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Bromodomains: translating the words of lysine acetylation into myelin injury and repair

Achilles Ntranos, MD^a and Patrizia Casaccia, MD, PhD^b

Achilles Ntranos: achilles.ntranos@gmail.com

^aDepartment of Neurology, Icahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY 10029, USA

^bDepartment of Neuroscience, Icahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY 10029, USA; Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY 10029, USA; Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Icahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY 10029, USA

Abstract

Bromodomains are evolutionary highly conserved α -helical structural motifs that recognize and bind acetylated lysine residues. Lysine acetylation is being increasingly recognized as a major posttranslational modification involved in diverse cellular processes and protein interactions and its deregulation has been implicated in the pathophysiology of various human diseases, such as multiple sclerosis and cancer. Bromodomain-containing proteins can have a wide variety of functions, ranging from histone acetyltransferase activity and chromatin remodeling to transcriptional mediation and co-activation. The role of bromodomains in translating a deregulated cell acetylome into disease phenotypes was recently unveiled by the development of small molecule bromodomain inhibitors. This breakthrough discovery highlighted bromodomain-containing proteins as key players of inflammatory pathways responsible for myelin injury and also demonstrated their role in several aspects of myelin repair including oligodendrocyte differentiation and axonal regeneration.

Keywords

Bromodomains; lysine acetylation; multiple sclerosis; remyelination; myelin injury

Introduction

Lysine acetylation is a reversible post translational modification of proteins that initially was studied in histone regulation, chromatin remodeling and gene expression and recently shown to modulate diverse cellular processes, including cell cycle regulation, RNA splicing,

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nuclear transport and actin nucleation [1]. The regulatory scope of lysine acetylation, therefore, is broad and comparable with that of other major posttranslational modifications such as phosphorylation. Acetylation is highly regulated by “writer” enzymes, the histone acetyltransferases (HATs), which add the acetyl group to lysine residues and “eraser” enzymes, histone deacetylases (HDACs), which remove the acetyl group from proteins. A deregulation of the acetylation levels of proteins in different cell types has been detected in several human diseases including autoimmune disorders and cancer [2]. Understanding how lysine acetylation is translated into various signals and cellular phenotypes could therefore allow its therapeutic manipulation in human diseases (Figure 1A).

Bromodomains are evolutionarily highly conserved protein modules that recognize and anchor to acetylated lysine-residues which can be found on histones or other protein domains [3]. Bromodomain-containing proteins have various functions ranging from histone acetyltransferase and chromatin remodeling activity to transcriptional activation. Thereby, bromodomains, as the “readers” of lysine acetylation, are responsible for transducing the signal carried by acetylated lysine residues and translating it into various normal or abnormal phenotypes (Figure 1B).

Deregulation of acetylation levels has long been associated with multiple sclerosis, an inflammatory demyelinating disease of the central nervous system that produces significant neurological disability in young adults [4]. The hallmark of the disease is immune mediated myelin injury and axonal damage that can be seen early in the disease course as well as in experimental autoimmune encephalomyelitis, the murine model of multiple sclerosis. Another characteristic of multiple sclerosis is failure of remyelination caused by a differentiation block of oligodendrocyte progenitor cells [5]. This is mostly seen in chronic demyelinating lesions, where oligodendrocyte precursor cells are found in a hyperacetylated state, thus making bromodomains potential effectors of this phenotype.

Bromodomain structure and function

Bromodomains were first identified as a novel structural motif by Tamkun et al when studying the drosophila gene Brahma (brm) [6] and were later identified as acetyl-lysine binding protein modules by Zhou et al [7,8]. The total number of currently known unique human bromodomain modules is 56. These can be clustered into eight groups, each one having at least two bromodomain modules with similar sequence length and at least 35% sequence identity, and eight outliers [3,9]. All available bromodomain modules have a conserved central hydrophobic pocket formed by four α -helix bundles (α_Z , α_A , α_B , α_C) where an acetylated lysine residue is anchored to a highly conserved asparagine residue. [3,8]. The α -helix bundles are linked by loop regions of variable charge and length, named ZA and BC loops. These diverse loop regions make the overall sequence similarity between bromodomain modules low [10].

Bromodomains modify their function and binding affinity by associating with neighboring modules

The modular nature of bromodomains enables them to act as a functional unit within a protein, either independently or in association with neighboring modules [3]. For example

the domain most frequently associated with a bromodomain is the plant homeodomain (PHD) finger, which is a C4HC3 zinc-finger-like motif present in nuclear proteins. Of the known 42 human bromodomain-containing proteins, 19 contain a PHD finger. In 12 of those, the two modules are separated only by a short amino-acid sequence of less than 30 residues, thus forming a unified, structurally interdependent arrangement with diverse functions, ranging from chromatin remodeling to lysine SUMOylation [3,11,12].

The second most common feature is the presence of another bromodomain, an association which strengthens the binding affinity of the bromodomain-containing proteins with their targets. Of the known 42 human proteins, 11 contain 2 bromodomains and 1 contains 6 bromodomains [3]. Most of them are separated by short amino acid sequences of less than 20 residues, thus forming tandem structural arrangements that can bind selectively to multiple acetylated histone H4 peptides [13]. While individual bromodomain modules, have a very low affinity to specific sites [14], the association of multiple modules with each other seems to be necessary to generate increased binding affinity and high target selectivity [14]. This property led to the suggestion that bromodomain-containing proteins recognize patterns of post translational modifications (“words”) rather than single chemical modifications (“letters”) of the epigenetic code [15].

Bromodomains and epigenetic modulation

The complexity and variability of the domain composition of human bromodomain-containing proteins and the influence of neighboring domains on the function of the module itself make it difficult to predict the function of bromodomain-containing proteins based on sequence similarity alone. The most prominent family of bromodomain-containing proteins is the Bromo- and Extra-Terminal domain (BET) family, which includes bromodomain-containing protein 2 (BRD2), BRD3, BRD4 and the testis-specific BRDT. These proteins have recently come to the forefront of research in cancer and immunology due to the discovery of specific small molecule inhibitors, such as iBET and JQ1, which led to the understanding of their function in cancer biology, viral infections and inflammation, as well as chromatin regulation, transcriptional control and signal transduction. However, many of the other bromodomain-containing proteins do not have well-characterized functions and their role in myelin injury and repair has been less studied.

The role of bromodomains in the immune system: potential target to decrease myelin injury

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system, which is a major cause of neurological disability in young adults. Immune-mediated myelin injury is the hallmark of the disease, but early axonal loss can also be found in demyelinating plaques. The pathophysiology of myelin injury in multiple sclerosis is complex, but begins with the activation of myelin reactive T cells in the periphery. There is increased production of Th17 cells, driven by the cytokine IL-23, and reduction in Foxp3 regulatory T cells. Autoreactive T cells infiltrate the CNS where they secrete proinflammatory cytokines such as IFN γ and TNF α , which activate microglia and macrophages and can also directly injure oligodendrocytes [16]. IL12 is also increased in

demyelinating plaques, which is a potent promoter of inflammation [17]. Activated microglia produce free radicals and proteases which break down myelin. Oligodendrocytes can also be targeted by CD8 T cells via cell mediated cytotoxicity and B cells via antibody mediated cytotoxicity. These mechanisms are also prominent in experimental autoimmune encephalomyelitis, the murine model of multiple sclerosis, where the effects of small molecule inhibitors of bromodomains can be studied more thoroughly.

The transcriptional control of the above pro-inflammatory cytokines and T cell differentiation pathways are orchestrated by transcription factors of the NF- κ B, FOXP3, IRF, and STAT families along with epigenetic phenomena, including DNA methylation and histone acetylation. [18]. As demonstrated in the current literature, the role of bromodomains in the inflammatory cascade is not only linked to the remodeling of chromatin, but also to the regulation of the above transcription factors and signaling pathways. Targeting bromodomain-containing proteins could therefore influence the balance of pro-inflammatory and anti-inflammatory cytokines and drive T cell differentiation towards a more regulatory phenotype, which can reduce or even prevent myelin injury in demyelinating diseases such as multiple sclerosis.

The central role of histone acetyltransferase P300 in chromatin remodeling and signal transduction of inflammatory pathways

The bromodomain-containing histone acetyltransferase P300/CBP is central to the transcriptional activation of several proinflammatory cytokines involved in myelin injury such as IL-1, IL-2, IL-8, IL-12, and TNF α . This occurs via acetylation of their promoter regions and chromatin remodeling as well as regulation of NF- κ B signaling [18,19]. Acetylation of histone H3 at their promoter regions results in the increased recruitment of NF- κ B to these regions [20]. Glucocorticoid receptor (GR) and HDAC2 can reverse this process, thus promoting repression of NF- κ B-dependent inflammatory genes [20]. P300 has also been involved in major inflammatory signaling pathways that contribute to myelin injury in multiple sclerosis. Choi et al showed that p300 can acetylate the p65 subunit of NF- κ B thus mediating its translocation to the nucleus and increase IL6 levels, an effect that can be reversed by gallic acid, a p300 inhibitor [21]. The bromodomain of p300 is found to play a role in IL6 signaling pathway by mediating the interaction of p300 with STAT3 amide-terminal domain and stabilizing the enhanceosome assembly [22]. Finally p300 and PCAF have been shown to regulate the cyclooxygenase 2 promoter and activate COX2 expression, a key enzyme in prostaglandin synthesis and inflammation [23].

Non-histone bromodomain proteins regulate cytokines via transcriptional mediation and co-activation

BRD4, a member of the BET family of proteins, is also strongly involved in the inflammatory cascade. It has been shown to act as a co-activator of NF- κ B via binding to the acetylated lysine-310 of the RelA subunit. BRD4 then recruits cyclin-dependent kinase 9 (CDK9), a component of the positive transcription elongation factor for RNA polymerase II-directed transcription, to phosphorylate the C-terminal domain of RNA polymerase II and facilitate the transcription of NF- κ B-dependent inflammatory genes [24]. BRD4 has also been implicated in the transcriptional control of IL1 β -induced IL-6 and CXCL8 expression

and BET inhibitors JQ1 and PFI-1 significantly reduced their expression in a model of chronic inflammation and oxidative stress [25]. BRD2, another BET family member, has been shown to be essential for proinflammatory cytokine production in macrophages, a major player in demyelination. Belkina et al demonstrated that BRD2 and BRD4 physically associate with the promoters of inflammatory cytokine genes in macrophages. They also showed that JQ1 ablated cytokine production in vitro and blunted the “cytokine storm” in endotoxemic mice by reducing levels of IL-6 and TNF-alpha while rescuing mice from LPS-induced death [26].

Bromodomains in T cell differentiation and regulation

Apart from the transcriptional control of cytokines, bromodomain-containing proteins have been implicated in T cell differentiation and activation. BET proteins were found to have a fundamental role in human and murine Th17 differentiation from naive CD4 T cells, as well as in the activation of previously differentiated Th17 cells, which have been strongly associated with multiple sclerosis. Mele et al showed that BET protein family members BRD2 and BRD4 associate with the IL17 locus in Th17 cells and control Th17 differentiation via direct regulation of multiple effector Th17-associated cytokines, including IL17, IL21, and GMCSF. Using JQ1 they also showed that BET inhibition protected mice from collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE) by preventing generation and/or function of Th17 cells [27]. Another bromodomain-containing protein, TRIM28, which is phosphorylated in T cells after antigenic stimulation via the T cell antigen receptor (TCR), has recently been found to be involved in the global regulation of CD4 T cells. By studying mice with conditional T cell-specific deletion of TRIM28 (CKO mice), Chikuma et al found that these mice had a spontaneous autoimmune phenotype with accumulation of autoreactive Th17 cells and Foxp3 T cells. These Foxp3 cells, however, were unable to prevent the autoimmune phenotype in vivo. These mice also exhibited a defect in the production of interleukin 2 and derepression of the TGF-beta3, as well as incomplete cell-cycle progression of their T cells [28].

Bromodomains are mainly implicated in pro-inflammatory pathways that are involved in myelin injury

All these results suggest that bromodomain-containing proteins are heavily involved in most of the detrimental processes that can cause myelin injury in autoimmune diseases, such as proinflammatory cytokine production, initiation of the inflammatory cascade and Th17 cell differentiation and function. Specifically the inhibition of the BET family of bromodomains was shown to significantly reduce inflammation and demyelination in experimental autoimmune encephalomyelitis, providing another therapeutic target for multiple sclerosis (Figure 2). However, other bromodomain-containing proteins were implicated in T cell regulation and prevention of autoimmunity, demonstrating the variability and diversity of bromodomain protein functions. Further research is required to delineate the functions of other bromodomain-containing proteins and clarify their role in autoimmunity and their therapeutic implications in myelin injury.

The role of bromodomains in myelin repair

Multiple sclerosis therapeutics are dominated by immunomodulatory therapies aiming to reduce myelin injury but there are none for myelin repair. Remyelination is the holy grail of multiple sclerosis research, hoping to restore the damage inflicted to the central nervous system and prevent the progression of disease. After the acute demyelinating attack there is a surge of oligodendrocyte progenitor cells (OPCs) in the area of demyelination in an attempt to repair the damage [29]. It has been long known that there is some degree of remyelination in multiple sclerosis lesions [30,31], but it is frequently transient and inadequate to sustain myelin formation as disease progresses. Kuhlmann et al more recently demonstrated that despite the presence of OPCs in chronic MS lesions, there seems to be a differentiation block that is responsible for the failure of remyelination [5]. This differentiation failure has been attributed to many different extrinsic and intrinsic factors of oligodendrocytes with epigenetic changes being one of them. A shift toward histone acetylation has been found in the white matter of the frontal lobes of patients with longstanding multiple sclerosis which was associated with higher levels of transcriptional inhibitors of oligodendrocyte differentiation, such as TCF7L2, ID2 and SOX2, and higher transcript levels of p300/CBP [4]. That was in contrast to patients with early disease, where a marked oligodendrocyte histone deacetylation was observed [4]. Hyperacetylation of OPCs in chronic MS plaques could therefore potentially explain the differentiation block that is observed in these patients and bromodomains, as the “readers” of histone acetylation, could be the effectors of that phenotype.

Several direct and indirect evidence support the role of bromodomains in myelin repair

The most concrete evidence of the role of BET proteins in oligodendrocyte lineage progression came from Gacias et al. In this study, selective chemical inhibition of only the first bromodomain module (BD1) of the BET proteins induced the differentiation of OPCs, which was independent of any effects on proliferation [32]. That was achieved by a small inhibitory molecule specific for BD1 called olinone. In human BRD4, BD1 has been shown to be responsible for binding to the diacetylated histone H4K5ac/K8ac and BD2 was associated with recruitment of non-histone proteins, i.e. transcription factors, to target genes. The opposite was true for BRD3, however, showing that bromodomain modules have protein specific roles and that olinone could only be affecting the binding of specific BET proteins. On the other hand, inhibition of both bromodomain modules of the BET proteins hindered the differentiation of OPCs and retained the cells at a progenitor stage, further supporting their role in myelination [32]. By blocking only one bromodomain module, olinone was therefore able to alter the way BET proteins read the words of lysine acetylation and translate them into a favorable phenotype (Figure 3).

Although not directly studied in oligodendrocytes, the transcriptional inhibitors of oligodendrocyte differentiation that were elevated in chronic MS lesions have been found to be regulated by BET proteins in various cancer cells. For example SOX2 expression has been shown to be enhanced by BRD4-NUT oncogenic fusion in NUT midline carcinomas [33] and BET protein inhibition by JQ1 was shown to reduce expression of SOX2 in medulloblastoma cells [34]. ID2 has been associated with BRD4 in super-enhancers of small

cell lung cancer cells [35]. Finally c-Myc, which when activated prevents the transition of OPCs from proliferation to differentiation [36], has been shown to be regulated by BET proteins in various cancer cell lines. BET inhibition by JQ1 downregulated c-MYC transcription, followed by genome-wide downregulation of c-Myc-dependent target genes in multiple myeloma [37] and medulloblastoma [38]. All these results indicate that BET proteins could be regulating the transcriptional inhibitors of oligodendrocyte differentiation in OPCs as well, but further research is required to definitely answer that question.

Bromodomain-containing proteins are involved in axonal regeneration in the CNS

Successful myelin repair, however, also requires the presence of healthy axons and it is already known that axonal injury can be found even in early demyelinating MS plaques. Interestingly, however, bromodomain-containing proteins have also been implicated in axonal regeneration, thereby providing the substrate for successful myelination. P300 overexpression has been shown to promote axonal regeneration in an optic nerve crush model of axonal injury, by targeting both the epigenome and transcriptome to unlock a post-injury silent gene expression program [39]. Moreover it has been shown that CBP/P300 and PCAF form a transcriptional complex with the transcription factor TRP53 in primary neurons to enhance promoter accessibility on select pro-regeneration genes thereby triggering an intrinsic pro-axonal outgrowth program [40].

Conclusions

Bromodomain-containing proteins have very diverse functions, but collectively they are key regulators of major cellular processes, such as cell proliferation, transcriptional regulation and differentiation. Their role in myelin injury and repair has just started to be investigated but the results so far are very promising. Bromodomains have been implicated not only in the inflammatory pathways responsible for myelin injury but also in the regulation of oligodendrocyte differentiation and remyelination, making them attractive targets for multiple sclerosis therapeutics. It has been shown that selective modulation of bromodomains can have important translational implications. Due to the possibility to specifically target the bromodomain fold, several distinct small molecule inhibiting bromodomains have been developed so far. It is envisioned that these small molecules can modify the ability of bromodomain-containing proteins to interpret the epigenetic code towards a more favorable phenotype. An example of this shift of function towards the desirable phenotype, was reported for the small molecule inhibitor olinone, which allowed the selective inhibition of BET proteins and favored oligodendrocyte differentiation. However, more research is needed to shed light into the various bromodomain functions, in order to develop a new therapeutic strategy to reduce myelin injury from inflammation, while restoring myelination and promoting axonal regeneration in multiple sclerosis.

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Highlights

- Lysine acetylation is involved in diverse cellular processes.
- Bromodomains are the readers and effectors of lysine acetylation.
- Bromodomain proteins range from histone acetyltransferases to transcription factors.
- Bromodomains play a role in major inflammatory pathways involved in myelin injury.
- Both remyelination and axonal regeneration are regulated by bromodomains.

Figure 1. Lysine acetylation and cell function

A. Lysine acetylation as a major post translational modification in cells. Various proteins (Pr) can be acetylated (Ac) by specific “writer” enzymes, called histone acetyltransferases (HAT), or can be deacetylated by the “eraser” enzymes, histone deacetylases (HDAC). Acetylation levels are tightly regulated by these enzymes and their deregulation is detected in many pathological states.

B. Bromodomains (Br) are protein modules that function as the “readers” of lysine acetylation on targets of bromodomain-containing protein (BRD). They can recognize and bind to acetylated lysine residues in histones and non-histone proteins, thereby transducing the signal carried by acetylation by recruiting various protein complexes (PC) and transcription factors (TF). (R): receptor

Figure 2. Bromodomains and inflammatory response

A. Immune mediated myelin injury is caused by autoreactive T cells that secrete proinflammatory cytokines, activating surrounding macrophages/microglia and causing demyelination. Bromodomain-containing proteins (i.e. P300, BRD2, BRD4), control the transcriptional activation of proinflammatory genes and major inflammatory signaling pathways (NF- κ B) all of which are involved in immune mediated myelin injury.

B. Small molecule bromodomain inhibitors, such as those against BRD2 and BRD4, have been shown to reduce proinflammatory cytokine production by T cells and macrophages as well as to inhibit the production and activation of Th17 cells, thereby reducing demyelination in murine models of multiple sclerosis.

Ac: acetylated lysine, BD: bromodomain module, BRD: bromodomain-containing protein, BDi: bromodomain inhibitor, TF: transcription factor, PC: protein complex, NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells transcription factor

Figure 3. Bromodomains and oligodendrocyte differentiation

A. In chronic demyelinating lesions, oligodendrocyte progenitor differentiation is stalled and remyelination impaired. In such chronic lesions, a hyperacetylated state of histones is detected in the nuclei of oligodendrocyte progenitors and this results in increased levels of transcriptional inhibitors of differentiation. As the readers of lysine acetylation, bromodomain-containing proteins could be the effectors of this phenotype.

B. Selective inhibition of single bromodomain modules might modify the way bromodomain-containing proteins translate the words of acetylation and remove the inhibitory stimulus of hyperacetylation, thus promoting differentiation of oligodendrocytes and restoration of myelin.

C. On the other hand, complete inhibition of both bromodomains keeps oligodendrocytes in the progenitor stage and prevents their differentiation into myelin producing cells. Ac: acetylated lysine, BD: bromodomain module, BRD: bromodomain-containing protein, BDi: bromodomain inhibitor, TF: transcription factor, PC: protein complex, OPC: oligodendrocyte progenitor cell