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REVIEW ARTICLE
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THE IMPACT OF EPIGENETICS AND TRANSCRIPTIONAL REGULATIONS IN THE PROGRESSION AND TREATMENT OF BREAST CANCER

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Abstract:
Breast cancer has become the second leading reason behind cancer-related deaths among women across the globe. The extensively reported chemoresistance has resulted in limited treatment options for this disease, emphasizing the urgent need for innovative therapeutic strategies. Epigenetics, a field of biological research,refers to heritable changes in gene expression that occur without alterations to the DNA sequence. This sophisticated phenomenon plays vital role in gene regulation. Breast cancer being a heterogeneous disease, undergoes various adaptive changes over time, leading to more aggressive biological characteristics and resistance to treatment. Epigenetic modifications significantly influence both the initiation and progression of breast cancer.Recent advances in epigenomic profiling have revealed aberrant DNA methylation, histone modification, and non-coding RNA expression patterns associated with tumour development and metastasis. These epigenetic markers not only serve as potential diagnostic and prognostic tools but also offer promising targets for therapeutic intervention. Drugs that reverse such modifications, termed epidrugs, are currently under investigation for their ability to re-sensitize tumors to conventional therapies. Moreover, combining epigenetic therapy with immunotherapy or chemotherapy is showing potential in overcoming resistance mechanisms. Understanding the dynamic nature of epigenetic regulation in breast cancer could pave the way for more personalized and effective treatment approaches in the near future.

Keywords: Breast cancer, chemoresistance, epigenetics.

1. Introduction: Breast cancer is one of the most prevalent cancers among women and is the second leading cause of cancer-related deaths, following lung cancer **(1-2)**. Currently, breast cancer is

classified into molecular subtypes that reflect the tumour's hormonal responsiveness **(3)**. The maintenance of tissue-specific expression and appropriate development relies on epigenetic mechanisms. These mechanisms are uniquely adapted to specific cellular events that occur both during development and throughout an individual's life. Epigenetics provides insight into the variations in phenotypes observed in cells and organisms that share the same genetic makeup. Key examples of epigenetic mechanisms include histone modifications, DNA methylation, and the regulation of noncoding ribonucleic acids (**4-5)**. The interplay between DNA methylation and chromatin structure is crucial, as these elements of the epigenome govern gene expression programming. Understanding the relationship between these processes in cancer development is essential for advancing the therapeutic application of methylation or demethylation inhibitors in cancer treatment (**6)**.

2.Materials and Methods

We used electronic databases, ScienceDirect, PubMed, SpringerLink, Google Scholar and Scopus to perform a comprehensive literature review in order to collect relevant and sufficient records for our review paper.

3.Epigenetic Tuning:Histone Acetylation and Deacetylation Dynamics in Breast Cancer:

Histone modifications such as acetylation, deacetylation, and methylation have been extensively studied in the context of breast cancer. Histone acetylation occurs when an acetyl group from an acetyl-CoA molecule is covalently attached to the amino group of lysine. Conversely, histone deacetylation refers to the removal of acetyl groups from the lysine residues located in the NH_2-terminal tails of core histones **(7)**. Research has demonstrated that various types of breast cancers display different levels of histone acetylation and methylation changes, with specific histone marks correlating to the biological subtype and tumour characteristics **(8)**.Research has examined the impact of unbalanced histone modifications on breast cancer signalling, metastasis, carcinogenesis, and the progression of tumour cells. Additionally, it has been found that genes associated with cell migration, proliferation, apoptotic regulation, intercellular signalling, and metabolic processes are linked to the imbalance of H3K9ac (**9)**. Alterations in histones influence the structure of chromatin, which plays a vital role in both cancer development and gene expression regulation **(10)**. Chromatin, a highly organized entity, consists of repeating nucleosomes connected by linker DNA. Each nucleosome contains approximately 146 base pairs of DNA wrapped around an octamer of histone proteins. These octamers are formed by two subunits each of the core histone proteins H2A, H2B, H3, and H4 **(11)**. Changes in histone modifications have been observed in the promoters of tumour suppressor genes, and a widespread decrease in histone H4K16ac and H4K20me3 is recognized as a characteristic feature of human cancers **(12)**. The balance between histone acetyltransferase (HAT) and histone deacetylase (HDAC) activities is essential for regulating histone acetylation modifications **(13-14)**. The processes of acetylation and deacetylation of histones are essential for regulating gene expression. The enzymes known as histone acetyltransferases (HAT) and histone deacetylases (HDAC) facilitate the acetylation of histones **(15)**. HAT, in particular, is an enzyme that alters the structure of chromatin and plays a vital role in breast cancer by affecting the expression of certain genes, which can lead to tumour development (**16)**. Research has shown that the markers for histone acetylation and methylation vary between normal cells and breast cancer cells, with strong evidence linking histone modifications to tumour prognosis **(17)**. Additionally, there is a relationship between tumour differentiation, tumour cell proliferation, and the expression levels of histone-modifying enzymes such as HDAC2, LSD1, and SIRT1 **(18)**.

3.1 Therapeutic Epigenetic Rewiring: Harnessing HDAC Inhibitors in Breast Cancer Management:

Histone lysine residues experience increased acetylation when the activity of histone deacetylases (HDACs) is suppressed by histone deacetylase inhibitors (HDACi). Clinical studies have explored the use of HDACi as a form of epigenetic therapy in cancer treatment, particularly for

haematological malignancies **(19)**. HDAC inhibitors play a significant role in both the prevention and treatment of breast cancer. They can influence cell mitosis, as evidenced by HDACi CG-1521, which has been shown to disrupt the formation of mitotic spindles and the process of abscission during cytokinesis, leading to apoptosis in cases of inflammatory breast cancer **(20)**.

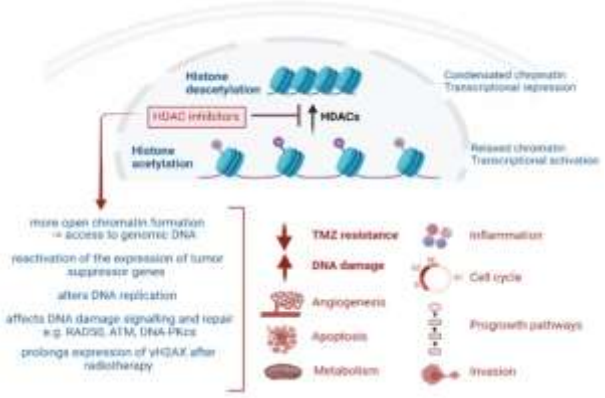


Fig:1 A visual representation that elaborates on the various effects of HDAC inhibitors.

3.1.1DNA Methylation Landscapes: Orchestrating Breast Cancer Initiation and Metastasis:
DNA methylation is the process of reversibly attaching methyl groups to the fifth carbon of cytosine, using S-adenosyl methionine (SAM) as a substrate. This function is performed by DNA methyltransferases (DNMTs), which include DNMT1, DNMT3A, and DNMT3B **(21)**. As an important epigenetic mechanism, DNA methylation significantly influences the initiation, progression, and metastasis of cancer **(22)**. To ensure genomic integrity, this methylation primarily occurs in repetitive genomic sequences present in normal cells, such as satellite DNA and transposable elements, including long interspersed transposable elements (LINEs) and short interspersed transposable elements (SINEs) (**23)**. In eukaryotes, methylation is characterized by epigenetic modifications to DNA that play a vital role in regulating transcription, guiding developmental processes, ensuring genomic imprinting, and maintaining genome integrity **(24)**. This process typically silences genes and noncoding regions of the genome through DNA methylation, which primarily occurs at the 5′ position of the cytosine ring within CpG dinucleotides. The transformation to 5-methyl cytosine is facilitated by the enzyme DNA methyltransferases (DNMTs) **(25)**. Among the three main DNMTs, DNMT1 is responsible for maintaining existing methylation patterns following DNA replication. In contrast, DNMT3A and DNMT3B are de novo enzymes that initiate methylation at unmethylated CpGs; they are expressed at low levels in adult tissues but are highly active during embryonic development **(26)**. By obstructing the binding of certain transcription factors, DNA methylation can effectively reduce gene expression. Furthermore, it can also suppress gene expression indirectly by attracting methyl-CpG-binding domain (MBD) proteins. These MBD proteins then recruit complexes to the methylated regions that modify histones and remodel the chromatin **(27)**. Studies have demonstrated a causal link between the structure of chromatin and DNA methylation. It is generally accepted that methylated DNA is a target for proteins like MeCP2, which binds to methylated sites. MeCP2 promotes an inactive chromatin configuration by recruiting co-repressor complexes, histone deacetylases, and histone methyltransferases to the affected genes (**28-30)**. Over the last decade, there has been a growing interest in the silencing of tumour suppressor genes and localized DNA hypermethylation in cancer. A wealth of data has led to the compilation of genes that exhibit hypermethylation in cancer, and recent whole genome studies have identified specific methylation patterns in breast cancer cells (**31-33**).

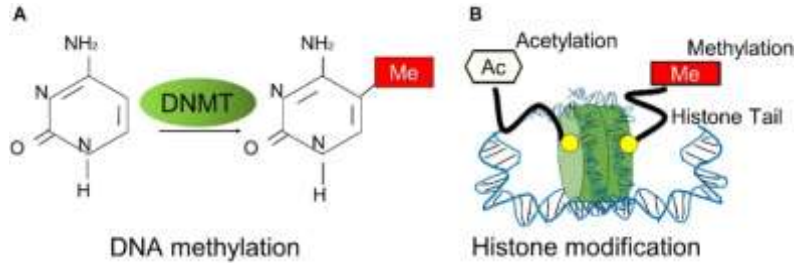


Fig:2 An overview of the epigenetic changes linked to breast cancer. **(A)** The DNA methylation process schematic. DNA methylation is mediated by DNA methyltransferases (DNMTs). **(B)** The schematic representation of histone modifications mostly occurred in breast cancer progression, such as histone methylation and histone acetylation**.**

*3.2*Transcriptional Master Regulators: NF-kB and STAT3 in Breast Cancer Pathobiology:

3.2.1 NF-kB Signalling Networks: Driving Breast Cancer Aggression and Therapy Resistance

The transcription factor known as nuclear factor κB (NF-κB) was first discovered in the nuclei of mature B lymphocytes. It is part of a family of transcription factors that includes NF-κB1 (p50/p101), NF-κB2 (p52/p100), RelA (P65), RelB, and c-Rel (**34-37)**. Research using a mouse model has shown that the proliferation of mammary epithelial cells during pregnancy is controlled by a sequential cascade involving at least six components of the NF-κB pathway, such as RANKL, RANK, IKKα, IkBα, p50/p65, and CyclinD1**(38)**. Recent findings suggest that NF-κB could play a role in resistance to endocrine therapy in breast cancer, and the development of inhibitors targeting the NF-κB pathway is still in its nascent stages. Various NF-κB inhibitors have been developed through research, yielding complex outcomes **(39)**. Research on resistance to endocrine therapy indicates that (i) the use of the NF-KB inhibitor parthenolide resulted in a decrease in cell proliferation and a significant reduction in NF-KB-dependent transcription in resistant cell lines when compared to MCF-7 cells **(40)**. (ii) Treatment with the proteasome inhibitor bortezomib or the NF-KB inhibitor parthenopid led to a decline in gene expression regulated by NF-KB and AP-1, while tamoxifen-resistant breast cancer cells showed heightened transcriptional activity of NF-KB and AP-1 **(41)**. Furthermore, a high-risk subgroup of ER-positive primary breast cancer patients, who experience early relapse despite receiving adjuvant tamoxifen treatment, can be identified by the pronounced DNA-binding activity of the p50 subunit of NF-KB **(42)**.

3.2.2 Role of STAT3 in ModulatingBreast Cancer Proliferation, Metastasis and Chemoresistance:

Within the family of signal transducers and transcription factors, known as STATs, lies signal transducer and activator of transcription 3 (STAT3). This protein serves as a critical junction for numerous signalling pathways activated by cytokines, growth factors, and various oncogenes, making it the most frequently associated member of the STAT family with cancer **(43-45)**. It is generally accepted that STAT3 is vital for the progression of numerous cancers, particularly breast cancer **(46)**. As established in earlier studies, the activation of STAT3 signalling occurs when growth factors and cytokines interact with their designated plasma membrane receptors **(47)**. Research involving breast cancer cells treated with surgical effluents (wound fluids obtained from patients' breasts within 24 hours after the main tumour's excision) revealed a significant activation of the STAT3 pathway in these cells **(48)**. STATs are compelling targets for cancer therapies as they are frequently activated across a range of cancers and are influenced by various oncogenic tyrosine kinases. Particularly, with STAT3 being activated in 70% of breast cancer cases, especially in the difficult-to-treat triple-negative tumours, targeting STAT3 could offer a promising new strategy for breast cancer treatment **(49)**. STAT3 acts as a key transcriptional activator in breast cancer, regulating a variety of target oncogenes and influencing critical aspects of the disease, including progression, proliferation, apoptosis, metastasis, and resistance to chemotherapy. Newly identified downstream targets of STAT3 that contribute to chemoresistance include fatty acid beta-oxidation (FAO), carnitine palmitoyl transferase 1B (CPT1B), the MAPK/AKT pathway, HIF-1, and octamer-

binding transcription factor-4. Evidence suggests that the JAK2/STAT3 signalling pathway enhances the levels of CPT1B and FAO, thereby increasing chemoresistance in breast cancer **(50)**.

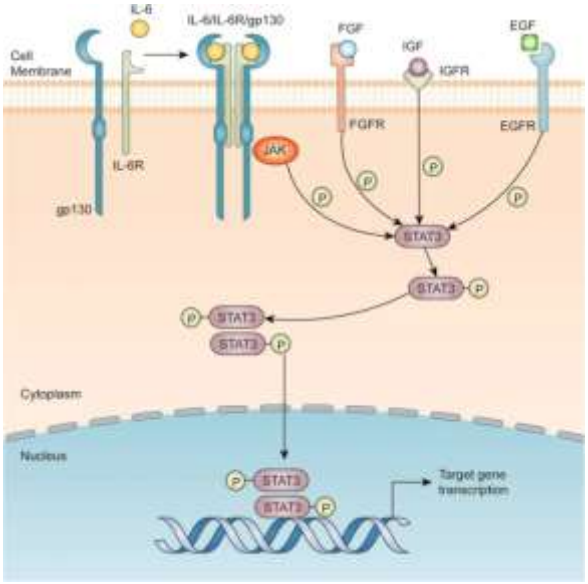


Fig:3 The traditional cancer cell IL-6/STAT3 signalling pathway.

Both IL-6 receptor α (IL-6R) and IL-6 receptor β (gp130), which are membrane-bound, are bound by IL-6. JAK phosphorylation is triggered by the IL-6/IL-6R/gp130 complex, which is followed by STAT3 phosphorylation and activation. Through their interaction to their corresponding membrane receptors, growth hormones including FGF, IGF, and EGF can also phosphorylate STAT3. After that, phosphorylated STAT3 assembles into a homodimer and moves into the nucleus to attach to the target gene's promotor region and initiate transcription of the target gene.

4. Conclusion:

Research into the epigenetic factors associated with breast cancer has revealed that these alterations can play a crucial role in the onset, development, and response to treatment of the disease. Researchers are currently exploring specific epigenetic modifications as potential therapeutic approaches, with the goal of improving the efficacy of existing treatments or offering new alternatives for patients dealing with resistant types of breast cancer. This emphasis on epigenetic therapy signifies a promising advancement in the continuous battle against breast cancer.The dynamics of chromatin and the regulation of transcription are profoundly influenced by histone modifications, particularly through processes such as acetylation and methylation. These modifications play a crucial role in the evolution of tumours and their response to therapies. Histone deacetylase inhibitors (HDACi) have emerged as groundbreaking therapeutic options, effectively reshaping abnormal epigenetic environments to restore normal gene expression and enhance the effectiveness and accuracy of cancer treatments.Moreover, transcription factors like NF-κB and STAT3 are significant contributors to the progression of breast cancer, influencing tumour cell growth, metastatic behavior, and resistance to therapies. By targeting these factors, it may be possible to enhance treatment efficacy, particularly in aggressive and resistant breast cancer subtypes.

As we explore this synergy further, it’s essential to understand how these innovative therapies can complement existing approaches. By integrating epigenetic strategies with conventional methods, we can potentially overcome challenges related to drug resistance and enhance the overall effectiveness of treatments for patients.

5. Future perspectives

Integrating epigenetic profiling with transcriptional regulation mapping will enable precision diagnosis and tailored therapies for breast cancer. Advances in next-generation sequencing, single-cell analysis, and CRISPR-based epigenome editing offer promising avenues to reprogram oncogenic networks and overcome therapy resistance. Combining selective epigenetic modulators with targeted or immune-based treatments, supported by robust clinical validation, may transform breast cancer into a more manageable and potentially curable disease.

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