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Bromodomain as New Targets in Drug Discovery

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Editorial

Epigenetics is the study of reversible forms of gene regulation characterized by changes in the pattern of post-translational modifications and responsible to develop new phenotypes that are encoded in the DNA sequence [1]. The main modifications in genetic material include DNA methylation, histone methylation and acetylation, ubiquitination and phosphorylation [2]. In the last years, many researches have demonstrated that inhibition of epigenetic modifications is considered valuable targets to drug development for several diseases such as cancer, neurodegenerative and neurological disorders, cardiovascular diseases and metabolic disorders [3].

Lysine acetylation is an important post-translational modifications involved in the control of gene transcription. Aberrant acetylation of lysine residues has been associated in post-translational increases of gene expression leading to several diseases [4]. Acetylation on histones are regulated by two main enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs); however, lysine acetylation is not limited to histones and can be found in several transcription-associated proteins (i.e. chromatin regulators) [5]. Bromodomains are proteins that recognize ε-*N*-acetylation of lysine residues and contribute to regulate the transcriptional mechanisms. It was identified from human proteome, sixty-one different bromodomains from forty-six proteins, grouped into eight families [6].

Triazolothienodiazepines was one of the first potent small molecules able to inhibit bromodomain that demonstrated anti-inflammatory and antitumoral activities [7]. After this chemotype, efforts are being made in order to find out potent and selective bromodomain and extra terminal domain (BET) inhibitors. Bromodomain inhibitors are categorized in two chemical classes (acetylated and non-acetylated lysine mimetics) based on the presence or absence of subunits that act as acetylated lysine mimetics [8].

(+)-JQ1 is a triazolothienodiazepine (acetylated lysine mimetic) that demonstrated potent and selective activity against BET bromodomains after evaluation against a panel of 46 human bromodomains. Interestingly, (+)-JQ1 has shown ability to act through competitive binding to BRD4 [9]. The role of BRD4 in recurrent t(15;19) chromosomal translocation in an aggressive form of human squamous carcinoma is widely known. In NUT midline carcinoma, a chimera of BRD4 and NUT (nuclear protein in testis) maintains the cell proliferation; therefore, the inhibition of BRD4 emerges as an important mechanism able to control the tumor growth [9,10]. BRD4 inhibition is also a useful target for acute myeloid leukemia, ovarian carcinoma, atherosclerosis progression, chronic obstructive pulmonary disease and several inflammatory conditions [11,12].

The bromodomain inhibitor I-BET752 (acetylated lysine mimetic) was discovered based on phenotypic screening strategy that aims to find out new anti-atherosclerotic compounds able to up-regulate apolipoprotein A1 (ApoA1). Surprisingly, I-BET752 was able to inhibit bromodomains BRD2, BRD3 and BRD4. For BRD4, for example, it was characterized Kd values of 55 nM using isothermal titration calorimetry [13].

For the time being, it is still unknown the impact of selectivity over the first and second BET bromodomain family. Despite that, selective BRD4 inhibitors have been reported in the literature. Researchers have described thienopyridinone, furopyridine and tetrahydroquinoline compounds 10-fold more selective for BRD4(1) than BRD4(2) [14]. On the other hand, compounds such as RVX-208 was 40-fold selective for BRD4(2) than BRD4(1) [15]. Kinase inhibitors (i.e. dinaciclib, LY294002, BI2536, TG101209 and TG101348) were described as binder of the KAc-pocket of bromodomains. For BI2536, described as a serine/threonine-protein kinase PLK1, it was found Kd value of 37 nM for BRD4(1) [16]. Based on these finds, it has been proposed that dual kinase-bromodomain inhibitors could be explored in cancer therapy in near future.

Nowadays, clinical trials are evaluating the efficacy of bromodomain inhibitors for several diseases in humans. The bromodomain inhibitor RVX-208, for example, was investigated to treat atherosclerosis and coronary artery diseases. Despite the compound failed to meet its primary endpoint, it was observed regression of coronary atherosclerosis that is amplified by synergic treatment with rosuvastatin [17]. Other study using RVX-208 showed a significant reduction of major adverse cardiovascular events in patients with diabetes mellitus (superior to 65% compared to placebo). Furthermore, RVX-208 was able to reduce blood glucose levels after 12 weeks of treatment [18]. Phase 1 clinical trials to evaluate the effect of OTX015 in haematological malignancies (Clinical Trials.- gov identifier: NCT01713582), recurrent glioblastoma multiform (Clinical Trials.- gov identifier: NCT02296476) and advanced solid tumor (Clinical Trials.- gov identifier: NCT02259114) are currently recruiting. Clinical trials for compound CPI-0610 is also recruiting patients to evaluate its efficacy against progressive lymphoma (Clinical Trials.- gov identifier: NCT01949883), multiple myeloma (Clinical Trials.- gov identifier: NCT02157636) and acute leukemia (Clinical Trials.- gov identifier: NCT02158858).

In summary, this editorial highlights the use of bromodomain inhibitors as perspective to treat several diseases (i.e. cancer, inflammation, cardiovascular diseases) in the future pharmacotherapy.

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