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Invited Review

Targeting bromodomain and extraterminal proteins in breast cancer

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ABSTRACT

Breast cancer is a collection of distinct tumor subtypes that are driven by unique gene expression profiles. These transcriptomes are controlled by various epigenetic marks that dictate which genes are expressed and suppressed. During carcinogenesis, extensive restructuring of the epigenome occurs, including aberrant acetylation, alteration of methylation patterns, and accumulation of epigenetic readers at oncogenes. As epigenetic alterations are reversible, epigenome-modulating drugs could provide a mechanism to silence numerous oncogenes simultaneously. Here, we review the impact of inhibitors of the Bromodomain and Extraterminal (BET) family of epigenetic readers in breast cancer. These agents, including the prototypical BET inhibitor JQ1, have been shown to suppress a variety of oncogenic pathways while inducing minimal, if any, toxicity in models of several subtypes of breast cancer. BET inhibitors also synergize with multiple approved anti-cancer drugs, providing a greater response in breast cancer cell lines and mouse models than either single agent. The combined findings of the studies discussed here provide an excellent rationale for the continued investigation of the utility of BET inhibitors in breast cancer.

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Abbreviations: BETi, bromodomain and extraterminal protein inhibitor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; EMT, epithelial-to-mesenchymal transition; BRD, bromodomain; HAT, histone acetyltransferase; RNAPII, RNA polymerase II; ERE, estrogen response element; H4K12ac, histone H4 acetylated at lysine 12; SE, super-enhancer; DCIS, ductal carcinoma in situ; siMEM, the siRNA/shRNA mixed effect model; Tam-R, tamoxifen-resistant; PDX, patient-derived xenograft; GSEA, gene set enrichment analysis; HIF, hypoxia-inducible factor; CA9, carbonic anhydrase 9; CSC, cancer stem cell; AML, acute myeloid leukemia; ECM, extracellular matrix; NMC, NUT midline carcinoma; PARPi, PARP inhibitor; HDACi, histone deacetylase inhibitor; CMAP, Connectivity Map database; RTK, receptor tyrosine kinase; LTED, long-term estrogen deprived; Eve-R, everolimus-resistant; Lap-R, lapatinib resistant; PROTAC, proteolysis-targeting chimeras; CDK7i, CDK7 inhibitor; IBC, inflammatory breast cancer.

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1. Introduction

Breast cancer is a heterogeneous disease, and multiple subtyping methods have been developed to group these diverse tumors. The most common and clinically relevant classification system is based on the expression of estrogen receptor (ER) and progesterone receptor (PR) and the amplification status of human epidermal growth factor receptor 2 (HER2). The status of these three receptors governs the first line of treatment for breast cancer patients. For example, patients with tumors expressing ER and/or PR are eligible for endocrine therapy while patients with tumors with HER2 amplification receive HER2-targeted therapies. Triple-negative breast cancer (TNBC) patients lack expression of ER/PR and amplification of HER2. There are currently no FDA-approved targeted therapies available for this disease, and the only treatment option is traditional cytotoxic chemotherapy.

Gene expression profiling led to the subdivision of breast cancers into six intrinsic molecular subtypes: luminal A, luminal B, HER2-enriched, basal-like, claudin-low, and normal-like [1–3]. These subtypes vary in terms of phenotype, response to treatment, and clinical outcome [4–6]. The vast majority of breast cancers fall into the luminal A and B subtypes. These tumors are characterized by expression of ER and/or PR with a low (luminal A) or high (luminal B) Ki67 index. They typically respond to ER-targeting agents including tamoxifen and are associated with good prognosis [7]. HER2-enriched tumors overexpress the *ERBB2* gene and, as a result, can be treated with anti-HER2 agents such as trastuzumab [8]. Most basal-like and claudin-low tumors can be categorized as TNBC, with basal-like tumors accounting for the majority of TNBCs. Basal-like tumors express a basal epithelial gene cluster which includes cytokeratins 5 and 17, laminin, and integrin-β4 [1]. Claudin-low cancers express low levels of the tight junction proteins E-cadherin and claudins 3, 4, and 7; are poorly differentiated; have a large cancer stem cell population; are enriched in epithelial-to-mesenchymal transition (EMT) markers; and express high levels of immune response genes [9,10]. Tumors of both TNBC subtypes respond well to cytotoxic chemotherapies such as doxorubicin and taxanes [7]. However, the incidence of metastatic recurrence for these cancers is high. Once metastasis occurs, the disease progresses quickly, with patients exhibiting a median survival of 13 months [4,5,11,12].

Breast cancers are driven by numerous oncogenic pathways which can be subtype-specific. As such, the various subtypes must be treated with different agents. To target a diverse array of breast tumors and to prevent recurrence, it should also be useful to develop therapies that can target multiple pathways simultaneously and have broad implications for this group of diseases as a whole. Here, we discuss targeting Bromodomain and Extraterminal (BET) proteins, an approach already in clinical trials that has the potential to provide benefits across all subtypes of breast cancer.

2. BET protein structure and function

2.1. BET protein structure

Various posttranslational modifications are added to nucleosomes that impact their association with chromatin and the recruitment of proteins to DNA. One such modification is lysine acetylation, which marks areas of chromatin for active transcription and is recognized by bromodomains (BRDs) in various proteins [13]. The BRD is a conserved 110 amino acid structural motif composed of four α-helices (αZ, αA, αB, and αC) that comprise a left-handed bundle [14]. Two loop regions (ZA and BC) connect the α-helices and form a surface that interacts with acetylated lysines in nucleosomal histones [15]. In humans, there are 61 BRDs found within 42 multi-domain proteins that regulate transcription, including ATP-dependent chromatin remodeling complexes, transcriptional co-activators, histone acetyltransferases (HATs), and BET proteins [16].

The BET protein family consists of four members (BRD2, BRD3, BRD4, and BRDT) that reside in the nucleus and play critical roles in transcription [17]. BET proteins act as epigenetic readers and are characterized by two tandem N-terminal BRD regions followed by an extraterminal domain. The BRD regions recognize and bind acetylated lysines in histone tails (histones H3 and H4) and transcription factors. The extraterminal domain is involved

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