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CURRENT KNOWLEDGE OF BET INHIBITOR AS A TARGET OF BROMODOMAIN IN EPIGENETIC REGULATION- REVIEW ARTICLE

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ABSTRACT

The structure of bromodomain consist of 110 amino acid, acts as a 'reader' for recognizing an acetylated lysine residue on N-terminal of histones tails and acetylated lysine responsible for uncoiling of chromatin structure feature of DNA, shows positive transcriptional elongation and helps in promoting transcriptional and chromatin remodeling. It was found that novel identified molecules has ability to alter effect of prostate cancer mainly in gene encoding process and helps in regulation of chromatin biology in epigenetic regulation. The bromodomain family that is BET inhibitors, disrupt the binding sites of proteins to acetylated histones help in preventing employ of RNA polymerase 2 to enhancers and promoters, especially super-enhancers, to inhibit gene transcription. The Bet inhibitors play essential role in treatment of both cancer and inflammatory disease. We review and update a key role of epigenetic therapy that targets the BET bromodomain, prostate cancer progression, therapy resistance and biomarkers.

KEYWORDS: bromodomain, chromatin, epigenetic, inflammatory disease.

1. INTRODUCTION

A bromodomain readers of acetylation lysine has 110 amino acid domain protein, recognizes acetylated lysine residues on the *N*-terminal of histones. Shows the epigenetic regulation in both normal cell and cancer cell depending of chromatin structure of cell inside the DNA.[2]

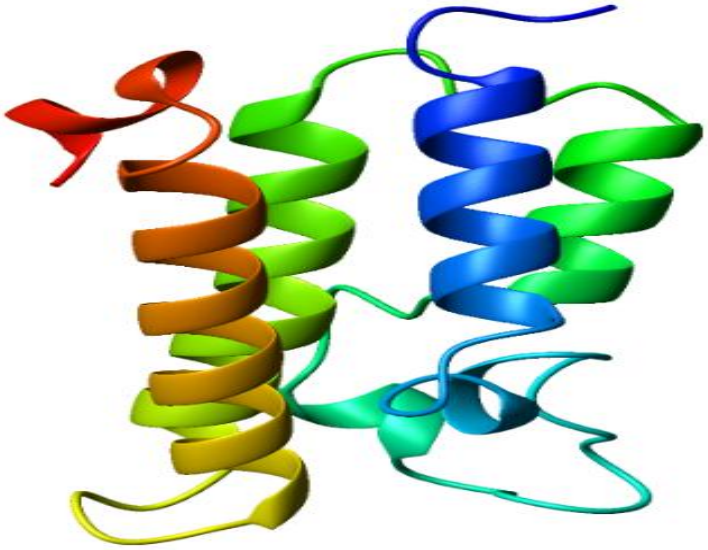

Fig. 1: Ribbon diagram of the GCN5 bromodomain from *Saccharomyces cerevisiae*, colored from blue (N-terminus) to red (C-terminus).[1]

The bromodomain domain has α protein fold, a bundle of four alpha helices, each one is separated by loop of variable length to form a hydrophobic pocket which is recognized by acetylated lysine.[1,3] Bromodomain has BET family that includes BRD1, BRD2, BRD3, BRD4 and BRDT. All bet family of bromodomain recognizes the N-terminal of histones, acetylated lysine residue and help in the epigenetic regulation.[4]

1.1 Bromodomain containing protein

The Bromodomain-containing proteins has many role including a histone acetyltransferase in epigenetic regulation, the chromatin remodeling to maintain stability and has role in various transcriptional mediation and co-activation process.[2] it is found that preparation of protein, determination of biochemical, and knowing the structure feature of the bromodomain containing proteins has mention below.[5]

1.2 Bromodomain-containing proteins in prostate cancer

Bromodomain containing proteins play key role in reading the structure feature of chromatin and help in recognizing the mono-acetylated histones, trigger chromatin remodeling to initiate transcription factor. It is common that mutations and deregulation of bromodomain containing protein in variety of cancers. It was found that in bromodomain containing proteins show 50%- 70% of metastatic in prostate tumors and neuroendocrine prostate cancer in genomic.[6] bromodomain containing proteins has catalytic feature and scaffolding functions and act as transcription factors, transcriptional co-activator factor and help in

various enzymatic function in epigenetic regulation including the methyl transferase, HATs, Helicases, ATP-dependent chromatin remodelers and help in gene expression regulation.[7]

1.3 Role of BRD4 in human disease

Bromodomains help in epigenetic regulation in normal cell and abnormal cell by interacting with acetylated lysine at N- terminal of histone and non-histone, recently several small molecule bromodomain inhibitors are developed. There are many common role of bromodomain containing proteins in cancer biology, inflammation and also in remyelination multiple sclerosis.[2] bromodomain BET family targets in human cancer[8,9] and multiple sclerosis and several other.[10] BET inhibitors shows therapeutic effects in cancer models and in different phase of clinical trials.[11] multiple sclerosis application are present in preclinical stage. Several small molecule inhibitors against bromodomain such as BRD7 and BRD9 was developed and shows good therapeutic effect.[12,13]

1.4 Features of BET family proteins

Many scientist were working on development of small molecules to inhibit bromodomain BET family proteins. The BET family consists BRD2, BRD3 and BRD4, which are expressed and BRDT expression in male germ cell. But the function of bromodomain bet family is not clear. Tandem amino terminal bromodomains localized in cell nucleus, acts as a nuclear localized signal. The BET family of bromodomain get interacts to Kac in histone tails which include H3 and H4. Among all the bet family the most study was on BRD4. The BRD4 binds with Kac of histone through its bromodomains and show positive transcription elongation factor b (P-TEFb), and regulates cyclin T transcription, leading to phosphorylation of the carboxyl-terminal of RNA polymerase II. Therefore BRD4 function as a transcriptional coactivator of several cellular genes.[14]

1.5 BET Bromodomain proteins

Bromodomain keep both normal cell regulation and abnormal phenotypic properties depending upon cell cycle regulation, Epigenetic modifications are reversible change and some time show heritable alterations to the DNA of a cell but does not show change in the nucleotide In epigenetic mechanisms there is changes in CpG island methylation patterns of histone tail and modifications lead to regulation of gene expression and maintain the normal cellular homeostasis but some time due to Dysregulation of macromolecular complexes of

proteins in DNA, arises in inflammatory cells and cancer cells that support the epigenetic regulation of gene expression and their contribution to disease pathogenesis.[15,16]

1.6 BET Bromodomain Inhibitors

Scientist are designing so many novel small molecules for the inhibitor of bromodomain containing protein and some of them show good modulator effect on protein–protein interactions. The inhibition of bromodomain become the challenge today, as the proper mechanism of bromodomain toward the inhibitor action is not clear, synthetic studies suggest that the BET family of bromodomain prone to be effective with (+)-JQ1 and I-BET762 inhibitor the (+)-JQ1 is a triazolothienodiazepine derivative and best BET-selector toward inhibition, the (+)-JQ1 used in lab on biological activities in various cell phase of cell cycle such as G1 arrest and apoptosis mainly in nuclear protein in testis and down-regulates MYC oncogene expression in multiple myeloma cells and it is also reported that (+)-JQ1 inhibitor is used in the treatment of cancers, cardiovascular diseases, human immunodeficiency virus (HIV) infection, and inflammatory diseases.[14]

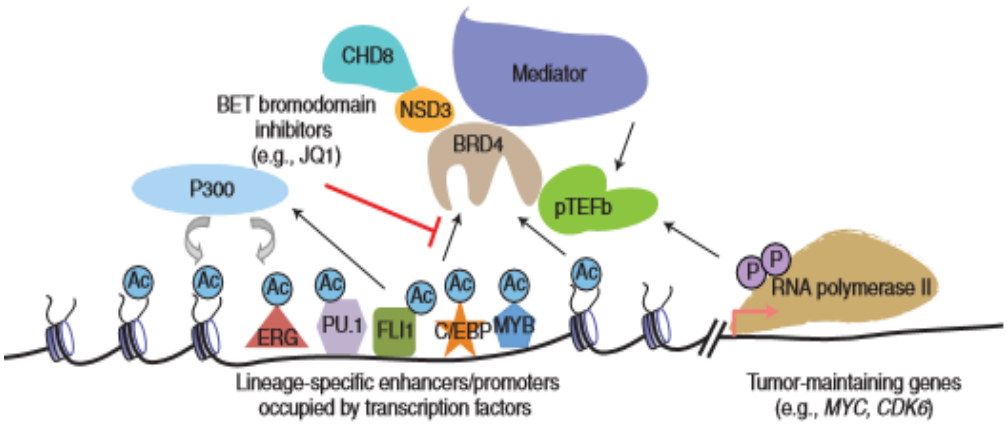

Fig. 1: BET Inhibition in cancer.

1.7 Combination strategies involving targeted inhibitors of BET proteins

The BET inhibitors shows therapeutic effect on a single agent, BET inhibitors shows exhibitory synergistic anti-tumor effect on combined with small molecule inhibitors.[17] Lenalidomide and pomalidomide has shown a potent immunomodulatory effect. The lenalidomide up-regulates with interferon-α, β, and γ expression and on combination with a BRD4 inhibitor show the anti-proliferative effects in cancer cell lines.[18,19,20] the combination therapy of BRD4 inhibitor along with lenalidomide can decrease tumor burden and increases

survival times and also help in the activation of BRD4-dependent MYC show cytotoxic effects.[19]

1.8 Small-Molecule Inhibitors of Bet Bromodomains

BET proteins has significant role in regulation and transcriptional via through acetylated TFs with interaction of histones serve as promoter's enhancers in the genomes study. Bet protein identified biological processes. The small molecule show inhibitors effect of BET bromodomains in *in vivo* study and modulates BET proteins in a myriad of animal models of disease. This study has shown a remarkable gene transcriptional effects of BET inhibitor serves as therapeutic targets.[21]

1.9 Why are cancer genes hypersensitive to bet inhibition?

Molecular function of BRD4 is difficult to understand the chemical inhibition of BET proteins and their role in cancer cells impairment verses non transformed cell types. BET inhibitors suppress 100 of genes in each cell type.[22] BET-dependent genes show variation in cell type to cell type, but mechanism of anticancer effects of BET inhibitors unidentified today, it is suggest that the design and synthesized compounds suppress expression of cancer promoting genes.[23]

2. Mechanisms of resistance to bet inhibition

Both cancer are mono-therapies and have populations of drug resistant cells, clinical trials have shown that BET inhibitors are no exception. It has demonstrated significant area of investigation and Resistance mechanisms to inhibition of the BET bromodomain. Many study has shown that the resistance to BET inhibition is linked with non-genetic mechanisms, global alteration of gene expression that contributes the effects of BET inhibition.[24,25,26,27]

2.1 Polypharmacology

Polypharmacology is the robust therapeutic agent, a single drug agent that modulates targets associated with several diseases. It is suitable for treating diseases with diverse pathogenic pathways such as cancers and inflammatory diseases. It cuts down prices, side effects.[14]

2.2 Dual Kinase/BET Inhibitors

The BET bromodomain acts as an atypical kinase that involves phosphorylates serine in the RNA polymerase II carboxyl-terminal domain, multiple kinase inhibitors engineered for the active bromodomain inhibitory activity against BRD4.[14]

3. CONCLUSION

The BET bromodomain, acts as a 'reader' of acetylated lysine residue at the N-terminal of histones tails and show target based epigenetic therapy and modulate transcriptional, chromatin remodeling. Here it is discussed on current knowledge of BET bromodomain inhibitors. Many BET inhibitors that are in the clinical trial for treatment of several. The poly pharmacology has increases the dual kinase/BET. In this review focus on both mono specific BET inhibitors and multi-target BET inhibitors for many disease such as cancers, inflammatory diseases, immune deficiency diseases, diabetes, and cardiovascular diseases.

4. Conflict of interest: Nil

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