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Epigenetic Reprogramming in Triple-Negative Breast Cancer: Molecular Mechanisms Driving Metastasis and Therapeutic Resistance

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Abstract

Triple-negative breast cancer (TNBC) represents one of the most aggressive and therapeutically challenging subtypes of breast malignancy, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. Owing to its profound molecular heterogeneity, high metastatic potential, and limited targeted therapeutic options, TNBC is associated with poor clinical prognosis and elevated recurrence rates. Increasing evidence indicates that epigenetic reprogramming constitutes a fundamental driver of TNBC initiation, progression, metastatic dissemination, immune evasion, and therapeutic resistance. Aberrant DNA methylation, histone modifications, chromatin remodeling dysfunction, enhancer rewiring, and non-coding RNA dysregulation collectively reshape transcriptional landscapes that promote epithelial-to-mesenchymal transition, cancer stemness, metabolic plasticity, and tumor microenvironment remodeling. Advances in next-generation sequencing, single-cell multi-omics, and epigenomic profiling have substantially improved the understanding of dynamic epigenetic heterogeneity within TNBC tumors. Importantly, the reversible nature of epigenetic alterations has generated considerable interest in epigenetic-targeted therapies, including histone deacetylase inhibitors, bromodomain inhibitors, DNA methyltransferase inhibitors, chromatin remodeling modulators, and immunoepigenetic strategies. Emerging precision oncology approaches integrating epigenomic biomarkers and artificial intelligence-assisted molecular profiling are further transforming therapeutic stratification in TNBC. This review discusses the molecular mechanisms underlying epigenetic reprogramming in TNBC, emphasizing metastasis, therapeutic resistance, tumor microenvironment interactions, and emerging translational opportunities for precision medicine.

1. Introduction

Chromatin Breast cancer remains the most frequently diagnosed malignancy among women worldwide and constitutes a major global public health challenge [1]. Among its molecular subtypes, triple-negative breast cancer (TNBC) is

distinguished by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 amplification, accounting for approximately 15–20% of all breast cancer cases [2]. TNBC is clinically characterized by aggressive biological behavior, early metastatic dissemination, elevated recurrence rates, and poor overall survival outcomes compared with hormone receptor-positive breast cancers [3]. Due to the lack of established receptor-based therapeutic targets, conventional chemotherapy remains the principal systemic treatment modality for TNBC patients, although therapeutic resistance frequently emerges during disease progression [4].

The remarkable molecular heterogeneity of TNBC represents one of the greatest challenges in clinical management. Transcriptomic and genomic analyses have revealed extensive diversity in signaling pathways, metabolic phenotypes, immune infiltration patterns, and differentiation states among TNBC tumors [5]. This heterogeneity contributes substantially to treatment failure, metastatic adaptation, and disease recurrence. Recent advances in molecular oncology increasingly indicate that epigenetic reprogramming plays a central role in orchestrating these complex biological processes [6].

Epigenetic regulation refers to heritable and reversible alterations in gene expression that occur independently of changes in DNA sequence [7]. Major epigenetic mechanisms include DNA methylation, histone modifications, chromatin remodeling, enhancer regulation, and non-coding RNA-mediated transcriptional control [8]. These regulatory systems collectively govern chromatin accessibility, transcriptional plasticity, cellular differentiation, and genome stability. In cancer, dysregulation of epigenetic machinery promotes oncogenic transcriptional programs, tumor evolution, immune evasion, and therapeutic resistance [9]. DNA methylation abnormalities represent among the earliest epigenetic events identified in breast carcinogenesis. Global DNA hypomethylation accompanied by promoter-specific hypermethylation contributes to genomic instability and silencing of tumor suppressor genes in TNBC [10]. Hypermethylation-mediated repression of genes involved in DNA repair, apoptosis, and immune signaling facilitates aggressive tumor progression and metastatic behavior [11]. Furthermore, epigenetic silencing of BRCA1 and homologous recombination-associated genes has been implicated in genomic instability and chemotherapeutic sensitivity within subsets of TNBC tumors [12].

Histone modifications also exert profound influence over TNBC biology. Histone acetylation and methylation regulate chromatin accessibility and transcriptional activation of genes involved in proliferation, epithelial-to-mesenchymal transition (EMT), stemness, and immune modulation [13]. Dysregulated activity of histone deacetylases (HDACs), enhancer of zeste homolog 2 (EZH2), and bromodomain-containing proteins has been associated with aggressive tumor phenotypes and poor prognosis [14]. Elevated EZH2 expression in TNBC promotes transcriptional repression of differentiation-associated genes and enhances metastatic potential through chromatin condensation and epigenetic silencing [15].

Chromatin remodeling complexes further contribute to TNBC progression through dynamic regulation of enhancer landscapes and transcriptional programs [16]. Alterations involving SWI/SNF chromatin remodeling subunits, chromatin accessibility networks, and super-enhancer organization facilitate lineage plasticity, metastatic dissemination, and adaptive therapeutic resistance [17]. Emerging studies suggest that enhancer rewiring enables TNBC cells to rapidly transition between epithelial, mesenchymal, and stem-like states during disease progression [18]. Non-coding RNAs, including microRNAs and long non-coding RNAs (lncRNAs), additionally regulate multiple oncogenic signaling pathways in TNBC [19]. Dysregulated expression of epigenetically controlled non-coding RNAs influences EMT, cancer stemness, metabolic adaptation, and immune escape mechanisms [20]. These regulatory networks further contribute to the remarkable transcriptional plasticity characteristic of TNBC tumors.

Metastasis remains the leading cause of TNBC-associated mortality. Epigenetic reprogramming profoundly influences metastatic cascades through modulation of EMT, extracellular matrix remodeling, angiogenesis, immune suppression, and circulating tumor cell survival [21]. Metastatic TNBC cells frequently acquire stem-like and mesenchymal phenotypes associated with enhanced therapeutic resistance and immune evasion [22]. Importantly, these phenotypic transitions are largely regulated through reversible epigenetic alterations rather than fixed genetic mutations. The tumor microenvironment (TME) also plays a crucial role in TNBC progression and therapeutic response. Cancer-associated fibroblasts, immune cells, endothelial cells, and extracellular matrix components collectively establish dynamic signaling interactions that influence tumor growth and

metastasis [23]. Epigenetic mechanisms critically regulate cytokine secretion, immune checkpoint expression, inflammatory signaling, and stromal remodeling within the TME [24]. Recent evidence further demonstrates that epigenetic dysregulation contributes substantially to immune exclusion and resistance to immunotherapeutic interventions.

Advances in next-generation sequencing, single-cell transcriptomics, spatial epigenomics, and multi-omics technologies have dramatically improved understanding of TNBC heterogeneity and evolution [25]. These technologies reveal remarkable intratumoral diversity involving chromatin accessibility states, enhancer landscapes, transcriptional programs, and immune microenvironment composition [26]. Such findings are facilitating the identification of epigenomic biomarkers and novel therapeutic vulnerabilities suitable for precision oncology approaches. Importantly, unlike irreversible genetic alterations, epigenetic modifications are potentially reversible, making them attractive therapeutic targets [27]. Pharmacological inhibition of HDACs, bromodomain proteins, DNA methyltransferases, and histone methyltransferases has demonstrated promising preclinical and clinical activity in TNBC [28]. Combination strategies integrating epigenetic therapies with chemotherapy, immunotherapy, and targeted molecular interventions are increasingly being explored to overcome therapeutic resistance and improve patient outcomes [29]. Collectively, accumulating evidence indicates that epigenetic reprogramming occupies a central position in TNBC pathogenesis and metastatic progression. Understanding the molecular interplay between chromatin remodeling, transcriptional plasticity, immune modulation, and therapeutic adaptation may therefore provide critical insights for development of innovative precision medicine strategies in TNBC.

2. Methodology

This review was conducted through a comprehensive literature search of peer-reviewed articles indexed in PubMed, Scopus, Web of Science, and Google Scholar databases. Relevant publications published primarily between 2000 and 2026 were identified using combinations of keywords including “triple-negative breast cancer”, “epigenetic reprogramming”, “DNA methylation”, “histone modification”, “chromatin remodeling”, “metastasis”, “tumor microenvironment”, “therapeutic resistance”, “cancer stem cells”, and “precision oncology”. Original research articles, systematic reviews, meta-analyses, and landmark mechanistic studies were prioritized. Particular emphasis was placed on studies investigating epigenetic mechanisms driving metastasis, lineage plasticity, immune modulation, and therapeutic resistance in TNBC. Additional studies focusing on translational applications, emerging epigenetic therapies, multi-omics technologies, and precision medicine strategies were also included. References cited within selected publications were manually screened to ensure scientific relevance and comprehensive coverage of the topic.

3. Epigenetic Dysregulation, Chromatin Plasticity, and Transcriptional Rewiring in Triple-Negative Breast Cancer Progression

The aggressive biological behavior of triple-negative breast cancer is strongly influenced by widespread epigenetic dysregulation that reshapes chromatin organization and transcriptional identity throughout tumor evolution [30]. Unlike luminal breast cancers, which are often driven predominantly by hormone receptor signaling, TNBC exhibits remarkable transcriptional plasticity characterized by dynamic transitions between epithelial, mesenchymal, stem-like, and immune-evasive phenotypes [31]. Increasing evidence suggests that these transitions are orchestrated primarily through epigenetic remodeling rather than fixed genetic alterations alone. DNA methylation abnormalities constitute major contributors to TNBC progression and heterogeneity. Global hypomethylation promotes genomic instability, chromosomal rearrangements, and activation of transposable elements, while promoter-specific hypermethylation silences tumor suppressor genes involved in apoptosis, differentiation, DNA repair, and immune surveillance [32]. Hypermethylation-mediated repression of BRCA1, PTEN, CDH1, and RASSF1A has been repeatedly associated with increased metastatic potential and therapeutic resistance in TNBC [33].

Importantly, DNA methylation dynamics also regulate cancer stem cell populations within TNBC tumors. Cancer stem cells possess enhanced tumor-initiating capacity, self-renewal potential, and resistance to conventional chemotherapy [34]. Epigenetic silencing of differentiation-associated pathways through DNA methyltransferase activity contributes substantially to maintenance of stem-like phenotypes and metastatic adaptation [35]. Experimental inhibition of DNA methyltransferases has demonstrated partial restoration of differentiation-associated transcriptional programs and increased chemosensitivity in preclinical models.

Histone modification imbalance further amplifies transcriptional instability in TNBC. Histone acetylation generally promotes open chromatin architecture and transcriptional activation, whereas histone deacetylation contributes to chromatin condensation and gene repression [36]. Elevated expression of HDAC1, HDAC2, and HDAC6 has been associated with enhanced proliferation, EMT activation, and poor clinical prognosis in TNBC patients [37]. HDAC-mediated suppression of epithelial differentiation genes facilitates acquisition of invasive mesenchymal characteristics required for metastatic dissemination. Histone methylation also exerts substantial influence over TNBC biology. EZH2, the catalytic subunit of Polycomb Repressive Complex 2 (PRC2), is frequently overexpressed in aggressive TNBC tumors [38]. EZH2-mediated trimethylation of histone H3 lysine 27 (H3K27me3) suppresses transcription of tumor suppressor genes and promotes stemness-associated transcriptional programs [39]. Elevated EZH2 activity additionally contributes to immune suppression, angiogenesis, and metastatic progression through widespread enhancer silencing and chromatin compaction.

Chromatin remodeling complexes such as SWI/SNF further regulate enhancer accessibility and transcriptional plasticity in TNBC [40]. Alterations involving ARID1A, BRG1, and other chromatin remodeling components disrupt enhancer landscapes and facilitate adaptive transcriptional responses during therapeutic stress [41]. Emerging evidence suggests that super-enhancer rewiring enables rapid activation of oncogenic pathways involved in EMT, immune evasion, and metastatic adaptation [42]. Enhancer-associated transcription factors including MYC, SOX9, YAP/TAZ, and STAT3 also cooperate with epigenetic regulators to promote aggressive TNBC phenotypes [43]. These transcriptional networks establish highly dynamic chromatin states that permit rapid cellular adaptation to hypoxia, metabolic stress, chemotherapy exposure, and immune surveillance. Such epigenetic flexibility contributes significantly to intratumoral heterogeneity and therapeutic failure.

Non-coding RNAs represent additional critical regulators of epigenetic reprogramming in TNBC. Dysregulated microRNAs including miR-200 family members, miR-21, and miR-10b regulate EMT, stemness, apoptosis resistance, and metastatic dissemination [44]. Long non-coding RNAs such as HOTAIR, MALAT1, and NEAT1 further modulate chromatin remodeling complexes and enhancer organization to sustain oncogenic transcriptional programs [45]. Epigenetic dysregulation establishes a highly plastic transcriptional landscape that enables TNBC cells to adapt dynamically during tumor progression and therapeutic exposure. Understanding these chromatin-based mechanisms is therefore essential for development of effective targeted therapeutic interventions.

4. Epigenetic Control of Metastatic Dissemination, Tumor Microenvironment Remodeling, and Immune Evasion in Triple-Negative Breast Cancer

Metastasis represents the principal cause of mortality among patients with triple-negative breast cancer and remains one of the greatest obstacles to effective clinical management [46]. Metastatic dissemination is not solely a consequence of genetic mutation accumulation but is profoundly regulated through epigenetic reprogramming that enables tumor cells to acquire invasive, stem-like, and immune-resistant phenotypes [47]. Epigenetic alterations dynamically regulate epithelial-to-mesenchymal transition, extracellular matrix remodeling, angiogenesis, immune suppression, and colonization of distant metastatic niches. Epithelial-to-mesenchymal transition constitutes a central mechanism underlying metastatic progression in TNBC. During EMT, epithelial tumor cells lose cell-cell adhesion properties and acquire migratory and invasive mesenchymal characteristics [48]. Epigenetic silencing of E-cadherin through promoter hypermethylation and histone deacetylation is among the earliest molecular events promoting EMT activation [49]. Simultaneously, transcription factors including SNAIL, TWIST, ZEB1, and SLUG recruit chromatin remodeling complexes and histone modifiers to establish mesenchymal transcriptional programs [50].

These EMT-associated epigenetic alterations are highly dynamic and reversible, allowing tumor cells to transition between epithelial and mesenchymal states during metastatic dissemination [51]. Such phenotypic plasticity enhances circulating tumor cell survival, resistance to anoikis, and adaptation within distant metastatic microenvironments. Importantly, mesenchymal TNBC cells frequently display stem-like properties and elevated resistance to chemotherapy and immunotherapy [52]. The tumor microenvironment further amplifies metastatic progression through reciprocal signaling interactions between tumor cells and stromal components [53]. Cancer-associated fibroblasts, endothelial cells, adipocytes, immune cells, and extracellular matrix proteins collectively establish

permissive environments for tumor invasion and immune evasion. Epigenetic mechanisms critically regulate secretion of cytokines, chemokines, growth factors, and matrix remodeling enzymes within the TME [54].

Hypoxia-induced epigenetic reprogramming additionally contributes to metastatic adaptation. Hypoxic regions within TNBC tumors activate HIF-1α signaling, leading to chromatin accessibility changes and activation of angiogenic, glycolytic, and EMT-associated pathways [55]. Histone demethylases and oxygen-sensitive chromatin modifiers further regulate adaptive responses to metabolic stress and oxygen deprivation. These alterations facilitate angiogenesis, invasion, and metastatic colonization. Immune evasion represents another hallmark of metastatic TNBC progression. Although TNBC often exhibits higher tumor mutational burden and immune infiltration compared with other breast cancer subtypes, many tumors eventually develop profound immunosuppressive microenvironments [56]. Epigenetic silencing of antigen presentation machinery, interferon signaling pathways, and immune stimulatory genes contributes substantially to immune escape [57].

PD-L1 expression in TNBC is also strongly influenced by epigenetic regulation. Histone modifications, enhancer accessibility, and inflammatory transcriptional networks collectively regulate immune checkpoint expression and T-cell exhaustion [58]. Recent studies demonstrate that epigenetic therapies may partially restore anti-tumor immune responses through reactivation of endogenous retroviral elements and interferon signaling pathways [59]. Tumor-associated macrophages and myeloid-derived suppressor cells further contribute to immunosuppressive TME remodeling [60]. Epigenetically regulated inflammatory signaling pathways including NF-κB, STAT3, and TGF-β promote secretion of cytokines that suppress cytotoxic T-cell activity and facilitate metastatic progression. Consequently, the metastatic TNBC microenvironment frequently becomes characterized by chronic inflammation coupled with impaired anti-tumor immunity.

Recent single-cell multi-omics studies have revealed extraordinary spatial and transcriptional heterogeneity within metastatic TNBC lesions [61]. Distinct epigenetic states coexist within tumors, allowing rapid adaptive evolution under therapeutic and immune pressures. Such findings underscore the importance of targeting dynamic chromatin plasticity in addition to static genetic mutations.

5. Therapeutic Resistance, Cancer Stemness, and Emerging Epigenetic Precision Oncology Strategies in Triple-Negative Breast Cancer

Therapeutic resistance remains a major determinant of poor clinical outcomes in TNBC patients [62]. Although many tumors initially respond to chemotherapy, residual resistant cell populations frequently survive treatment and eventually drive relapse and metastatic progression. Increasing evidence suggests that epigenetic plasticity plays central roles in acquisition and maintenance of drug-resistant phenotypes. Chemotherapy exposure induces extensive chromatin remodeling and transcriptional adaptation within TNBC cells [63]. Drug-tolerant persister populations frequently exhibit stem-like and mesenchymal phenotypes associated with enhancer rewiring, histone modification imbalance, and altered chromatin accessibility states [64]. These epigenetically reprogrammed cells display reduced apoptotic sensitivity, enhanced DNA repair capacity, metabolic flexibility, and immune resistance.

Cancer stem cells are particularly important mediators of therapeutic failure in TNBC. These populations possess remarkable self-renewal capacity and resistance to cytotoxic stress [65]. Epigenetic regulators including EZH2, HDACs, LSD1, and BET bromodomain proteins sustain stemness-associated transcriptional programs required for tumor regeneration following therapy [66]. Importantly, therapeutic stress itself may induce epigenetic transitions that expand cancer stem cell populations during treatment. PARP inhibitor resistance in BRCA-mutant TNBC additionally involves epigenetic adaptation mechanisms [67]. Restoration of homologous recombination activity, enhancer rewiring, replication fork stabilization, and chromatin accessibility alterations contribute to acquired resistance following prolonged PARP inhibition. Similar epigenetic mechanisms influence resistance to platinum agents, taxanes, and immune checkpoint inhibitors.

The reversibility of epigenetic alterations has stimulated intense interest in epigenetic-targeted therapies for TNBC [68]. HDAC inhibitors have demonstrated anti-proliferative and pro-apoptotic effects through restoration of tumor suppressor gene expression and suppression of EMT-associated transcriptional programs [69]. Combination strategies integrating HDAC inhibitors with chemotherapy or immunotherapy have shown promising synergistic activity in preclinical studies. DNA methyltransferase

inhibitors also possess significant therapeutic potential. Pharmacological inhibition of DNMTs may reactivate silenced immune pathways, tumor suppressor genes, and differentiation-associated transcriptional networks [70]. Such interventions may additionally enhance sensitivity to immune checkpoint blockade through increased antigen presentation and interferon signaling.

Bromodomain and extra-terminal domain (BET) inhibitors represent another emerging therapeutic class in TNBC [71]. BET proteins regulate enhancer-mediated transcription of oncogenic drivers including MYC and inflammatory signaling networks. BET inhibition suppresses metastatic progression, stemness, and immune evasion in experimental TNBC models [72]. EZH2 inhibition has likewise generated substantial clinical interest. Suppression of EZH2-mediated H3K27 trimethylation restores differentiation-associated gene expression and reduces stem-like phenotypes [73]. Importantly, EZH2 inhibition may also enhance anti-tumor immunity and improve responsiveness to immunotherapeutic interventions.

Recent advances in single-cell sequencing and spatial epigenomics are transforming precision oncology approaches in TNBC [74]. Integrative multi-omics analyses now permit characterization of chromatin accessibility states, enhancer landscapes, immune composition, and therapeutic vulnerabilities at unprecedented resolution. Artificial intelligence-assisted biomarker discovery is further improving patient stratification and prediction of therapeutic responses. CRISPR-based epigenome editing technologies additionally offer promising future therapeutic possibilities [75]. Unlike permanent genome editing, epigenome editing enables reversible modulation of chromatin states and transcriptional programs without altering DNA sequences. Such approaches may eventually permit highly precise correction of oncogenic epigenetic alterations within TNBC cells. Despite substantial progress, multiple challenges remain regarding therapeutic specificity, toxicity, tumor heterogeneity, and adaptive resistance mechanisms [76]. Future therapeutic strategies will likely require rational combinatorial approaches integrating epigenetic therapies with immunotherapy, targeted molecular inhibitors, and biomarker-guided patient selection.

6. Conclusion

Triple-negative breast cancer represents one of the most aggressive and therapeutically challenging malignancies, characterized by profound molecular heterogeneity, metastatic plasticity, and resistance to conventional therapies. Increasing evidence demonstrates that epigenetic reprogramming occupies a central mechanistic position in TNBC initiation, progression, immune evasion, and therapeutic adaptation. Aberrant DNA methylation, histone modification imbalance, chromatin remodeling dysfunction, enhancer rewiring, and non-coding RNA dysregulation collectively establish dynamic transcriptional landscapes that drive tumor aggressiveness and metastatic dissemination.

Recent advances in epigenomics, single-cell sequencing, and multi-omics technologies have substantially improved understanding of TNBC heterogeneity and chromatin-based regulatory mechanisms. These findings have further identified multiple therapeutic vulnerabilities involving HDACs, EZH2, BET proteins, DNA methyltransferases, and chromatin remodeling complexes. Importantly, the reversible nature of epigenetic alterations provides significant opportunities for development of innovative precision oncology strategies.

Future integration of epigenetic therapies with immunotherapy, biomarker-guided stratification, artificial intelligence-assisted molecular profiling, and CRISPR-based epigenome editing may significantly improve therapeutic outcomes for TNBC patients. Continued investigation into chromatin plasticity, tumor microenvironment interactions, and metastatic evolution will therefore remain essential for advancing next-generation translational approaches capable of overcoming therapeutic resistance and reducing TNBC-associated mortality.

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