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Research update

Bromodomains: Structure, function and pharmacology of inhibition

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ABSTRACT

Bromodomains are epigenetic readers of histone acetylation involved in chromatin remodeling and transcriptional regulation. The human proteome comprises 46 bromodomain-containing proteins with a total of 61 bromodomains, which, despite highly conserved structural features, recognize a wide array of natural peptide ligands. Over the past five years, bromodomains have attracted great interest as promising new epigenetic targets for diverse human diseases, including inflammation, cancer, and cardiovascular disease. The demonstration in 2010 that two small molecule compounds, JQ1 and I-BET762, potently inhibit proteins of the bromodomain and extra-terminal (BET) family with translational potential for cancer and inflammatory disease sparked intense efforts in academia and pharmaceutical industry to develop novel bromodomain antagonists for therapeutic applications. Several BET inhibitors are already in clinical trials for hematological malignancies, solid tumors and cardiovascular disease. Currently, the field faces the challenge of single-target selectivity, especially within the BET family, and of overcoming problems related to the development of drug resistance. At the same time, new trends in bromodomain inhibitor research are emerging, including an increased interest in non-BET bromodomains and a focus on drug synergy with established antitumor agents to improve chemotherapeutic efficacy. This review presents an updated view of the structure and function of bromodomains, traces the development of bromodomain inhibitors and their potential therapeutic applications, and surveys the current challenges and future directions of this vibrant new field in drug discovery.

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1. Introduction

1.1. Chromatin structure and post-translational modifications

The fundamental unit of eukaryotic chromatin organization is the nucleosome: ~146 base pairs of DNA wrapped around a histone octamer formed by an $(H3\text{-}H4)_2$ tetramer and by two H2A-H2B dimers [1]. Depending on the cell's needs for gene expression, chromatin can either assume a compact conformation (heterochromatin), in which gene expression is silenced, or a more open structure (euchromatin), in which the DNA is accessible to the transcriptional machinery [2]. The regulation of these two states depends on several phenomena collectively referred to as "epigenetic", a term originally coined to refer to heritable changes in gene activity that occur without changes in the underlying nucleotide sequence [3] but now commonly used to designate DNA-related regulatory mechanisms not involving alterations to the DNA sequence, regardless of whether the effects are heritable or not. Epigenetic phenomena include methylation of the genome, the expression of histone variants, and the action of histone modifying enzymes, chromatin remodeling factors, and non-coding RNA molecules [4].

An important epigenetic determinant of chromatin structure and function is the presence of post-translational modifications (PTMs) on histones. Histone PTMs were first reported over 50 years ago with the discovery of histone acetylation and methylation [5]. Since then, the list of histone PTMs has grown remarkably, and now includes: the acetylation, methylation, ubiquitination, SUMOylation, butyrylation, propionylation and crotonylation of lysine residues; the methylation, ribosylation and citrullination of arginine residues; and the phosphorylation and glycosylation of serine and threonine residues [4]. PTMs may occur within the folded histone domains or on the N- and C-terminal histone tails that extend beyond the nucleosome core [6,7]. These modifications

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regulate chromatin structure and function by directly modulating the affinity of DNA for histones, by altering histone-histone interactions, and by affecting the ability of histones to bind chaperones. In addition, PTMs act as docking sites for proteins that specifically recognize these modifications and which in turn recruit or stabilize factors involved in chromatin-templated processes such as nucleosome remodeling, gene transcription and DNA recombination, repair, and replication [4]. The dynamic combinatorial application of histone PTMs to epigenomic regulation is commonly, and sometimes controversially [8], called "the histone code" [9,10].

1.2. Epigenetic writers, erasers, and readers

The histone code is established, modulated, and interpreted by epigenetic "writer" enzymes that catalyze the addition of PTMs, by "eraser" enzymes that catalyze PTM removal and by epigenetic "reader" domains that mediate PTM recognition. Writers include histone acetyltransferases (HATs) and histone methyltransferases (HMTs), whose effects are reversed by the corresponding erasers, namely, histone deacetylases (HDACs) and histone lysine or arginine demethylases (KDMs or RDMs), respectively. Readers display affinity for a specific PTM, and are often found in key epigenetic regulators in combination with writers, erasers and other types of reader domains, to form large multi-protein complexes [2,11]. The specificity of a reader for its cognate PTM derives from a direct interaction between the modified histone residue and the reader's ligand binding pocket, as well as by secondary contacts involving the flanking histone sequence [2]. Writers and erasers of acetylation and methylation, the two most abundant histone PTMs, have been intensively studied and targeted in drug discovery efforts for their roles in cancer, inflammation and various other diseases [12,13].

Epigenetic proteins can contribute to disease in two ways. Mutations altering the activity or expression level of an epigenetic protein may directly cause or maintain the disease state [13]. In such cases, epigenetic proteins may be good candidates for direct drug targeting. Alternatively, epigenetic proteins may mediate altered gene expression which is driven by upstream signals. In this scenario, when the main drivers of the disease are not druggable (*e.g.*, oncogenic transcription factors), epigenetic proteins may be ideal targets to affect the disease indirectly. So far, four drugs specifically targeting epigenetic modifiers have been approved for clinical use: the DNA methylase inhibitors azacitidine and

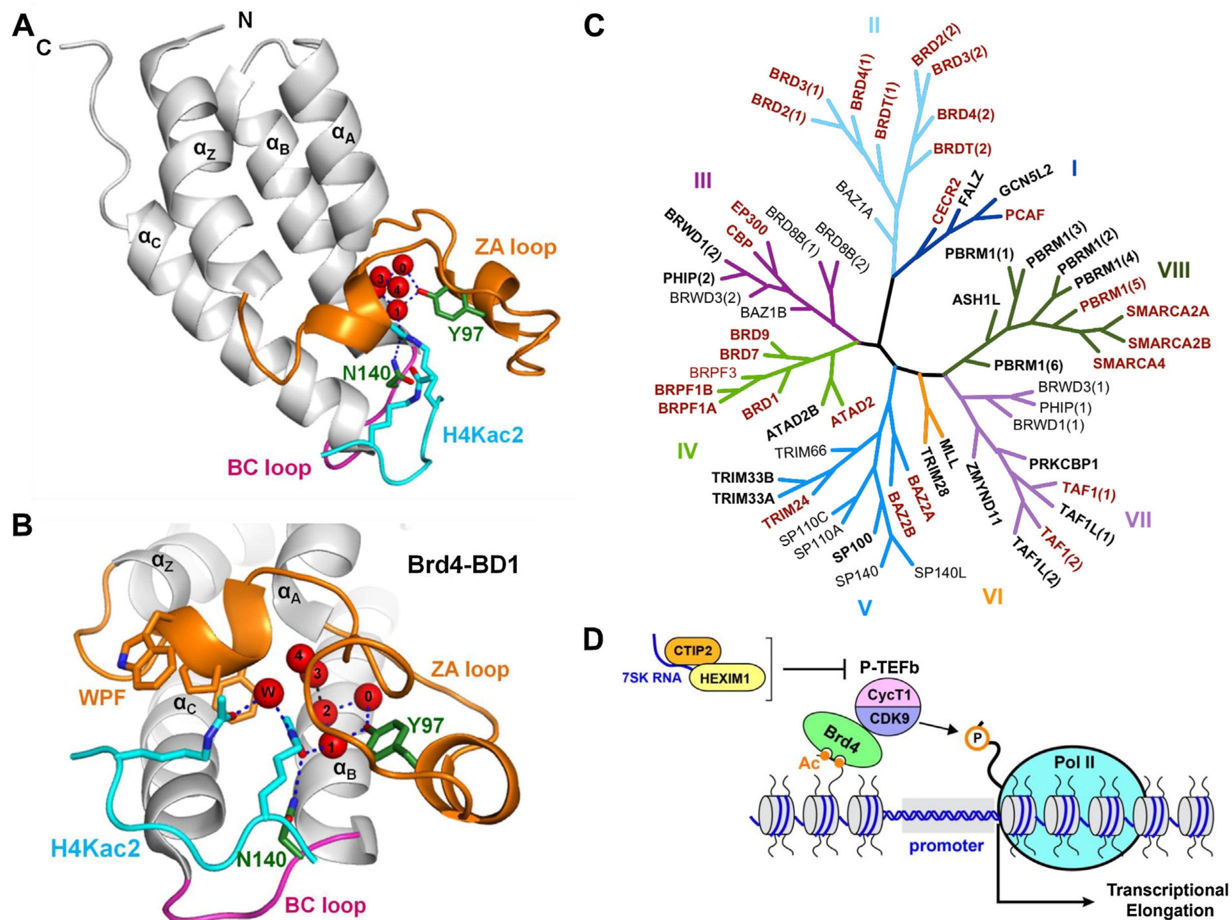

Fig. 1. Structure and function of bromodomains (BRDs). (A, B) Structure of BRD4(1) bound to a diacetylated histone peptide ligand (H4K12acK16ac) showing the overall fold (A) and details of ligand recognition (B) (PDB: 3UVX). Shown are the four helices that define the BRD fold (grey), the binding pocket formed by the ZA (orange) and BC (magenta) loops, and the peptide ligand (cyan). One acetylated lysine (Kac) forms a hydrogen bond with Asn residue N140 (green) and a water-mediated hydrogen bond with Tyr residue Y97 (green), as indicated. These interactions and the network of water molecules (red spheres, numbered as in [27]) are conserved across most human BRDs. The second Kac forms a water-mediated hydrogen bond with the first Kac and interacts with the hydrophobic "WPF" shelf (orange sticks) in the ZA loop. (C) Phylogenetic tree of all 61 human BRDs, adapted from [124]. The eight families are shown in different colors and numbered with roman numerals. BRDs for which an atomic structure is available are shown in bold. BRDs for which a (selective or non-selective) inhibitor has been described are shown in red. (D) Transcriptional activator function of BRD4. BRD4 binds acetylated nucleosomes through its BRDs and recruits P-TEFb to transcription start sites. Phosphorlyation by P-TEFb of the Pol II C-terminal domain and of additional regulatory factors releases paused Pol II complexes and allows transcriptional elongation. The interaction of P-TEFb with BRD4 prevents P-TEFb from being inactivated via sequestration by the 7SK/HEXIM1 complex.

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