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Commentary

Epigenetic therapy: BBC1115, a novel BET inhibitor with broad antitumor activity

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Epigenetic dysregulation plays a crucial role in the onset and progression of cancer, positioning them as compelling targets for therapeutic intervention. In a recent issue of *Molecular Therapy – Nucleic Acids*, Jeong et al. describe the identification of a novel selective bromodomain and extra-terminal motif (BET) inhibitor, BBC1115, using DNA-encoded library (DEL) screening.[1] The study highlights the successful application of DEL-based small-molecule compound screening coupled with intensive biological characterization to discover new chemotypes with selectivity, efficacy, and safety profiles for targeting proteins involved in epigenetic regulation in human malignancies.

Epigenetic alterations contribute to cancer development by disrupting DNA methylation, histone modifications, and nucleosome positioning.[2] Targeting proteins involved in epigenetic regulation has gained significant attention in cancer drug discovery. Three categories of epigenetic regulators, namely writers, readers, and erasers, play crucial roles in installing, binding to, and removing epigenetic marks.[3,4] Recent efforts have focused on developing targeted strategies, leading to the FDA approval of tazemetostat, an HMT (histone methyltransferase) inhibitor, in 2020.[5] Among the epigenetic readers, BET proteins (BRD2, BRD3, BRD4, and BRDT) have been implicated in various cancers, offering potential targets for BET inhibitors. While BET inhibitors show promise in inhibiting oncogenic functions, adverse effects have been observed in clinical trials.[6,7] DELs combined with high-throughput screening offer a valuable approach for discovering novel inhibitors, including BET inhibitors. Building upon this knowledge, Jeong et al. employed a DEL screening approach to identify novel BET inhibitors (Figure 1).

The application of DEL screening in this study led to the discovery of BBC1115, a selective BET inhibitor that possesses a unique chemical structure. Through extensive biological characterization, it was found that BBC1115 effectively targets BET proteins, with a particular emphasis on BRD4, resulting in the suppression of aberrant cell fate programs. Despite its distinct chemical structure from known BET inhibitors such as OTX-015, BBC1115 demonstrated potent binding to all three BET proteins. *In vitro* studies have shown that BBC1115 effectively inhibits the growth of various cancer cell lines, including acute myeloid leukemia, and colorectal, pancreatic, and ovarian malignancies. In addition, *in vivo* studies confirmed that intravenous administration of BBC1115 efficiently decreases the formation of subcutaneous tumor xenografts while demonstrating low toxicity and favorable pharmacokinetic properties. Notably, BBC1115 exhibited comparable activity with OTX-015 in terms of suppressing MYC, a key oncogenic driver in various cancers. The inhibition of BET proteins by BBC1115 led to the dissociation of BRD4 from chromatin, resulting in the downregulation of BRD4-dependent genes expression. Comprehensive ChIP-seq analysis further unveiled a significant reduction in BRD4 occupancy at enhancer regions enriched with acetylated histones. Furthermore, the loss of BRD4 mediated by BBC1115 led to a preferential downregulation of oncogenic gene expression. Functionally, BBC1115 demonstrated potent anti-leukemogenic effects, including the suppression of leukemia stem cells, decreased surface expression of Kit, and inhibition of proliferation and colony formation in leukemia cells.

The discovery of BBC1115 expands the range of BET inhibitors and highlights the potential of DEL screening in identifying novel chemotypes with targeted therapeutic implications for cancer treatment by modulating the epigenome. BBC1115's efficacy in targeting MYC expression suggests its utility in diverse malignancies. However, further investigations are needed to assess its impact on normal cell function and elucidate its precise mechanism of action and potential synergistic effects when combined with other therapies. While the discovery of BBC1115 as a selective BET inhibitor holds promise, there are limitations and important questions that warrant further investigation. Comprehensive evaluation of its effects on normal cell function is crucial, considering the ubiquitous distribution of epigenetic regulations. In addition, the mechanisms underlying asymmetric changes in gene expression upon BET inhibition and the functional consequences of BBC1115-mediated BRD4 loss require further study. Understanding these mechanisms will enhance our knowledge of BET protein biology and facilitate the development of targeted and efficacious therapies. The identification of BBC1115 as a selective BET inhibitor with broad antitumor activity holds great promise for the development of targeted therapies in various cancers. It underscores the importance of exploring diverse chemotypes that modulate epigenetic regulators and suggests that additional DEL screening efforts may uncover novel inhibitors with unique properties. Further exploration of BBC1115 and its derivatives may provide valuable insights into optimizing the therapeutic potential of BET inhibitors for patients with epigenetically driven malignancies.

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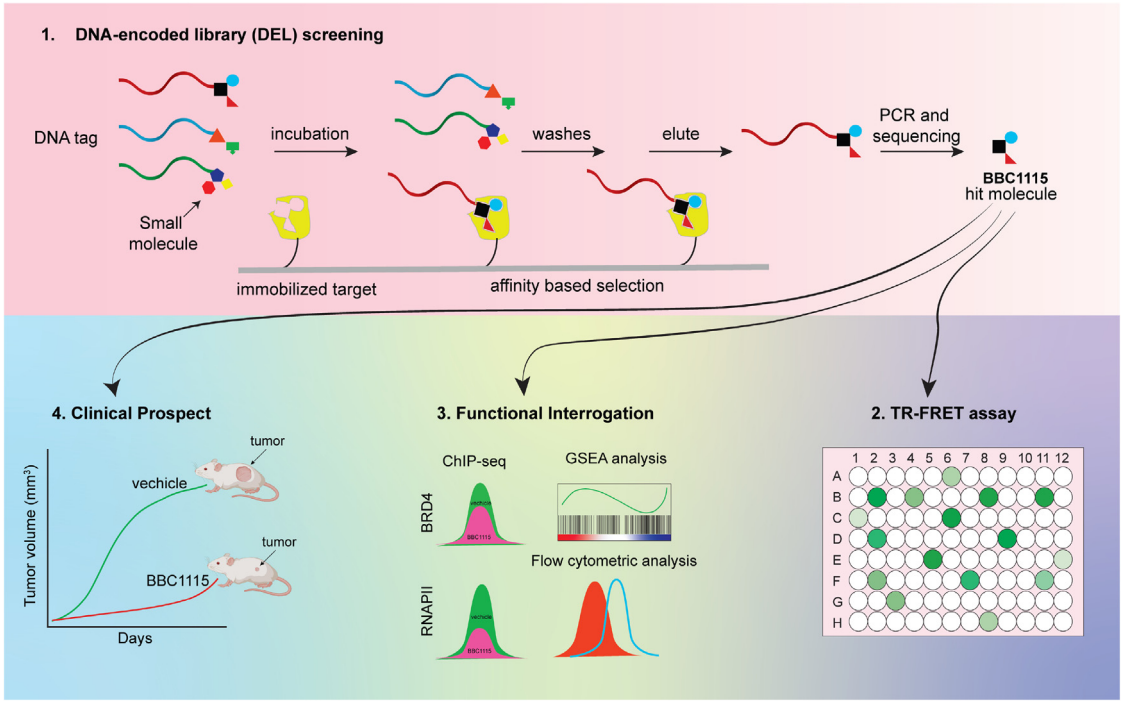

Figure 1. Streamlined identification of novel chemotypes targeting BET proteins through DNA-encoded small-molecule library screening and validation
(1) Schematic representation of the rational design of DEL screening for identifying BET inhibitor compounds. (2) Assessment of BET inhibitor binding affinity using the time-resolved fluorescence resonance energy transfer (TR-FRET) assay. (3) Elucidation of the molecular mechanisms of action of BBC1115, a novel BET inhibitor. (4) Demonstration of the *in vivo* activity and anti-tumorigenic effects of BBC1115.

The innovation of BBC1115 through DEL screening represents a significant advancement in the field of epigenetic cancer therapy. The study expands the landscape of BET inhibitors by identifying a novel chemotype that effectively targets BET proteins and suppresses aberrant cell fate programs. The findings underscore the importance of DEL-based compound screening in identifying new chemical entities with therapeutic potential. BBC1115 exhibits potent anti-leukemogenic effects and broad growth-suppressive activity across multiple cancer cell lines, indicating its potential utility in various malignancies. Future research should focus on optimizing BBC1115 therapeutic potential, elucidating its specific mechanisms of action, investigating its synergistic effects with other therapies, and comprehensively evaluating its safety and efficacy in both pre-clinical and clinical trials. Overall, this study represents an important step in the advancement of epigenetic-based therapies for human cancers.

AUTHOR CONTRIBUTIONS

P.R.C. conceived and wrote this commentary.

DECLARATION OF INTERESTS

The author declares no competing interests.

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