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Review article

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

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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.

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ABSTRACT

Bromodomains are evolutionarily 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.

Contents

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1. 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, 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 (Fig. 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 (Fig. 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.

2. 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 Zeng and co-workers [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_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].

2.1. 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 that single chemical modifications ("letters") of the epigenetic code [15].

2.2. 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-contaning 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.

3. 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

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