

Abstract

Estrogen receptor-positive (ER+) breast cancer represents the majority of breast cancer cases and is characterized by complex molecular heterogeneity shaped by genetic and epigenetic factors. Epigenetic regulation—including DNA methylation, histone modifications, and non-coding RNAs—plays a pivotal role in modulating estrogen receptor signaling, influencing tumor progression, therapeutic response, and resistance mechanisms. Environmental exposures, lifestyle factors, and aging contribute to dynamic epigenetic alterations that affect gene expression and endocrine therapy efficacy. Recent advances in understanding ER biology reveal the significance of pioneer transcription factors and intratumoral heterogeneity in driving diverse clinical outcomes. Therapeutically, novel endocrine agents such as oral selective estrogen receptor degraders (SERDs) and selective estrogen receptor covalent antagonists (SERCAs) show promise in overcoming resistance, while combination strategies incorporating CDK4/6 and PI3K/AKT/mTOR inhibitors improve clinical benefit. Epigenetic therapies, including HDAC and DNMT inhibitors, alongside emerging CRISPR-based epigenome editing tools, offer innovative avenues to reverse resistance, though challenges remain in toxicity management and biomarker development. Liquid biopsies and multi-omics integration enhance real-time disease monitoring and precision medicine approaches. This review synthesizes current molecular insights and epigenetic mechanisms in ER+ breast cancer, emphasizing their implications for therapeutic innovation and overcoming endocrine resistance.

Molecular Mechanisms and Epigenetic Regulation in Estrogen Receptor-Positive Breast Cancer: Implications for Therapy and Resistance

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Introduction

ER-positive (ER+) breast cancers represent about 70% of breast cancer cases. Epigenetic regulation—including DNA methylation, histone modification, and non-coding RNAs influences estrogen receptor (ER) signaling, contributes to endocrine resistance, and shapes tumor evolution. Overcoming resistance to traditional endocrine interventions—including tamoxifen, aromatase inhibitors (AIs), and intramuscular selective estrogen receptor degraders (SERDs) — has become a primary clinical imperative. This resistance frequently arises through secondary epigenetic alterations, rendering the discovery of novel therapeutic modalities and epigenetic modulators highly critical. This review synthesizes current understanding of epigenetic mechanisms in ER+ breast cancer progression and resistance, focusing on DNA methylation, histone modification, and non-coding RNA expression, and their roles in biomarker development and epigenetically targeted therapies.

Methods

This review synthesizes current literature on the molecular mechanisms and epigenetic regulation of estrogen receptor-positive (ER+) breast cancer. Relevant literature was identified through PubMed and examined for information on DNA methylation, histone modifications, and non-coding RNAs and their roles in ER signaling, tumor progression, endocrine therapy response, and therapeutic resistance. The review also examined environmental and lifestyle factors that may contribute to epigenetic alterations, intratumoral heterogeneity, and differences in ER biology. Finally, therapeutic strategies—including endocrine therapies, CDK4/6 and PI3K/AKT/mTOR inhibitors, epigenetic therapies, CRISPR-based epigenome editing, immunotherapy, and potential epigenetic biomarkers—were evaluated based on the literature reviewed.

Results

DNA methylation can silence genes through promoter hypermethylation. Hypermethylation of the ESR1 promoter is associated with reduced ERα expression and resistance to endocrine therapies. Histone modifications also influence transcription: HDACs promote chromatin compaction, while EZH2 and PRMT5 contribute to repressive epigenetic states. HDAC inhibitors have been investigated for their ability to restore ERα expression and endocrine sensitivity.

ncRNAs further regulate ER+ breast cancer. miRNAs, lncRNAs, and circRNAs can influence ER signaling, epithelial-mesenchymal transition, transcription, and tumor progression. Environmental exposures, diet, aging, and other lifestyle factors may contribute to epigenetic alterations affecting ER signaling.

ER+ tumors also demonstrate intratumoral heterogeneity, including differences in epigenetic states and ER expression. Therapeutic strategies targeting endocrine signaling, CDK4/6, PI3K/AKT/mTOR pathways, and epigenetic mechanisms are being investigated.

Therapy/Medicine	Mechanism for Action	Notes
Selective Estrogen Receptor Modulators (SERMs)		
Tamoxifen	Selective estrogen receptor modulator (SERM); blocks ER binding to DNA, inhibiting estrogen-driven transcription	Common endocrine therapy; resistance can occur via epigenetic silencing of ER or activation of alternate pathways
Aromatase Inhibitors		
Aromatase Inhibitors(AIs)	Inhibit aromatase enzyme, reducing estrogen synthesis	Used to deprive tumors of estrogen; resistance often involves epigenetic changes affecting ER expression
Selective Estrogen Receptor Degraders (SERDs)		
e.g., Fulvestrant, Elacestrant, ^{Text} Giredestrant	Bind ERα causing its degradation and downregulation; reduce ER signaling	Oral SERDs improve bioavailability over fulvestrant; effective against ESR1 mutations
Selective Estrogen Receptor Covalent Antagonists (SERCAs)	Irreversibly bind and inactivate ER, including mutant forms	Potential to overcome resistance mediated by ER mutations or conformational changes
CDK4/6 Inhibitors		
Palbociclib, Ribociclib, Abemaciclib	Inhibit cyclin-dependent kinases 4 and 6, blocking cell cycle progression downstream of ER signaling	Combined with endocrine therapy; improve progression-free survival
PI3K/AKT/mTOR Pathway Inhibitors		
e.g., Everolimus	Block signaling pathways that allow tumor escape from endocrine therapy	Effective in resistant cancers; toxicity management is challenging
Epigenetic Inhibitors		
e.g., Vorinostat, Entinostat	Inhibit HDAC enzymes, increasing histone acetylation and chromatin relaxation; restore ER expression and sensitivity	Used in combination with endocrine therapy to overcome resistance
DNA Methyltransferase Inhibitors (DNMTis)	Inhibit DNA methylation, reversing gene silencing	Challenges include hematologic toxicity; intermittent dosing and novel agents are being developed
BET Bromodomain Inhibitors	Block epigenetic reader proteins that regulate oncogenic transcription	Preclinical promise; clinical data still emerging
CRISPR-Based Epigenome Editing Tools	Targeted modification of DNA methylation or histone marks at ER target genes	Experimental approach aiming for high specificity and fewer off-target effects
Immunotherapies		
e.g., PD-L1 inhibitors	Modulate tumor immune microenvironment; block immune checkpoints to enhance anti-tumor immune response	More established in triple-negative breast cancer; gaining interest in ER+ disease

Discussion

The findings demonstrate that epigenetic regulation is closely connected to ER signaling and therapeutic resistance in ER+ breast cancer. DNA methylation, histone modifications, and ncRNAs can alter gene expression and contribute to changes in tumor behavior and endocrine sensitivity. These mechanisms may also interact with environmental exposures, aging, and lifestyle factors, contributing to the molecular heterogeneity observed among ER+ tumors.

Because epigenetic changes can be reversible, epigenetic therapies provide potential strategies for restoring treatment sensitivity. However, challenges including toxicity, tumor heterogeneity, limited predictive biomarkers, and the need for further clinical validation remain. Integrating genomic, transcriptomic, and epigenomic information with liquid biopsies and single-cell analyses may improve patient stratification and the development of more precise approaches to overcoming endocrine resistance.

Conclusion

DNA methylation, histone modifications, and ncRNAs shape transcriptional programs and modulate endocrine response, serving as biomarkers and therapeutic targets. Epigenetic drugs hold promise for reversing resistance and extending endocrine therapy efficacy. However, identifying predictive biomarkers and managing toxicity are ongoing challenges. Future precision oncology will integrate genomics, transcriptomics, and epigenomics to enable real-time monitoring of tumor evolution. Translational research and biomarker validation are vital to translating epigenetic therapies into clinical practice. The complexity of tumor heterogeneity, evolving resistance mechanisms, and variability in patient response continue to present major translational challenges. Future studies integrating longitudinal clinical data with multi-omics approaches will be necessary to validate many of these emerging therapeutic strategies.

References

Number references sequentially by order of appearance, not alphabetically. Refer to the reference number, as [3] or [5]-[8].

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