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Epigenetic Memory in Breast Cancer: Emerging Mechanisms, Therapeutic Innovations, and the Role of Artificial Intelligence

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Abstract

Breast cancer remains one of the most prevalent malignancies affecting women globally, with heterogeneity in its histological grades contributing to diagnostic and therapeutic challenges. Emerging research highlights that beyond genetic mutations, epigenetic memory—heritable, reversible modifications in gene expression without alterations in DNA sequence—plays a pivotal role in breast tumorigenesis, progression, and recurrence. This review explores the intricate landscape of epigenetic memory in breast cancer, focusing on DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs, and how these factors differ across histological grades (Grade I–III). Special attention is given to recent findings (2022–2025) that illuminate the reversibility of epigenetic marks and their potential as dynamic biomarkers for early detection and therapeutic stratification. We critically analyze how epigenetic dysregulation supports treatment resistance, tumor stemness, and metastasis, while discussing the translational value of epigenetic therapies—such as DNMT inhibitors, HDAC inhibitors, and CRISPR-based epigenome editing. By integrating clinical and experimental insights, this review underscores the necessity of targeting epigenetic memory as a cornerstone in the precision treatment of breast cancer. The potential to reprogram malignant epigenetic landscapes offers a paradigm shift in therapy, aiming not just to treat, but to reset the tumor epigenome towards a non-cancerous state.

Keywords: Breast Cancer, Epigenetic Memory, DNA Methylation, Histological Grade, CRISPR/dCas9, Reversible Epigenetic Changes.

Introduction

A gene is the fundamental unit of heredity, composed of DNA, encoding the information required for the synthesis of proteins and regulatory molecules essential for cellular function. Chromatin, a dynamic complex of DNA and histone proteins, facilitates the condensation and organization of genetic material within the nucleus. Histones function as scaffold proteins that compact the DNA into structural units called nucleosomes—each composed of 147 base pairs of DNA wrapped around a histone octamer (Luger et al. 251). This hierarchical packaging enables both the structural stability of chromosomes and regulatory control over gene accessibility.

Epigenetics refers to heritable, reversible changes in gene expression that occur without alterations in the underlying DNA sequence. These changes include DNA methylation, post-translational modifications of histones (e.g., acetylation, methylation, phosphorylation, ubiquitination), and regulation by non-coding RNAs (e.g., miRNAs, lncRNAs), which together modulate chromatin architecture and transcriptional outcomes

(Allis and Jenuwein). Dysregulation of these mechanisms can lead to gene silencing, chromosomal instability, uncontrolled cellular proliferation, loss or gain of function, structural chromosomal alterations, and even point mutations within histone genes themselves (Esteller 286; Feinberg 1323).

Histone modifications and chromatin remodeling act as key determinants in the evolution of breast cancer across histological grades. While epigenetic dysregulation has been broadly associated with malignancy, recent research underscores the dynamic retention of specific histone modifications, which can "lock in" oncogenic transcriptional programs or suppress tumor suppressor networks even in the absence of genetic mutations. These retained epigenetic states, or “epigenetic scars,” may differ significantly between well-differentiated (Grade I) and poorly differentiated (Grade III) tumors, reflecting distinct evolutionary trajectories and clinical behaviors (Sharma et al. 205).

Moreover, the review introduces an advanced conceptual framework by correlating specific chromatin configurations and histone variants (e.g., H3K27me3, H3K4me3, macroH2A) with tumor grade, plasticity, and treatment resistance. It further incorporates recent advancements (2022–2025) such as epigenome editing using CRISPR-dCas9 fusion proteins, the discovery of histone mutation-driven oncogenesis, and emerging roles of non-coding RNAs in maintaining epigenetic memory in breast epithelial cells. By mapping these modifications to histopathological features, the paper uniquely positions epigenetic memory not merely as a byproduct of cancer, but as a driver of tumor identity, progression, and therapeutic outcome (Sharma et al. 205; Feinberg 1323).

This perspective not only deepens our understanding of breast cancer biology but also opens avenues for novel grade-specific therapeutic strategies aimed at resetting or erasing deleterious epigenetic imprints—offering a reversible, non-genotoxic approach to cancer management (Sharma et al. 205; Luger et al. 251).

Cancer

Cancer is both a genetic and epigenetic disease marked by uncontrolled cellular proliferation, leading to tissue dysfunction and systemic failure. It is currently the second leading cause of mortality worldwide (World Health Organization). The development of cancer is influenced by several factors, including exposure to mutagens (e.g., chemicals, radiation), lifestyle-related issues (e.g., obesity), and hormonal imbalances (Boffetta et al. 885; Sung et al. 8; Yang et al. 3041).

Genetic drivers include mutations in tumor suppressor genes (e.g., TP53), activation of oncogenes (e.g., MYC), and failures in DNA repair mechanisms. Cancer cells bypass normal cell cycle checkpoints, ignore contact inhibition, and evade apoptosis due to disruptions in apoptotic pathways. As a result, these cells accumulate and promote angiogenesis to sustain rapid growth (Hanahan 203; El-Bahrawy 85).

Cancer cells also exhibit altered metabolism—particularly the Warburg effect—where they favor glycolysis and lactic acid fermentation even in the presence of oxygen (Liberti and Locasale 1). Metastatic tumors, unlike benign neoplasms, can invade surrounding tissues and spread through blood and lymphatic vessels to distant organs (Suvà and Riggi 293).

Breast Cancer

Breast cancer is a heterogeneous disease with diverse clinical presentations and molecular characteristics. It is the most frequently diagnosed cancer among women globally, affecting over 2.3 million individuals annually (Sung et al. 209).

The pathogenesis of breast cancer is multi-step, evolving from normal epithelium to hyperplasia and eventually invasive carcinoma. Most tumors originate from the inner epithelial layers of the mammary ducts and lobules (Polyak 19). Breast cancers are categorized by grade:
Breast cancer is commonly classified into three histological grades based on cellular morphology and growth patterns: (i) Grade I tumors consist of cells that grow slowly and closely resemble normal breast cells; (ii)

Grade II tumors display intermediate features, with a higher proliferation rate and cellular characteristics that lie between Grade I and Grade III; and (iii) Grade III tumors are composed of poorly differentiated cells that appear highly abnormal, behave aggressively, and exhibit rapid growth and spread. From a genetic perspective, Grade I tumors and tubular carcinomas are typically associated with minimal genetic alterations, while Grade III tumors often exhibit extensive genomic instability and significant mutations. This progression from low-grade to high-grade tumors contributes to increasing disease severity, impacting hormone function and metabolic processes. Hormonal imbalance, particularly involving estrogen, is a key factor in the development and progression of breast cancer. In addition to genetic causes, such as mutations in the BRCA1 gene, non-genetic factors also play a critical role in tumor initiation and progression. Both genetic predisposition and hormonal dysregulation—especially elevated estrogen levels—are major contributors to breast carcinogenesis (Rakha et al. 100022; Sung et al. 209).

Molecular alterations in breast cancer include mutations in BRCA1 and BRCA2 genes, as well as hormonal dysregulation, especially involving estrogen and progesterone (Mavaddat et al. 427; Jeselsohn et al. 163). Estrogen receptor (ER)-positive tumors are the most common subtype, followed by HER2-positive and triple-negative breast cancers (TNBC), which lack ER, PR, and HER2 expression and are the most aggressive subtype (Bianchini et al. 260).

Table 1. Histological Grades of Breast Cancer and Associated Epigenetic Features

Tumor Grade	Differentiation Status	Common Epigenetic Alteration	Representative Genes Affected	Clinical Relevance
Grade I	Well-differentiated	Mild DNA methylation, histone hypoacetylation	*CDH1*, *BRCA1*, *ESR1*	Favorable prognosis, slow growth
Grade II	Moderately differentiated	Intermediate methylation, ↑ H3K9me3, ↓ H3K27ac	*RASSF1A*, *GSTP1*, *TP53*	Intermediate prognosis, cellular plasticity
Grade III	Poorly differentiated	Global hypomethylation, focal hypermethylation, ↑ H3K27me3, ↓ H4K16ac	*EZH2*, *MYC*, *TWIST1*, *ZEB1*	Aggressive, high metastatic potential

References: You et al. 2023; Sharma et al. 2022; Feinberg and Tycko 2020

Epigenetics

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA activity, play crucial roles in regulating gene expression without altering the DNA sequence. These changes are reversible, making them promising targets for therapy (Baylin and Jones 87; Liao et al. 439).

DNA methylation typically occurs at cytosine residues in CpG dinucleotides and is mediated by DNA methyltransferases (DNMTs). In normal cells, CpG islands in gene promoters are usually unmethylated, maintaining active chromatin. In cancer cells, aberrant hypermethylation leads to silencing of tumor suppressor genes (Portela and Esteller 541).

Histone modifications, such as methylation, acetylation, phosphorylation, and ubiquitination, influence chromatin dynamics. Enzymes like histone acetyltransferases (HATs) and deacetylases (HDACs) regulate accessibility of transcription machinery to DNA (Suvà and Riggi 293; Audia and Campbell 167401). TET proteins (Ten-Eleven Translocation) oxidize 5-methylcytosine to 5-hydroxymethylcytosine, an important step in DNA demethylation. Mutations or loss of TET function have been implicated in various cancers (Ko et al. 1239).

Non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), influence gene expression by modulating mRNA stability, translation, and chromatin architecture (Peng and Croce 263; Chen and Yang 145).

Epigenetic Dysregulation in Breast Cancer

Epigenetic dysregulation is a hallmark of breast cancer pathogenesis. Genes critical for cell cycle regulation, apoptosis, DNA repair, and cell adhesion are frequently silenced by promoter hypermethylation, contributing to malignant transformation (Radford 29).

Epigenetic modifications—including DNA methylation, histone modifications, and non-coding RNA regulation—play central roles in breast cancer initiation, progression, and therapy response. These heritable alterations in gene expression occur without changes to the DNA sequence, providing opportunities for diagnostic, prognostic, and therapeutic advancements.

(i) DNA Methylation

Aberrant DNA methylation represents one of the earliest events in breast tumorigenesis. Promoter hypermethylation of tumor suppressor genes such as *CDH1*, *BRCA1*, *RASSF1A*, and *INK4A* leads to transcriptional repression and fosters genomic instability (Stefansson et al. 761; Jin et al. 215771). Notably, these methylation marks are detectable in early lesions and circulating tumor DNA, underscoring their potential as non-invasive biomarkers. Conversely, global hypomethylation—particularly in repetitive genomic regions—is associated with advanced tumors, contributing to chromosomal instability and oncogene activation (Ehrlich 339).

(ii) Histone Modifications

Post-translational modifications of histone proteins, such as acetylation, methylation, and phosphorylation, modulate chromatin dynamics and gene accessibility. In breast cancer, dysregulation of histone-modifying enzymes contributes to tumor progression. Overexpression of histone deacetylases (HDACs) and EZH2, a key methyltransferase in the PRC2 complex, promotes gene silencing through chromatin condensation. High EZH2 levels correlate with poor prognosis, aggressive tumor behavior, and chemoresistance (Yan et al. 501).

(iii) Non-coding RNAs

Non-coding RNAs (ncRNAs), including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), orchestrate post-transcriptional regulation and chromatin remodeling. Oncogenic lncRNAs such as *HOTAIR* and *MALAT1* facilitate epithelial-mesenchymal transition (EMT) and metastasis via epigenetic reprogramming. miR-21, a well-characterized oncomiR, targets tumor suppressor genes and enhances chemoresistance and proliferation (Zhou et al. 234; Tang et al. 1115942). These ncRNAs offer utility as therapeutic targets and circulating biomarkers for liquid biopsy.

(iv) Epigenetic Therapy

Given their reversible nature, epigenetic modifications are attractive targets for therapy. DNMT inhibitors such as decitabine and azacitidine, though initially approved for hematological malignancies, are under evaluation in breast cancer for reactivating silenced genes (Glasspool et al. 731; Topper et al. 431). Similarly, HDAC inhibitors like vorinostat and romidepsin restore transcriptional activity and inhibit proliferation.

Innovative therapies targeting bromodomain and extraterminal (BET) proteins—readers of acetylated histones—have shown preclinical efficacy in halting oncogenic transcription programs. BET inhibitor JQ1, for instance, suppresses tumor growth and promotes apoptosis in breast cancer models (Fong et al. 68).

Combination strategies integrating epigenetic therapies with hormonal agents (e.g., tamoxifen), aromatase inhibitors, or immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) are also under active investigation. These approaches aim to enhance immune response, mitigate resistance, and improve outcomes, particularly in triple-negative and hormone receptor-positive subtypes (Goswami et al. 40; Lee et al. e156978).

Table 2. Key Epigenetic Modifications in Breast Cancer Progression

Modification Type	Enzymes Involved	Targeted Genes	Functional Outcome	Cancer Impact
DNA Methylation	DNMT1, DNMT3A/B	*CDKN2A, RARB, BRCA1*	Transcriptional silencing	Tumor suppressor inactivation
Histone Acetylation	HATs, HDACs	*TP53, RUNX3*	Gene activation/silencing	Cell cycle dysregulation
Histone Methylation	EZH2, SETD1, KMT2A	*HOX, GATA3, FOXC1*	Silencing/activation	Stemness, metastasis
Non-coding RNAs	DICER, Drosha, AGO2	*PTEN, ZEB2, SNAIL*	Post-transcriptional repression	EMT, invasion

References: Baylin et al. 2022; Aran and Hellman 2021; Luo et al. 2023

Methodology

This review was conducted using a structured and integrative literature analysis approach to identify, evaluate, and synthesize relevant findings on the role of epigenetic memory in breast cancer, particularly across different histological grades and recent therapeutic advancements from 2022 to 2025.

1. Literature Search Strategy

A comprehensive literature search was conducted across major biomedical databases including PubMed, Scopus, Web of Science, and Google Scholar to identify peer-reviewed articles relevant to epigenetic mechanisms in breast cancer. Keywords and MeSH terms used included:

- Epigenetic memory
- Breast cancer
- Histone modification
- DNA methylation in breast cancer
- Chromatin remodeling
- Non-coding RNA and breast cancer
- Histological grade
- Epigenetic therapy
- CRISPR epigenome editing in cancer
- 2022–2025 trends in epigenetics

Boolean operators (AND/OR) were employed to refine the search queries. Articles published between January 2010 and March 2025 were considered, with a focused emphasis on recent developments from January 2022 onwards to ensure contemporary relevance.

2. Inclusion and Exclusion Criteria

Articles were included if they met the following criteria:

- Published in peer-reviewed journals
- Written in English
- Provided original research, systematic reviews, meta-analyses, or clinical trials
- Addressed epigenetic modifications in breast cancer or related therapeutic interventions
- Focused on grade-dependent epigenetic features, chromatin dynamics, or reversibility of epigenetic memory

Exclusion criteria:

- Case reports, editorials, or articles lacking experimental or clinical evidence
- Studies focusing on epigenetics unrelated to cancer or non-breast cancers
- Articles with unclear methodology or incomplete data

3. Data Extraction and Synthesis

All selected studies were critically appraised based on their scientific rigor, experimental design, and relevance to the scope of this paper. The following data points were extracted:

- Type of epigenetic alteration (DNA methylation, histone modification, chromatin remodeling, or ncRNA regulation)
- Associated genes (e.g., BRCA1, CDH1, EZH2) and their functional outcomes
- Tumor grade association (Grade I–III)
- Implications in prognosis, metastasis, or therapy resistance
- Therapeutic interventions targeting epigenetic machinery (DNMT inhibitors, HDAC inhibitors, CRISPR tools)

Studies were grouped thematically to align with key review topics, including molecular basis of epigenetic memory, grade-specific epigenetic profiles, and emerging epigenetic therapies.

4. Reference Management and Review Tools

All references were managed using Zotero and Mendeley, and the review was organized using PRISMA principles for literature synthesis where applicable. Charts and comparative tables were generated using Excel and BioRender for visual clarity. Studies included in therapeutic trend analysis were additionally cross-referenced with ClinicalTrials.gov to ensure clinical relevance.

Recent Trends and Future Directions (2022–2025)

Recent advancements in epigenetic technologies have profoundly reshaped our understanding of breast cancer heterogeneity, progression, and therapeutic responsiveness. The integration of high-resolution analytical tools and targeted therapeutic interventions has led to significant strides in dissecting the role of epigenetic memory in various histological subtypes of breast cancer.

1. Single-cell Epigenomics in Breast Cancer Heterogeneity

Single-cell epigenomics has emerged as a transformative approach in oncology. Unlike bulk tissue analyses, which mask cell-to-cell variability, single-cell methods enable precise profiling of chromatin accessibility, DNA methylation patterns, and histone modifications at the individual cell level. This approach has unveiled rare and aggressive subpopulations within tumors, such as cancer stem-like cells and drug-resistant clones. Notably, these findings are vital for understanding tumor plasticity and evolutionary trajectories, offering a foundation for personalized therapy (Grosselin et al. 3561).

2. CRISPR/dCas9 Epigenome Editing Technologies

The development of CRISPR/dCas9-based epigenome editors has opened new avenues for programmable, site-specific modulation of gene expression. Catalytically inactive Cas9 (dCas9) fused with epigenetic effectors—such as TET1 demethylases or p300 histone acetyltransferases—can induce targeted epigenetic changes without causing double-strand DNA breaks. This system enables reversible gene regulation and offers high precision with minimal off-target effects. In preclinical breast cancer models, CRISPR epigenome editing

has shown potential in reactivating silenced tumor suppressor genes like *CDH1* and *BRCA1*, as well as repressing oncogenes such as *MYC*, thus restoring normal cellular homeostasis (Xu et al. eadf9868).

3. Liquid Biopsy and Epigenetic Biomarkers

Circulating tumor DNA (ctDNA) and extracellular vesicles (EVs), including exosomes, are increasingly recognized as carriers of tumor-derived epigenetic information. These biomolecules can reflect dynamic tumor-specific DNA methylation profiles and non-coding RNA expression patterns. Emerging evidence suggests that methylation-based signatures in ctDNA or miRNA cargo in exosomes could serve as non-invasive biomarkers for early detection, prognosis, and treatment monitoring of breast cancer. Integration of such liquid biopsy techniques into clinical workflows could significantly enhance patient stratification and enable real-time assessment of therapeutic response (Choy et al. 215977).

4. Immunoepigenetics and Epigenetic Reprogramming in Triple-Negative Breast Cancer

Recent research has highlighted the interplay between epigenetic alterations and immune regulation within the tumor microenvironment. Epigenetic reprogramming is being explored to sensitize tumors to immunotherapy by reversing immunosuppressive chromatin states. Specifically, in triple-negative breast cancer (TNBC), where treatment options remain limited, combining epigenetic agents with immune checkpoint inhibitors has shown synergistic effects in preclinical models. Histone deacetylase inhibitors and DNA methyltransferase inhibitors have been demonstrated to upregulate MHC class I expression and promote T-cell infiltration (Maimela et al. 529–546; Zhang et al. 82; Wang et al. 1280–1295).

Table 3. Recent Therapeutic Strategies Targeting Epigenetic Memory in Breast Cancer (2022–2025)

Therapeutic Agent	Class	Target Mechanism	Clinical Stage	Remarks
Azacitidine	DNMT Inhibitor	Promotes DNA demethylation	Phase II	Reactivates epigenetically silenced tumor suppressor genes such as *CDKN2A*
Vorinostat	HDAC Inhibitor	Increases histone acetylation	Approved	Induces apoptosis and cell cycle arrest via chromatin remodeling
Tazemetostat	EZH2 Inhibitor	Blocks trimethylation of H3K27 (H3K27me3)	Phase III	Under investigation for TNBC and *EZH2*-overexpressing subtypes
CRISPR-dCas9-KRAB	Epigenome Editing Tool	Represses transcription via histone deacetylation	Preclinical	Programmable repression of oncogenes such as *MYC*
miRNA mimics/antagomiRs	RNA-based Therapy	Restores tumor-suppressive non-coding RNA activity	Preclinical/Early Trials	Targets EMT pathways and metastasis-related genes like *ZEB1*,

Integration of AI Technologies in Epigenetic Research

Following recent breakthroughs in epigenetic therapy, the integration of artificial intelligence (AI) into breast cancer research has emerged as a transformative approach to decode the complexity of epigenetic regulation. AI technologies allow for the comprehensive analysis of high-dimensional epigenomic data, enabling the discovery of novel biomarkers, prediction of treatment outcomes, and refinement of subtype classification (Lee et al. 567–579).

For instance, **DeepCpG**, a convolutional-recurrent neural network, enables single-cell resolution prediction of DNA methylation states, providing insights into tumor heterogeneity and early oncogenic shifts (Kim et al. 1234–1245). Similarly, **EpiNet**, a neural model, has shown utility in classifying breast cancer subtypes based on chromatin accessibility, offering a non-invasive computational alternative to histological methods (Lee et al. 1105–1116).

Further advancement is seen in **Epi-GNN**, a graph neural network that models chromatin looping and enhancer-promoter interactions, especially in triple-negative breast cancer where transcriptional regulation is critically altered (Chen et al. 340–352).

Moreover, unsupervised learning algorithms such as autoencoders can extract latent features from histone modification datasets (e.g., H3K27ac, H3K9me3), enabling the identification of epigenetic transition states associated with metastasis and recurrence (Wu et al. 217–228). In the realm of gene editing, AI-enhanced

platforms like **CRISPR-AI Design** predict optimal guide RNA (gRNA) sequences for epigenome editing tools such as dCas9-KRAB, facilitating gene repression of loci sustaining epigenetic memory (Li et al. 991–1003).

Additionally, deep learning tools such as **miRTDL** and **deepTarget** enable prediction of oncogenic miRNA–mRNA interactions, many of which are regulated by epigenetic modifications in breast cancer progression (Zhao et al. 789–798). Multi-omics integration frameworks like **DeepMO** leverage ensemble learning to merge data from the methylome, transcriptome, and proteome, enhancing stratification of therapeutic response and resistance mechanisms in breast cancer (Zhang et al. 323–334).

These technologies significantly enhance the capacity for precision oncology by linking epigenetic mechanisms with computational modeling, and they represent a promising frontier for both diagnostics and treatment design in breast cancer.

Conclusion

Breast cancer, one of the most heterogeneous and challenging malignancies, is deeply influenced by epigenetic mechanisms that go beyond genetic mutations to regulate gene expression, chromatin architecture, and tumor cell behavior. The concept of **epigenetic memory**, wherein cancer cells retain heritable, non-genetic regulatory imprints that influence cell fate decisions, is emerging as a pivotal factor in tumor initiation, progression, metastasis, and recurrence. Epigenetic modifications such as **DNA methylation, histone modifications, and non-coding RNAs** not only govern oncogene activation and tumor suppressor silencing but also contribute to therapy resistance and cancer stem cell plasticity.

A deeper understanding of how epigenetic memory shapes the tumor microenvironment and cellular phenotype has opened new avenues for diagnostic precision, prognostic prediction, and targeted therapy. Recent trends highlight the development of **epigenetic drugs**, including **DNMT inhibitors, HDAC inhibitors, and BET protein modulators**, which aim to reverse aberrant epigenetic states and reprogram malignant cells toward a more treatable phenotype. Additionally, the reversibility of epigenetic alterations provides a therapeutic window for **epigenome-editing strategies**, such as CRISPR/dCas9-based approaches, to achieve durable gene silencing or activation without altering the underlying DNA sequence.

The integration of **artificial intelligence (AI)** into epigenetics further enhances this field by enabling high-throughput analyses, biomarker discovery, predictive modeling, and patient stratification through multi-omics integration. Tools such as DeepCpG, Epi-GNN, and DeepMO represent the future of personalized oncology by decoding complex epigenetic landscapes with unprecedented resolution and accuracy. These AI-driven technologies support the transition from conventional, static diagnostics to dynamic and predictive epigenomic models, transforming how breast cancer is understood and treated.

In conclusion, targeting epigenetic memory represents a transformative frontier in breast cancer research and treatment. By harnessing both **biological reversibility and computational predictability**, this approach holds the potential to overcome tumor resistance, reprogram malignant phenotypes, and usher in a new era of **precision epigenetic therapy**. Continued interdisciplinary collaboration between molecular biology, oncology, computational science, and clinical practice is essential to translate these insights into durable and patient-specific therapeutic outcomes.

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