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Review Article

Role of BRD4 in cancer – A review

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ABSTRACT

Bromodomain containing protein (BRD4) play a major role in the gene expression, both in normal cell and cancerous cell through direct interaction with acetylated lysine residue at the N- Terminal of histone tail with the help of transcription factors such as RELA, ER, P53. In healthy body, It promotes cell cycle regulation, cell growth and development and a help in serving as scaffold that control the recruitment of other transcription regulator to chromatin network which can finally modulate the transcription machinery itself but due to dysregulation of BRD4, lead to changes in macro molecular complexes of DNA and supporting gene expression and epigenetic regulation that contribution to pathogenesis of disease.

1. Introduction

Bromodomain 4 (BRD4) is the chromatin reader protein, belong to the family of Bromodomain and Extra Domain (BET). The BET family consist of BRD1, BRD2, BRD3, BRD4 and BRDT among all sub unit of bromodomain, BRD4 are responsible for pathogenesis when it get over expressed in the body. They interact directly on N-terminal of histones tail with acetylated lysine residue and keep the epigenetic regulation and promotes the normal gene expression.[1,2] The BRD4 locates genomic areas to discrete through interactions with acetylated chromatin reader and regulates RNA polymerase-II through elongation and transcription factor directly on the mediator complex.[3,4] BRD4 keep oncogenic gene expression by direct interaction with acetylated transcription factor that includes RELA, ER, P53 and twist.[5,6] normally BRD4 protein is needed to maintain chromatin stability to control the cell cycle, cell division, cell growth and cell proliferation in the healthy body. The *in-vitro* studies shows that heterozygous Brd4+/ mice have serious differentiation of cells and organogenesis abnormalities.[7] Epigenetic regulation promotes the normal gene expression in the body by maintaining the chromatin reader. Epigenetic modifications are reversible changes to DNA that does not include a nucleotide sequence shift a range of epigenetic processes including changes in patterns of CPG island modifications in methylation and histone control gene keeping ordinary cellular homeostasis. Protein dysregulation responsible for communication and alteration of DNA macro molecular complexes and which promotes the notion of gene expression to that of epigenetic regulation and contributes to pathogenesis of disease.[8,9]

2. Functions of bromodomain and extra domain proteins on mammalian, herpesvirus associated with Kaposi sarcoma, INF, interferon, bovine papillomavirus, and human papillomaviruses

2.1. BET Protein (BRD2)

2.1.1. Functions

1. Promotion of cells cycle.[10,11]

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2. Closure of the embryos neural tube of the mouse.[12,13]
3. Maintenance of the neocortex number of GABAergic neurons and mice striatum.[14]
4. Transcription assistance in hyper acetylated Chromatin (histone-chaperone property).[15]
5. HOXA11and D11 transcriptional activation in HEK293 cells[16]
6. Improvement of GATA1 activation in mediated erythroid gene.[17]
7. HV LANA interact with mediated episomal Replication and viral genomic persistence[18,19]

2.2. BET Protein (BRD3)

2.2.1. Functions

1. Transcription assistance in hyper acetylated chromatin (histone chaperone property).[15]
2. Improvement of GATA1 activation mediated the erythroid gene.[17]
3. BRD3 nut fusion protein induced carcinogenesis.[20]

2.3. BET Protein (BRD4)

2.3.1. Functions

1. Transition stimulation of G2/M in HELA cells.[21]
2. Cell cycle continuation in P19 embryonic carcinoma cells.[22]
3. Inner cell mass maintenance in mouse blastocyst.[23]
4. NANOG transcriptional activation required to maintain ES cells pluripotency.[24]
5. Release from a transcription elongation pause.[25,26]
6. Transcription assistance in hyper acetylated chromatin histone chaperone property.[27]
7. Regulation of genes involved in mice's learning and memory transcription.[28]
8. Improvement of gene transcription induced by INF.[29]
9. Cellular signal transducer response for oxidative stress.[30]
10. Post mitotic gene bookmark for cell transcription reactivation.[31,32]
11. Protein BRD4 nut fusion induced carcinogenesis.[20,23]
12. KSHV LANA interact with mediated episomal replication and viral genomic survival.[2,33,34]
13. KSHV LANA interaction mediating episomal replication and viral genomic survival[2,33,35]
14. Genome BPV binding to host mitotic chromosome.[34]
15. E2 transcription control mediate and maintain genome DNA replication.[36–38]

2.4. BET Protein(BRDT)

2.4.1. Functions

1. Transcription of gene regulation during spermatogenesis responsible for meiotic progression.[39]
2. Machinery for splicing in testicular cells[40]
3. Remodeling of chromatin in cells.[41–43]

2.5. BRD-containing cancer proteins

BRD-containing proteins, deregulated in many cancer like breast cancer, colon cancer and stimulate and suppress malignant phenotypes expression.[44]

2.6. Effects of BRD4 cancer dysregulation

Bromodomain has BET protein family that was originally identified and play significant role in epigenetic regulation, BET proteins are frequently deregulated in cancer and lead to aberrant chromatin remodeling and tumorigenesis-mediated gene transcription.[45,46] A number of human cancers have reported where BRD4 over expression is one of the reason for genes mutations.[47] BRD4 promotes the production of cell line metastasis *in-vitro* cell cycling, invasion, and cancer.[48]

2.7. Regulating of the cell cycle in cancer and non-cancer

BRD4 containing protein has significant role in cell cycle regulation and transcription in both cancer and non-cancer. the expression level of BRD4 indicate the function to control their expression in cell and their multiplication level in mitosis indicate cancer.[49] depletion of BRD4 results in aberrant mitosis with an abnormal occurrence of chromosomes to micronuclei and bridging chromosomes leading to cytokinesis failure and multilobulated nuclei.[50] BRD4 significantly associated with mitotic chromosomes, and mitotic bookmark for early G1 phase in cell cycle qualities like Myc.[51–53]

The transition from G1 phase to M phase in cell cycle rely on both BRD4's chromatin decompaction related HAT activity and its kinase mediated transcription.[54,55] BRD4 with M / G1 phase in genes expression is correlated With the maintenance of high levels of chromatin acetylation during mitosis.[52] the BRD4 brief isoform B, which is devoid of HAT activity, contributes to chromatin structure and chromothrypsis alterations.[56] BRD4 promotes their fast postmitotic transcription by binding to the transcription sites of M / G1 phase in cell cycle during genes expression. BRD4 depletion is therefore related with newly synthesized low production of RNAs of the M / G1 phase in gene expression.[53]

BRD4 offers transcriptional gene memory which is association through mitosis outcomes in rapid gene expression in the preceding cell cycle.[57] Furthermore BRD4 was revealed to control G2 to M phase in cell cycle through its SPA 1 difference protein interaction.[58] SPA1 is generated in lymphocytes in reaction to mitogen activation.[59] Ectopic SPA 1 also blocks the shift in HELA cells from G2 to M phase. BRD4 adjusts SPA 1 which relieves the barrier to the development of the cell cycle.[58]

Deletion of BRD4 in HELA cells arrests G1 phase in cell cycle while ectopic expression of BRD4 paradoxically gets inhibited.[52,53] Alternatively the depletion of BRD4 causes apoptosis.[60] In both the reaction to DNA damage and oxidative stress, BRD4 was reported to result for aberrant stress reactions.[61,62]

2.8. BRD4 differentiation and development in cell

BRD4 has great role in controlling cell cycle and promoting the cell growth, BRD4 is not only a general transcription factor but also about 10% of the gene regulatory components which are associated with both super enhancer and traditional promoters.[63] BRD4 regulates genes expression and identify the status of the cell type as well as the cell cycle.[63–65] For instance, BRD4 has vital role in conservation of human and mouse embryonic stem cell identity.[66] Differentiation reflects the down regulation of embryonic stem cell that relates genes such as OCT4 NANOG and PRDM14 and the up regulation of EMT related genes and Neuro-ectodermal differentiation.[66] BRD4 controls the expression of OCT4 genes silencing of BRD4 by either Short hairpin RNA or BET inhibitor treatment that allows the cells to accumulate in G1 phase of the cell cycle and gain cell morphology differentiation.[67]

BRD4 is also needed for the re-expression of genes during MEF reprogramming to induced pluripotent stem cell.[68] Reprogramming of C / EBP activated somatic B cells into induced pluripotent stem cells often relies on binding BRD4 to the super enhancers of the pluripotential gene that are likely to mediate chromatin remodeling and transcription.[69]

In the absence of BRD4, bone marrow stem cells cannot produce lymphoid stem cells, resulting in a failure to differentiate between B and T cells.[70] mature blood cells are not formed on OP9 culture due to depletion of human BRD4.[71] BRD4 Plays an important role in preserving cell identity whether stem cells or differentiated cells in line with its role in controlling the composition and transcription of chromatin.[72]

SSustained silencing of BRD4 in mice resulted in numerous developmental flaws among these skin hyperplasia, dysplasia and abnormal hair development and the loss of communities of secretory cells lysozyme.[70] Where there is a correlation between chromatin hyper acetylation and BRD4 binding during spermatogenesis to active genes. In conjunction with chromatin condensation and loss of hyperacetylated-histonesBRD4relocatestospermatidacrosomes during spermiogenesis.[73] Latest laboratory trials show that the lack of BRD4 during early thymic growth leads to a significant loss of peripheral T cells.[73]

2.9. Initiation of BRD4 and transcription

Transcription initiation starts with the recruitment of RNA Polymerase II on the pre-initiation complex at the gene promoter region followed by serine 5 RNA polii phosphorylation and RNA poliipromoter interaction stabilization. The pre-initiation complex assembly is commonly affected by ENHS and are regulated by TFS and other regulatory proteins for transcription.[74] RNA-Polymerase II has a transcription mediator which is a big modular organisation complex that translates signals from TFs and ENH and promoters, timing pre-initiation complex formation and initiation of transcription.[75,76]

2.10. Regulation on BRD4 and transcription

BRD4 contains 110 amino acid and recognized as a first protein that control cell cycle which are associated with chromosomes during mitosis to mark genes transcription in cell cycle in G1 phase.[77,78] BRD4 null mice die soon after implantation due to a lack of survival of the mass of the internal cell resulting in ESS.[79] Through selective regulation of lineage specific genes. BRD4 is crucial for determining cell identity later during growth lee and collaborators using two conditional mouse knockout models have shown that adipogenesis and myogenesis require BRD4 expression.[80] The use of human fetal osteoblasts by najafowa et al proved that perturbation of activity impedes the entire cycle of osteoblast differentiation from early engagement to late mineralization and bone formation.[81]

2.11. Roles in gene regulation

BRDs containing proteins have various physiological functions either alone or as part of bigger protein complexes and most notably through transcription modulation that are engaged in gene regulation, first it is known that these proteins are engaged in regulatory chromatin changes that lead to chromatin remodeling and further histone modifications including acetylation and methylation. BRD containing proteins can also regulate transcription by specifically recognizing histones and by acting as scaffolds to control the recruitment of other chromatin transcription regulators, eventually the transcription machinery itself can be modulated.

2.12. Epigenetic regulation in the tumor microenvironment of BRD4 gene expression

Tumors consist of a heterogeneous cell that contains neoplastic tumor cells as well as non-neoplastic cells that produce the tumor microenvironment. The TME (tumor microenvironment) is made up of various kinds of cells including immune cells, fibroblasts inflammatory cells that are derived from the bone marrow and those of endothelial cells which promote the development of tumor blood

vessels and continuous cellular signaling. The tumor cells recruited into the microenvironment within the TME (tumor microenvironment) collectively. The molecular signaling events occurring within the TME function to join the growth of tumors and allow cancer cells to obtain phenotypic characteristics such as improved invasion and migration that are critical to cancer metastasis growth.[50,69]

2.13. Therapeutic strategies for targeting cancer with BET bromodomain proteins

Bromodomain is the family of BET protein which has important role in controlling biological mechanisms include inflammation and inflammatory disease. The dysregulation of BET proteins leads to the progression and metastatic activity in cancer cells.[82] Importantly the maintenance of malignant phenotype in cancer cells in both hematopoietic and solid tumor cells depends on epigenetic deregulation.[83] In addition human phase 1 clinical trials evaluating the safety and effectiveness of novel small molecule. BET inhibitors exhibit minimal and reversible clinical toxicity in patients with human cancer[84] both in-vitro and in-vivo studies. BET inhibitors has reported target inhibition and indicate prospective therapeutic impacts, but phase I clinical trials with BET inhibitors in patients with human cancer have not shown substantial therapeutic benefit.[85]

2.14. Bromodomain-inhibited processes and pathways in cancer

BRD proteins affect the regulation of essential oncogenes in tumor cells, such as Myc. BRD's pharmacological inhibition offers better ways of targeting and manipulating key pathways such as Janus kinase / signal transducer, transcription activator (JAK / STAT) and kappa light. The polypeptide gene enhancer nuclear factor (NF-kB) in B Cells has mechanistic signals inhibitors activity which is activated by BRD4 displacement in regions of super enhancers that are massive clusters of gene expression as compared to the few hundred bases covered by standard enhancer regions the super enhancers regions occupy up to 50 kb that exist in oncogenes and tumor progression related genes.[86,87]

2.15. Importance of BRD4 in cancer

BRD4 containing protein has play significant role in elongation and transcription in both normal cell and cancerous cell. The increases rate of BRD4 expression in normal cell lead to cancerous cell because of its ability to form fusion proteins with other nuclear proteins which suggest that BRD4 has great role in the development of cancer, the NUT carcinoma midline is active human cancer arising from nuclear protein in the gene for testis.[88,89] BRD4 overexpression was found to be associated with poor prognosis in patients with liver cancer. BRD4

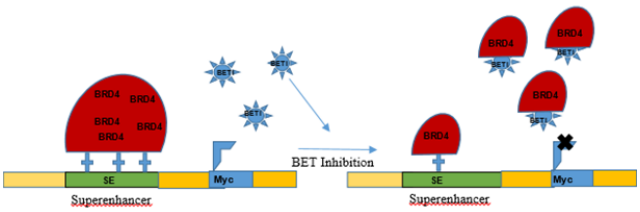

Fig. 1: Extra terminal Bromodomain (BRD) inhibition displaces BRD4 from super enhancers regions. Inhibition of BRDs by small molecules effectively displaces BRD4 from these super enhancer regions compared to normal enhancer regions, thereby allowing oncogenes to be specifically targeted.

over-expression facilitates hepatocellular carcinoma cell growth and invasion[90] among melanoma tissues, BRD4 is significantly higher than melanocytes.[91]

3. Conclusion

Bromodomain (BRD4) consist of 110 amino acid domain protein and belongs to the chromatin reader protein that has BET family which include BRD1, BRD2, BRD3, BRD4 and BRDT. Normally All bet family are present in the body for their specific function but when they over expressed in the body they lead to cause disease pathogenesis but among all the bet family most challenging bromodomain protein is BRD4 which interact with acetylated lysine residue at N-terminal of histone tail in presence of acetyltransferase enzyme for epigenetic regulation such as cell division, cell proliferation, cell growth and maintain cellular mechanism but dysregulation of BRD4 due to mutation leads to the progression and metastatic activity in cancer cells, many inhibitor are designed and synthesized for the inhibition of bromodomain (BRD4) but none of them show good pharmacological activity due to poor selectivity and poor therapy The main reason for improper inhibition of bromodomain is that it doesn't identify the bet family properly during targeting of bromodomain protein therefore it doesn't have clear mechanism of action.

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5. Source of Finding

None

6. Conflict of Interest

None

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