, 14) using the following accession numbers retrieved from GenBank databases: hBrd2, NM_005104; hBrd3, NM_007371; hBrd4, NM_058243; dBrd4, NM_207189; dFsh, M23221; yBdf1, NP_013503 (derived from NC_001144); and yBdf2, Z74119. Motifs A and B (grey boxes) indicate the amino acid boundaries for four α-helices (αA, αD, αB, and αC) and two loops (ZA and BC) forming BDI and BDII of human Brd4, characterized to be essential for its nuclear localization (20). Accession numbers for additional coding sequences: mBrd4, NM_020508; mouse Brd4 short, NM_198094; human Brd4 short, NM_014299; and human Nut, NM_175741.

FIGURE 2. Identifed Brd4 domains and amino acid residues important for protein-protein interactions. A, BDI and BDII of human Brd4. Numbers above the boxes indicate the amino acid boundaries for four α-helices (αA, αD, αB, and αC) and two loops (ZA and BC) forming BDI and BDII of human Brd4. According to the structural designation of human Brd2 (15) and the crystal structure of human Brd4 (14), amino acid residues important for binding acetyl-lysine that are conserved with human Brd2 (4) are indicated in red and conserved with yeast Bdf1 (15) indicated in blue. Green letters indicate Brd4 residues conserved with human Brd2 likely involved in homodimeric formation as characterized in BDII of human Brd2. B, domains in mouse Brd4 critical for interaction with different cellular and viral proteins. The last four lines depict similar domains in other BET proteins involved in interaction with respective proteins indicated on the right.

Chromatin Adaptor Brd4

Formation of homodimeric (e.g. BDI-BDI) or heterodimeric bromodomains (e.g. BDI-BDII), likely helps determine the binding specificity between bromodomains and different acetyl-lysine residues. The secondary binding pocket may also provide an independent surface for acetyl-lysine-independent bromodomain-histone interactions (15) and underlie the observation that deletion of one bromodomain in a BET protein fails to eliminate its chromatin-binding and transcriptional activity (4, 17). Based on the characterized residues in human Brd2 (supplemental Fig. 1), the amino acids in human Brd4 potentially involved in homodimeric interactions include but are not limited to Glu-62, Met-126, Glu-127, Tyr-137, Ile-138, Glu-154, Leu-158, Ile-161, and Glu-166 in BDI, and Glu-353, Gly-419, Ala-420, Tyr-430, Lys-431, Gly-437, Glu-451, Phe-454, and Asp-459 in BDII (see green letters in Fig. 2A).

Besides binding acetylated chromatin, BDII also interact with nonhistone proteins to regulate transcription, DNA replication, cell cycle progression, and other cellular activities. A BDII-containing region in mouse Brd4 has been shown to interact with several cellular and viral proteins, including the cyclin T1 component of human positive transcription elongation factor b (P-TEFb) (18, 19), the RFC-140 subunit of human replication factor C (20), signal-induced proliferation-associated protein 1 (SPA-1) (21), and HPV-1 E2 protein (17) (Fig. 2B). Whether these interactions are truly mediated by BDII or amino acids further downstream remains
to be defined. In the cases of cyclin T1 and HPV-11 E2, a second interaction region separate from the BDII-containing region of Brd4 has also been identified. The ET domain seems to serve as a protein-protein interaction module between human Brd4 and Kaposi’s sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen 1 (LANA-1) (22, 23) and between yeast Bdf1 and the TAF7 subunit of the general transcription factor TFIIID (24). A region containing the SEED motif downstream of the ET domain in human Brd2 is critical for interaction with E2F1 and E2F2 and thus may underline the role of Brd2 in E2F-dependent transcription and cell cycle control (3). The CTM encompassed in a larger C-terminal domain of mouse and human Brd4 has been shown to interact with E2 encoded by different types of papillomaviruses and appears to be important for viral genome segregation (see below). An alanine substitution of Phe-1349 or Asp-1352 in the CTM of human Brd4 abolishes Brd4 interaction with HPV-16 E2 (12). These two residues are also conserved in the CTM of mouse Brd4, human Brdt, and Drosophila Fsh (see Fig. 1 and supplemental Fig. 2).

Role of Brd4 in Cell Cycle Progression

Brd4 is a ubiquitously expressed protein of ~200 kDa first identified in mouse as MCAP because of its chromosome binding activity (6). As described for yeast Bdf1 (25) and human Brd2 (4), association of Brd4 with chromatin persists throughout the cell cycle (7). A unique feature of the BET proteins lies in their ability to associate with mitotic chromosomes, unlike other bromodomain-containing proteins, such as p300, CBP, GCN5, and the hBrm/hSNF2α and hBrg1/hSNF2β subunits of human SWI/SNF chromatin remodeling complexes (26), which are typically displaced from condensed chromosomes during mitosis. Inhibition of mouse Brd4 function by injecting anti-Brd4 antibodies into proliferating cells leads to G2/M arrest (6), presumably because of an imbalance between Brd4 and SPA-1 activity needed in G2 for cell division (21). In contrast, overexpression of Brd4 in cultured cells results in G1/S arrest (20). This may be caused by Brd4-mediated repression of replication factor C function during DNA replication (20). Not surprisingly, knockout of Brd4 in mice is embryonic lethal (11), and severe knockdown of Brd4 in cultured human cells significantly reduces cell growth (17). Because Brd4 haptainsufficiency in Brd4+/− cells is linked to reduced levels of acetylated Lys-14 on H3 and acetylated Lys-12 on H4 as well as impaired reloading of Brd4 onto chromosomes following removal of antimicrotubule drugs that disrupt Brd4 binding to chromosomes (27), it seems that Brd4 also plays an important role in maintaining the global acetylation state of chromatin in the cell. In this aspect, it will be of interest to examine whether t(15;19) chromosomal translocation leads to Brd4 haptainsufficiency, which may correlate with increased chromosomal missegregation observed in Brd4+/− cells (27) and whether ectopic expression of Brd4-Nut that also causes G1/S arrest (28) can substitute for (or antagonize) some function of Brd4.

Brd4 Found in Selective Forms of Mediator Complexes

An indication that Brd4 is directly implicated in transcriptional control is provided by the analysis of a mouse Mediator complex that contains an uncharacterized subunit with sequence homology to human Brd2/RING3 (29). Comparison of the RING3-like peptide sequences with known Brd2 family proteins suggests that the RING3-like protein is likely to be mouse Brd4 (11). This issue is now resolved by experimentation illustrating that human Brd4, rather than Brd2, is the RING3-like protein found in human Mediator complexes purified from the P11 0.5 M KCl fraction (P.5) (30) prepared from a HeLa-derived cell line expressing the FLAG-tagged Med7 (fMed7) subunit of human Mediator (supplemental Fig. 3, lane 2). Because Mediator-P.5 contains at least two forms of Mediator differing in the presence or absence of a Cdk8-containing module (30), we separated these two forms by immunodepletion of Cdk8 (30) and found that the amount of Brd4 associated with Mediator-P.5 remains the same (supplemental Fig. 3, lane 2 versus lane 3). Interestingly, Brd4 was not detected in human Mediator isolated from the P11 0.85 M KCl fraction (P.85) (30) and in human TFIIID (31) (supplemental Fig. 3, lanes 4 and 5). This finding demonstrates that Brd4, rather than Brd2, is indeed associated with Mediator, but only selective forms of Mediator complexes contain Brd4, most likely through its interaction with a subunit of Mediator not present in the Cdk8 module. It should be noted that yeast Bdf1, considered to be the counterpart of the C-terminal region of human and Drosophila TAF1, is only found in some populations of yeast TFIIID (24, 32). Perhaps a dynamic association of Brd4 with Mediator allows it to interact with different protein complexes in responding to the specific need of gene activity in a cell.

Brd4 Present in Distinct Forms of P-TEFb Complexes

A proteomic analysis of human proteins associated with mouse Brd4 identified cyclin T1, Cdk9, and several components of human Mediator in the Brd4 complexes (18). Interestingly, Brd4 is only found in the P-TEFb complex containing cyclin T1 and Cdk9 without the inhibitory protein HEXIM1 and 7SK small nuclear RNA (19). It is estimated that the active form (cyclin T-Cdk9-Brd4) and the repressive form (cyclin T-Cdk9-HEXIM1–7SK RNA) of P-TEFb each account for ~50% of P-TEFb in the cell (19). The association of Brd4 in active P-TEFb suggests that Brd4 is involved in transcription by RNA polymerase II (pol II). Indeed, transcription of some cellular genes, such as c-myc and c-jun, and the HIV-1 promoter, is enhanced by Brd4, which also stimulates Cdk9-mediated phosphorylation of serine 2 at the C-terminal domain (CTD) of pol II (18). Recruitment of Brd4 and Cdk9 to an integrated HIV-1 promoter is significantly increased by treatment of cultured cells with a histone deacetylase inhibitor (18). These experiments illustrate a positive role of Brd4 in pol II-dependent transcription through enhanced recruitment of the active P-TEFb complex to acetylated chromatin in the promoter region. However, Brd4-mediated enhancement of pol II-dependent transcription can also occur in vitro with nuclease-free DNA templates containing the HIV-1 promoter with or without the Tat-responsive region (19). This Tat-independent stimulation requires Brd4, as transcription of the HIV-1 promoter in Cdk9-depleted nuclear extracts could only be restored by adding back wild-type Cdk9 but not the Cdk9-S175D mutant that retains CTD kinase activity but fails to interact with Brd4 (19). Moreover, a Mediator component (TRAP220) could only be found in pull-down complexes containing wild-type Cdk9 but not the S175D mutant, suggesting P-TEFb
interaction with Mediator is Brd4-dependent (19). It is likely that Brd4 binding to acetylated chromatin, facilitated by a Brd4-interacting DNA-binding protein (see below), helps recruit Mediator to the promoter region (Fig. 3A). Following initiation of transcription and serine 5 phosphorylation of the pol II CTD by TFIIH and presumably Mediator as well, Brd4-associated Mediator then recruits core P-TEFb (cyclin T1/Cdk9) when pol II is stalled at the downstream promoter region due to promoter clearance and enhances cyclin T1-mediated serine 2 phosphorylation of the pol II CTD. Clearly, Brd4 plays a multiple role in stimulating pol II-dependent transcription at both chromatin and DNA levels.

**Brd4 Found in an HPV Transcriptional Silencing Complex**

HPV E2 is a sequence-specific DNA-binding protein involved in viral DNA replication, transcription, genome maintenance, and segregation. Intriguingly, Brd4 is identified in a protein complex containing E2 encoded by either bovine papillomavirus type 1 (BPV-1) (33) or HPV-11 (17). As a transcriptional regulator, HPV E2 mainly acts as a repressor to inhibit viral gene expression, including E6 and E7 oncoproteins that antagonize p53 and pRB tumor suppressor activity (17). The identification of Brd4 as a component in a dominant form of E2 complexes indicates that Brd4 may be the long sought cellular cofactor for HPV E2 repressor function. Indeed, recombinant Brd4 and E2 are both necessary and sufficient to replace the purified E2 repressor complex in inhibiting AP-1-dependent HPV chromatin transcription in an E2-binding site-specific manner, as illustrated by reconstituted chromatin transcription experiments in which the in vitro assembled HPV chromatin faithfully recapitulates the positioning of nucleosomes typically observed in vivo (17). The requirement of Brd4 in E2-mediated repression of HPV transcription is further demonstrated in living cells by both transient and stable knockdown of Brd4. Apparently, chromatin-bound Brd4 recruits E2 that in turn prevents the recruitment of TFII D and pol II to the HPV promoter. Surprisingly, the levels of acetylated H3 and H4 in the E6 promoter region are not reduced, suggesting that acetylated chromatin is probably necessary for binding of Brd4 and thereby for E2-mediated repression (17). Interestingly, enhanced binding of Brd4 to acetylated chromatin following sodium butyrate (a histone deacetylase inhibitor) treatment of HeLa cells that express HPV-11 E2 only occurs at the region where an E2-binding site is situated. As expected, the recruitment of E2 to its cognate binding site is also augmented, paralleling with enhanced Brd4 recruitment (17). This finding suggests that acetylated chromatin alone is not sufficient to stabilize Brd4 binding to chromatin and that a synergistic binding between Brd4 and a sequence-specific DNA-binding protein that interacts with Brd4, such as E2, is necessary for mutual enhancement of binding to acetylated chromatin (Fig. 3B). This notion is consistent with a rapid “on” and “off” mode of Brd4 binding to acetylated chromatin in living cells (7, 34). It is important to mention that although Brd4 is efficiently recruited to HPV chromatin, it is not universally found in every gene. Furthermore, at least one bromodomain of Brd4 is required for chromatin targeting and for E2 recruitment to acetylated chromatin (17). Once E2 accesses its binding sites adjacent to the TATA box, it blocks TFIID binding and further prevents TFII F-escorted pol II entry to the promoter region (35, 36). It is likely that Brd4 also modulates E2 interactions with DNA and with general cofactors Mediator, TFIID, and positive cofactor 4 (PC4), as well as components of the general transcription machinery (37) to fine-tune the efficiency of preinitiation complex assembly, correlating with its involvement in gene activation and repression.

**Brd4 Is an Authentic Transcriptional Cofactor**

The dual role of Brd4 in gene activation (Fig. 3A) and repression (Fig. 3B) classifies it as an authentic transcriptional cofactor, similar to the regulatory properties exemplified by general cofactors Mediator, TFIID, USA-derived components (38), and p300 (39). A coactivating role of Brd4 in E2-mediated activation of heterologous promoters containing multimerized E2-binding sites has also been reported (40–42). It will be interesting to see whether E2-mediated activation also requires Mediator and P-TEFb, as seen with the HIV-1 promoter. Equally important is to define chromatin-independent properties of Brd4 in transcriptional activation and repression.

**Brd4 in Viral Genome Segregation and Beyond**

Because E2 is also implicated in viral genome maintenance and segregation (12, 33, 43–45), it is intriguing to find that Brd4 is able to bridge E2-bound BPV-1 and HPV genomes onto mitotic chromosomes and thus facilitate viral genome segregation during mitosis. Based on the defined interaction domains, the structure of the N-terminal 201 amino acids of HPV-16 E2 in complex with the C-terminal 20 amino acids of human Brd4 has been solved by x-ray crystallography at 1.59-angstrom resolution (12). Two amino acids in the human Brd4 peptide (Phe-1349 and Asp-1352) shown to be critical for E2 interaction are conserved among CT M-containing BET proteins (see Fig. 1A). This conservation suggests that
CTM-binding cellular proteins may exist in the cell to modulate Brd4 activity, a caveat potentially complicating the interpretation of data relying on the use of CTM-containing domains as dominant negative mutants for functional studies. Although Brd4 appears to be the cellular adaptor for some animal and HPV types, E2 encoded by other HPVs does not colocalize with Brd4 in mitotic chromosomes (42–44). This discrepancy, even for the same type of viral genomes mapped in different laboratories, raises the concern of whether Brd4 is the only cellular adaptor for tethering viral genomes to mitotic chromosomes or other mitotic apparatus, such as spindles (46). Indeed, another E2-interacting human protein, ChlR1 (chromosome loss-related protein 1), has recently been shown to be the tethering factor for BPV-1 genomes (47). Interestingly, HPV-11 E2 also associates with SMC5 (structural maintenance of chromosome 5) and SMC6 (17), which in turn interact with cohesin components SMC1 and SMC3 (48) that also complex with ChlR1 (49). Accordingly, E2 may interact sequentially or simultaneously with multiple chromosome-binding proteins to facilitate viral genome maintenance, tethering, and segregation in latently infected cells. Whether each of these E2-interacting chromatin adaptors also plays a role in HPV transcription, as demonstrated for Brd4, will be of great interest for future investigations. Undoubtedly, Brd4 has emerged as a central player in transcription, DNA replication, cell cycle control, oncogenesis, and viral genome segregation and is clearly an excellent working model for many chromatin adaptors.

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