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Genetic and Epigenetic Factors in Breast Cancer Progression

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ABSTRACT

Genetic and epigenetic processes are intertwined in a complex manner in order to enhance the development of breast cancer by regulating the fundamental cellular processes including DNA repair, proliferation, differentiation and metastasis. This review provides an overview of the findings of animal model experiments to explain the causes of the significant changes in genetic aspect including RAD51C mutations and dys-regulation of the BAF chromatin remodeling complex and epigenetic alterations, such as DNA methylation, histone modification, and microRNA dys-regulation. The animal models are where the researcher can study the mechanism by which these changes of the molecules cause tumorigenesis, stimulate tumor growth and metastatic potential. The data received in the course of such studies denotes the dynamism and reversibility of the epigenetic processes which may be utilized in treating diseases by selectively regulating the expression of the said molecules with an aim of modifying DNA methylation, histone-modifying enzymes, and miRNAs. Integration of genetic and epigenetic understanding will not only enhance our understanding of breast cancer biology, but also design the precision therapies, and also expose potential biomarkers that can be utilized to identify and diagnose the disease at the earliest phase. In total, the significance of the animal-based research in the context of finding mechanistic information and design interventions to limit the occurrence of breast cancer is highlighted in this review as a foundation of the subsequent use of the translation research and clinical interventions.

Key Words:

Breast Cancer, Genetic Mutations, Epigenetic Modifications, RAD51C, BAF Complex, DNA Methylation, Histone Modifications, Micrornas, Tumor Progression, Animal Models.

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1. INTRODUCTION

Breast cancer is still one of the major causes of deaths that are associated with cancer among women all over the world. Although studying human beings has brought in good information, animal models give controlled conditions to study how the molecular processes improve breast cancer progression[1]. These models have also played a vital role in the process of the identification of genetic mutations and epigenetic alteration that catalyze tumorigenesis and metastasis[2]. This review dwells on research conducted on animals in order to examine the genetic and epigenetic aspects that help in breast cancer development[3].

1.1. Background Information and Context

Breast cancer has been identified to be among the most common malignancies seen in women around the globe and it has been one of the biggest causes of cancer morbidity and mortality[4]. Its growth and evolution is also affected by a sophisticated interaction of genetic and epigenetic factors that control the cellular mechanisms including DNA repair, cell proliferation, cell differentiation, cell apoptosis, and metastasis[5]. Genetic changes such as mutations in DNA repair genes and components of chromatin remodeling have the capability of interfering with cellular homeostasis and triggering tumorigenesis[6]. At the same time, altering the DNA sequence, epigenetic changes, including DNA methylation, histone changes, and microRNA deregulation, further regulate the expression of genes, and all add to cancer development and metastasis[7]. Animal models have been critical in understanding these mechanisms and gave controlled systems to study the relationship between specific genetic and epigenetic alterations and the development and progression of breast cancer.

1.2. Objectives of the Review

The review aims to:

- To explore the impact of genetic mutations, such as RAD51C mutations and alterations in the BAF chromatin remodeling complex, on tumor initiation and progression.
- To analyze the contribution of epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation, to breast tumor growth and metastasis.
- To integrate findings from animal models to provide mechanistic insights into how these factors interact to influence breast cancer biology.
- To highlight potential therapeutic strategies targeting these genetic and epigenetic pathways.

1.3. Importance of the Topic

The genetic and epigenetic basis of breast cancer is essential in improving the use of precision medicine strategies[8]. The observations of animal models do not only clarify the basic biology of tumorigenesis, they also have provided preclinical proof of the design of targeted therapy and epigenetic intervention. Through a detailed review of these mechanisms, this piece of work contributes towards a better understanding of the breast cancer progression processes and opportunities to further research that can help in enhancing patient outcomes.

2. GENETIC FACTORS

Genetic changes which interfere with normal cellular processes including DNA repair, cell cycle regulation, and chromatin organization are highly associated with breast cancer progression. These genetic alterations in animal models yield important information on the processes involved in the initiation, growth, and metastasis of tumors. The analysis of genes such as RAD51C that play a key role in DNA repair and the elements of the BAF chromatin remodeling complex that governs the expression of genes has shown that certain mutations are capable of impairing the stability of the genome and the homeostasis of cells[9]. Knowing these genetic drivers in controlled experimental models, in addition to clarifying the biology of breast cancer, is also a pointer of possible therapeutic targets of intervention.

2.1. RAD51C Mutations

RAD51C gene is the gene that encodes a protein, which is the key component of the homologous recombination (HR) pathway, which is one of the most conserved mechanisms that repair the double strand breaks (DSBs) in DNA. HR plays a crucial role in the preservation of genomic stability, especially in cells with a rapid division rate like the mammary epithelial cells[10]. It is established that proper functioning of RAD51C leads to appropriate DNA repair, a reduced number of mutations, and resistance to tumorigenesis. On the other hand, RAD51C mutations or loss of activity impairs DNA repair, induces genomic instability, chromosomal abnormalities, and oncogenic mutations oncogenic mutations are the characteristics of cancer onset and progression.

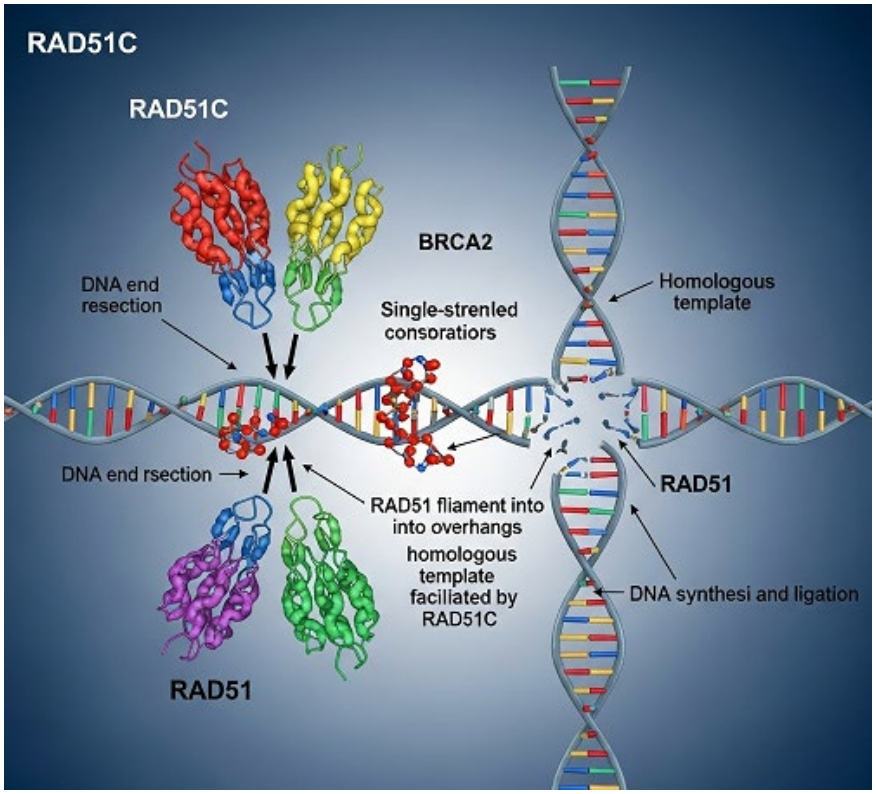

Figure 1: RAD51C Gene[11]

Insights from Animal Models

Animal models have proved to be instrumental in the study of the role of RAD51C in breast cancer. The mice with heterozygous and homozygous mutations in RAD51C have a very high prevalence of tumors in the mammary than the controls with the wild type, which suggests that the gene has a dose dependent effect on tumor suppression[12]. RAD51C-deficient mice exhibit:

- Chromosome breakages and rearrangements of the chromosomes increase.
- An increase in DNA damage indicators (e.g. γ-H2AX foci).
- Dysfunctional cell cycle controls in the mammary epithelial cells.
- Greater vulnerability to tumor development and accelerated tumor development.

All these studies bring to the fore the dual involvement of RAD51C: it inhibits tumor formation by stabilizing genomic integrity, and regulates tumor progression by altering the response to DNA damage in the formation of the mammary gland development.

Tumor Aggressiveness and Metastasis

Preclinical animal research RAD51C deficiency not only triggers the formation of tumors, but also leads to aggressive tumor phenotypes. Mice with RAD51C deficiencies exhibit improved growth rates, higher growth indices, and greater metastasis potentials than the mice with the wild type. Such results indicate that therapeutic intervention can be targeted at RAD51C-related pathways and this approach may be applied to develop a successful intervention strategy, especially in breast cancer where the deficiency of homologous recombination is observed[13].

Key Insight

Studies involving animals reveal that RAD51C plays a critical role in ensuring genomic stability and its loss or mutation initiates and progresses breast tumors. The results indicate that RAD51C is a breast cancer susceptibility biomarker and therapeutic target of homologous recombination-deficient tumors.

2.2. BAF Complex Alterations

BAF (BRG1/BRM-associated factor) is a multi-protein chromatin remodeling complex, which is instrumental in the regulation of gene expression through changes in the positioning of the nucleosomes and accessibility of chromatin[14]. This dynamical remodeling is critical in the regulation of transcriptional programs, which control the growth of cells, their differentiation, DNA damage response and tissue development. The BAF complex has also been identified as a key genetic and epigenetic cause of various cancers, breast cancer being one of them.

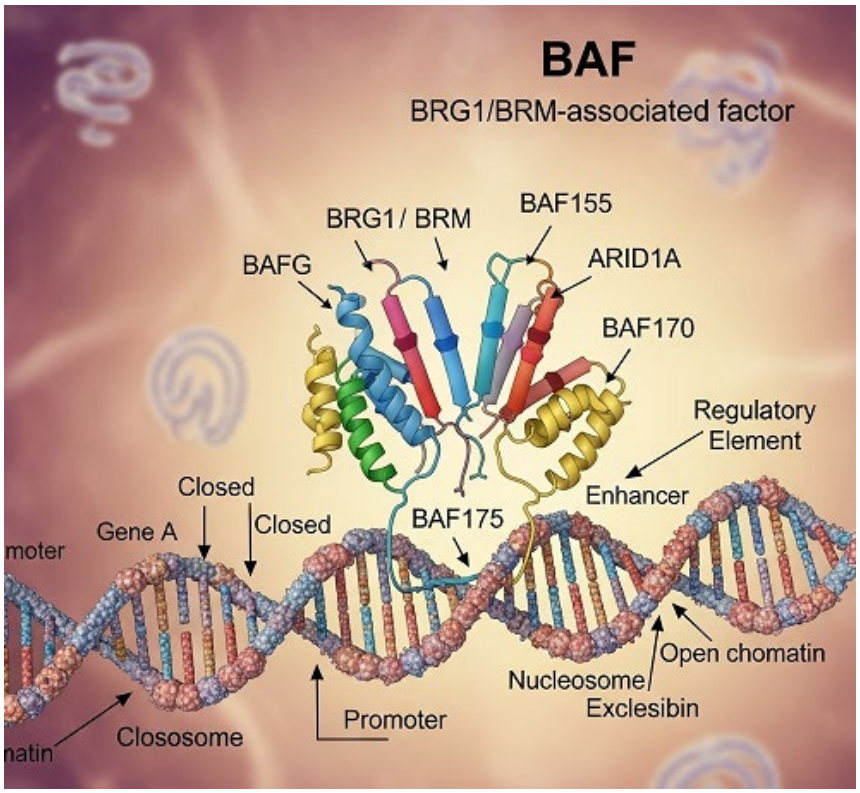

Figure 2: BAF (BRG1/BRM-Associated Factor)[15]

Mechanistic Role in Breast Cancer

The BAF complex itself is a global controller of chromatin structure, which allows or inhibits the transcriptional machinery to interact with DNA. The complex has BRG1 (Brahma-related gene 1) as a central ATPase subunit and this supplies energy needed to remodel chromatin[19]. Deletions, mutations or functional loss of BRG1 interferes with regular chromatin structure resulting in abnormal gene expression[16]. In particular, BRG1 loss has been reported to be associated with:

- Oncogenes upregulation (e.g. MYC, CCND1)
- Tumor suppressor gene downregulation (e.g. p21, p53)
- Defected DNA damaged repair, which paves the way to genomic instability.
- Increased ectoderm-mesenchymal transition (EMT), which facilitates tumor invasion and metastasis.

Insights from Animal Models

The contribution of the BAF complex in breast cancer has been shown to be quite convincing through animal research[17]. The genetic engineered mice with a deletion in BRG1 in mammary epithelial cells generate mammary tumors much more frequently than the wild type controls. These mice with BRG1 deficiency have disturbed chromatin remodeling, cell proliferation disregards and distorted mammary glands development that has distinctly shown the tumor suppressive role of BAF complex.

Mechanistic investigations of these models indicate that BRG1 deficiency provokes global transcriptional imbalance, which enhances the development of tumor and increases its progression. Also, complemented EMT in BRG1-diluted mammary cells adds to high tumor invasiveness and possible metastasis possibility. These findings highlight the fact that the BAF complex is not exclusive as a tumor initiating sentinel, but also a tumor aggressiveness and metastatic potential modulator.

Key Insight

The integrity of the complex of BAF is essential to the normal biology of the mammary glands. Breast tumor development occurs by mutation or loss of the BRG1 in animal models, and these mutations disrupt the chromatin structure and modify gene expression programs[18]. This underscores the BAF complex as a target therapy and approaches to correcting the abnormality of chromatin remodeling is promising as a way of treating breast cancer.

Integration with RAD51C

Combined with BAF complex dysregulation, these RAD51C mutations demonstrate how genetic changes are combined to impair the cellular homeostasis of breast cancer. Rad51 C is largely involved with DNA repair and genomic integrity and BAF complex mutations with chromatin architecture and transcriptional regulation. A combination of these genetic abnormalities in animal models offers important information on the processes of tumor formation, development and how they metastasize, giving a solid foundation on the basis of exploring targeted therapy to remedy these alterations[19].

Table 1 provides a summary of some of the important studies into genetic factors including RAD51C and related pathways with emphasis on the gene focus, main findings and the model or approach applied.

Table 1: Key Studies on Genetic and Epigenetic Factors in Breast Cancer

Author's Name	Focus / Gene Studied	Key Findings	Model / Method
Byler et al., 2014[20]	RAD51C, BAF complex, and other genetic/epigenetic alterations	Genetic mutations and epigenetic changes drive breast cancer progression; highlight therapeutic targets	Literature review / preclinical insights
Stephens et al., 2017[21]	Cytokine gene variations	Genetic and epigenetic variations associated with post-surgical breast pain; highlights interplay of genetic and epigenetic factors	Human study (clinical)
Dumitrescu, 2018[22]	Breast cancer subtypes	Interplay between genetic and epigenetic changes influences subtype-specific tumor progression	Review / precision medicine focus
Griseri et al., 2016[23]	RET gene expression	Genetic and epigenetic factors regulate RET expression; impact patient survival in breast cancer	Cell lines and patient data
Karsli-Ceppioglu et al., 2014[24]	Epigenetic mechanisms	Summarizes epigenetic alterations in breast cancer and their role in progression	Review / epigenomics perspective
Bombonati & Sgroi, 2011[25]	Molecular pathology of breast cancer	Genetic and epigenetic changes drive tumor initiation and progression; provides mechanistic insights	Literature review / pathology focus

3. EPIGENETIC FACTORS

Heritable alterations in the gene expression are called epigenetic modifications, which do not involve alterations in DNA sequence. They are important in controlling cellular events like proliferation, differentiation, apoptosis and repair of DNA. These mechanisms can be disrupted to promote tumors, tumor progression, and tumor metastasis. Animal models have played a significant role in identifying the role of epigenetic changes in the pathogenesis of breast cancer in animal models, which have served as helpful preclinical outcomes in understanding possible treatment options[26].

3.1. DNA Methylation

The main epigenetic modification, which involves the addition of a methyl group to the 5' carbon of cytosine residues, is called DNA methylation and is generally found in CpG islands within the regions of gene promoters. DNA methyltransferases (DNMTs) catalyze this process, which is important in the regulation of gene expression, genomic stability as well as cell differentiation. DNA methylation in normal cells assists in silencing repetitive sequences, genomic instability prevention and appropriate control of gene transcription.

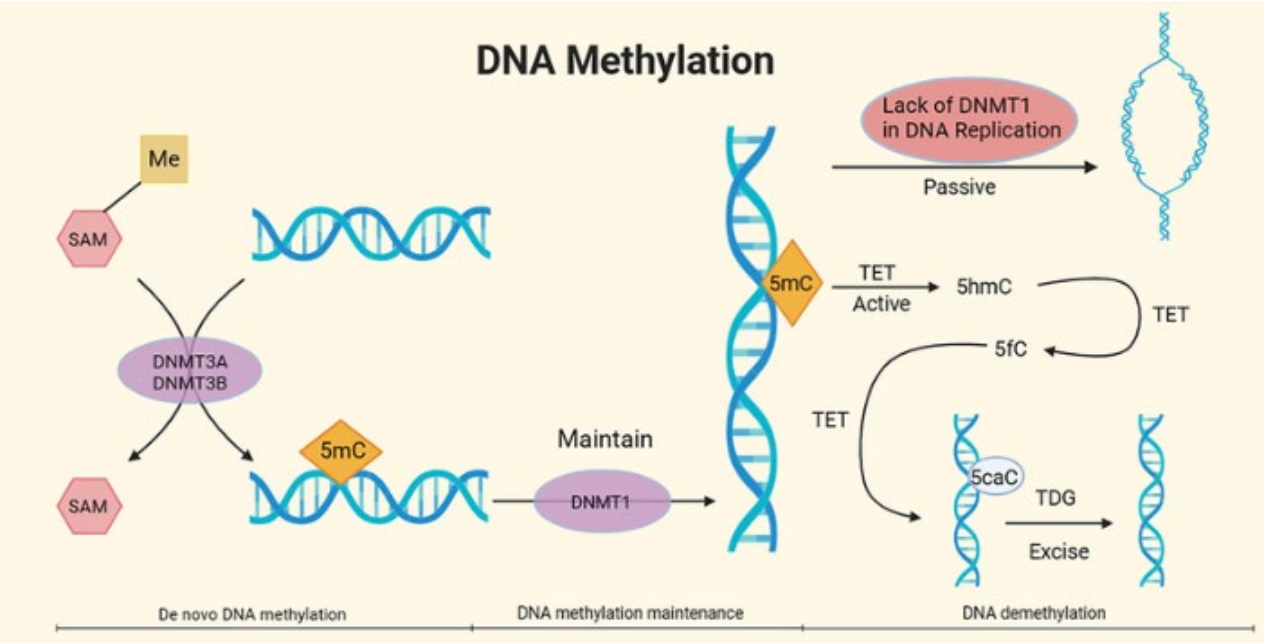

Figure 3: DNA Methylation[27]

Aberrant patterns of DNA methylation are signature disease progressions in breast cancer and are involved in tumor initiation as well as metastasis. These perversions may be broadly classified into two categories:

1. **Hypermethylation of Tumor Suppressor Genes**

Tumor suppressor genes containing cell cycle checkpoint genes, DNA repair genes, and apoptotic genes may be hypermethylated at the promoter. This results in transcriptional silencing, which virtually eliminates important mechanisms that ensure uncontrollable proliferation. Hypermethylation of tumor suppressor genes is associated with earlier development of mammary tumor as well as greater number of tumors in animal models which shows that epigenetic silencing is a direct cause of tumor progression and formation.

2. **Hypomethylation of Oncogenes**

On the other hand, hypomethylation is the process where the DNA regions which are normally methylated are deprived of their methyl groups. Oncogenes are prone to this loss in order to overexpress, proliferate more and become more aggressive. The research on animals indicates that hypomethylation of oncogenes in mammary epithelial cells facilitates the growth of the primary tumors and the metastatic spread, thus relaxing the contribution of hypomethylation to the progression of the breast cancer.

Therapeutic Implications in Animal Models

The research of DNA methyltransferase inhibitor (DNMTis) has been carried out in preclinical animal models as a way of reversing aberrant patterns of methylation[28]. These inhibitors are able to demethylate hypermethylated tumor suppressor genes, which are turned back to their expression and at the same time, downregulate the expression of oncogenes. The major results in animal research are:

- Normalization of mammary tumors gene expression patterns.
- Inhibition of tumor proliferation and tumor shrinkage.

- Blocking of the spreading of malignancies to other body parts like the lungs.
- Enhancement of universal survival in preclinical models.

These results are good indications that DNA methylation pathway is a promising treatment option in breast cancer. Additionally, animal models enable the researcher to investigate the use of combinatorics, including DNMT suppressors with chemotherapeutic medicine or other epigenetic regulators to improve effectiveness and decrease cancer malignancy.

Table 2: Functional Impacts of DNA Methylation Alterations in Breast Cancer Animal Models[29]

Mechanism	Effect on Gene Expression	Consequence on Tumor Progression
Hypermethylation of tumor suppressor genes	Silencing of critical protective genes	Tumor initiation, uncontrolled growth, early tumor onset
Hypomethylation of oncogenes	Overexpression of oncogenic drivers	Enhanced proliferation, invasiveness, metastasis
DNMT inhibition	Reactivation of silenced tumor suppressor genes	Suppression of tumor growth, reduced metastasis, improved survival

Key Insight

Animal model research findings indicate that DNA methylation is an active and reversible epigenetic process, which has direct effects on breast cancer development, progression and metastasis. Hyper- or hypomethylation may cause tumor development, whereas treatment with DNMT inhibitors can reestablish the normal functioning of genes and greatly prevent tumor development. This highlights the curative opportunity of DNA methylation regulation in preclinical trials of breast cancer and gives a base to future translational investigations.

3.2. Histone Modifications

Histone modifications refer to a collection of post-translational modifications of histone proteins such as acetylation, methylation, phosphorylation, ubiquitination and SUMOylating[30]. These changes control the chromatin structure, modulating the level of wrapping DNA around histones that, in turn, regulates accessibility of transcription factors to DNA. In breast cancer, histone modification dysregulation is one of the major mechanisms, which results in the abnormal expression of genes, uncontrolled cell expansion, and development of a tumor.

Mechanisms and Roles in Breast Cancer

1. **Histone Acetylation:** Acetylation is a process that is done by the histone acetyltransferases (HATs) and this action neutralizes the histone positive charges thus creating a more relaxed and open chromatin structure. This open chromatin permits entry of transcription machinery to DNA, which usually results in gene expression. In breast cancer, acetylation of the promoters of tumor suppressor genes might be increased to restore gene expression which is lost[31].
2. **Histone Deacetylation:** The histone deacetylases (HDACs) strips acetyl groups constricting the chromatin and suppressing transcription. HDAc overexpression or

hyperactivity in breast cancer causes silencing of essential tumor suppressor genes, thus increasing tumor growth and survival.

3. **Histone Methylation:** Histone methylation may be performed on either lysine or arginine residues and may either activate or suppress the transcription of a gene, depending on the location and extent of the methylation. As an illustration, the H3K4 trimethylation typically activates transcription, and the H3K27 trimethylation usually suppresses the expression of the genes. The imbalance in histone methylation patterns in the breast cancer may modify the oncogene and tumor suppressor expression thus helping to cause the malignancy.

Animal Model Insights

The animal research has played a critical role in proving the therapeutic benefit of histone targeting in breast cancer.

- In mammary tumor models, HDAC inhibitors are able to silence silenced tumor suppressors, slow tumor cell proliferation, cause apoptosis and slow tumor growth.
- Methylation of histones in transgenic or xenograft mouse models is inhibited, and the gene expression pattern is restored to normal, as well as the metastatic expansion is restrained.

These interventions demonstrate that histone-modifying enzyme is very dynamic and reversible, and is, therefore, an attractive target of epigenetic therapy in preclinical breast cancer research.

Table 3: Functional Impacts of Histone Modifications in Breast Cancer Models[32]

Modification	Effect on Chromatin	Impact on Tumor Progression
Acetylation	Open chromatin, gene activation	Promotes tumor suppressor expression, reduces malignancy
Deacetylation	Closed chromatin, gene repression	Silences tumor suppressors, increases tumor growth
Histone methylation	Context-dependent (site-specific)	Can either promote oncogene expression or repress tumor suppressors
HDAC/Methyltransferase inhibition	Restores normal chromatin and gene expression	Suppresses tumor growth, reduces metastasis, improves survival

Histone modifications play a major role in regulation of genes and chromatin. The occurrence of abnormal acetylation/methylation pattern in breast cancer interferes with regulation of normal transcriptional programs and contributes to uncontrolled cancer growth, invasion and metastasis. The therapeutic value of the epigenetic modulators on breast cancer is evidenced by the fact that animal models show that the histone-modifying enzyme targets can restore normal regulation of genes and suppress tumor progression significantly.

3.3. MicroRNAs

MicroRNAs (miRNAs) are non-coding, small, non-coding endogenous RNAs of about 22 nucleotides, which control the post-transcriptional level of gene expression. They mainly act through the binding to complementary sequences in the 3'-untranslated regions (3'-UTRs) of

target messenger RNAs (mRNAs) leading to the degradation of the mRNA or translational repression. It is through this mechanism that miRNAs are able to regulate numerous cellular functions such as proliferation, differentiation, apoptosis, and the responses to stresses[33]. The role of miRNAs dysregulation in tumorigenesis and pathogenesis of a variety of cancers, including breast cancer, is becoming increasingly accepted. In this regard, miRNAs may act as OncomiRs (oncogenes, or oncolytic), which enhance cancer development, or as tumor suppressors, which inhibit the malignant transformation.

Mechanistic Role of miRNAs in Breast Cancer

1. Oncogenic miRNAs (OncomiRs)

Oncogenic miRNAs are commonly overexpressed in breast cancer, where they contribute to tumor initiation, growth and metastasis, through down-regulation of expression of important tumor suppressor genes. For example:

- miR-21 is among the most popular OncomiRs of breast cancer. High expression levels of miR-21 have been associated with the amplified proliferation, suppression of apoptosis, and amplified invasiveness of breast cancer cells. Mechanically, miR-21 suppresses tumor suppressor proteins, including P53 and PDCD4 which play a critical role in cell cycle regulation and apoptosis.
- miR-155 is also an OncomiR that suppresses genes in DNA repair, immune surveillance and cell cycle regulation. Increased miR-155 expression in cancer cells causes genomic instability, increased migration of tumor cells and metastasis[34].

The direct evidence of the functional role OncomiRs play in breast cancer is provided by animal studies. The example is that the mice that are genetically engineered to over-express miR-21 in the mammary epithelial cells spontaneously form mammary tumors at an accelerated time with the augmented tumor proliferation and metastatic foci on the distant organs. On the same note, transgenic mouse models that have been over-expressing miR-155 promote tumor invasiveness as well as metastatic burden, which substantiates the pro-tumorigenic effects of these OncomiRs in vivo.

2. Tumor Suppressor miRNAs

The tumor suppressor miRNAs are generally down-expressed in the circumstances of breast cancer, and their absence eliminates an important post translation gene control mechanism, which usually curtails the oncogenic processes[35]. Key examples include:

- miR-34a is a previously characterized tumor suppressor that suppresses the expression of several oncogenes that mediate proliferation, survival, and metastasis. The loss or silencing of miR-34a in the tumor cells in the breast causes unrestrained oncogenes, which supports the expansion and spread of the tumor.
- RAS and HMGA2 are examples of genes of the Let-7 family miRNAs, and their decreased expression in breast cancer is linked to tumor aggressiveness and adverse outcomes.

Tumor-suppressive role of these miRNAs is also confirmed by animal models. There have been reports of miR-34a restoring tumor volume, proliferation, and apoptosis and limiting the extent of tumor metastasis in breast cancer xenografts or in transgenic mice, making miRNAs such as

miR-34a promising tumor suppressors. Equally, the upregulation of the Let-7 family members in the preclinical models inhibits the oncogenic signaling and retards tumor growth.

Therapeutic Modulation of miRNAs

MiRNA expression is easily reversible, and thus dynamic, which makes them good therapeutic targets. In animal models, preclinical studies have been done on two significant approaches:

1. **Inhibition of OncomiRs**
   - Synthetic anti-miRNA oligonucleotides or miRNA sponges have the potential to bind OncomiRs and inhibit them (miR-21 or miR-155).
   - In animal models, these inhibitors have been found to lower the oncogenic signaling, repair the tumor suppressor gene expression, diminish tumor growth, and metastasis.
   - The effectiveness of OncomiRs inhibition is proved by the finding that the anti-miR-21 therapy of mice with mammary tumors leads to reduced tumor mass, the reduction in the number of metastatic nodules, and the extension of the survival.
2. **Restoration of Tumor Suppressor miRNAs**
   - On the concept that the restoration of Tumor Suppressor miRNAs can suppress tumor growth, the experiment-initiated treatment with miRNAs and showed that tumor growth was suppressed.
   - Synthetic miRNA mimics or Viral vectors can be used to replenish the tumor suppressor miRNAs that are downregulated in breast cancer.
   - In preclinical research, pre-treatment of tumor-bearing mice with miR-34a or Let-7 mimics decreases tumor growth, induces apoptosis, and prevents the metastatic spread, which is a good indication that miRNA replacement therapy is an effective method of controlling the progression of breast cancer.

These treatment approaches demonstrate that miRNAs may be used as diagnostic biomarkers, as well as intervention targets to control the main oncogenic or tumor-suppressive pathways. Animal research is especially vital here due to the opportunity to test miRNA delivery, stability and functional impact in vivo that is necessary before clinical translation.

Table 4: Functional Impacts of miRNAs in Animal Models[36]

miRNA Type	Target Genes	Observed Effect on Tumor Behavior
Oncogenic (OncomiRs)	Tumor suppressor genes	Promotes tumor proliferation, invasion, and metastasis
Tumor Suppressor	Oncogenes	Reduces tumor growth, inhibits invasion, suppresses metastasis
Therapeutic Modulation	Oncogenes or tumor suppressors	Restores normal cellular pathways, reduces tumor burden, improves survival

Integration with Epigenetic Regulation

miRNAs do not work alone and the expression and functions of miRNAs are tightly linked to other epigenetic processes including DNA methylation and histone modification. For example:

- DNA methylation may suppress miRNA tumor suppressors causing enhanced oncogene expression.
- Histone modifications may be able to change miRNA promoter region chromatin accessibility, so that they can be altered to increase or decrease their transcription.
- On the other hand, the miRNAs themselves may also control the epigenetic modifiers and the loop becomes rather intricate. This interaction indicates that control of gene expression in breast cancer is multilayered and that the use of a combination of epigenetic and post-transcriptional pathways would be more effective than targeting one pathway.

Significance of Animal Studies

Animal models are significant in explaining the role of miRNAs in breast cancer since they:

- Facilitate in vivo verification of miRNA role in tumor development, progression and metastasis.
- Offer an opportunity to test miRNA-based therapeutics, such as delivery, stability, and off-target effect.
- Enabling the research of miRNA interactions with other epigenetic and genetic factors, including RAD51C mutations or dysregulation of BAF complexes, to discover concerted actions on tumor biology.

These models have shown that alterations in miRNA expression can cause a major change in the tumor behaviour and this gives a strong justification to include miRNA-based interventions in the breast cancer treatment of the future.

MicroRNAs are an influential and multifaceted epigenetic process that tunes the expression of genes in breast cancer. Tumor initiation, progression and metastasis are dysregulated by miRNAs whether via OncomiRs overexpression or tumor suppressor miRNA loss. Animal experiments have been able to give credible evidence that miRNA modulation therapy can successfully manage both breast tumor growth and metastatic progression and thus it has offered an exciting approach in the future therapeutic intervention strategy. In addition, miRNA-based therapies applied in conjunction with other epigenetic therapies could lead to the development of multi-targeted, precision therapies in the management of breast cancer.

4. DISCUSSION

The development of breast cancer is a complex multifactor process that is based on a complex interaction of genetic mutations and epigenetic changes[37]. Although genetic defects including RAD51C mutations and BAF complex regulation lead to impaired DNA repair and chromatin regulation, epigenetic defects, such as DNA methylation, histone alterations, dysregulation of microRNAs, etc., further change the patterns of gene expression, which govern cell proliferation, differentiation, and metastasis. The use of animal models has played a significant role in dissecting these processes to give important clues about tumor occurrence, progression, and potential to metastasize. This discussion has interpreted these findings, assessed its implications, provided gaps existing on the current research and provided future research directions to translate these preclinical findings into effective therapeutic approaches.

4.1. Interpretation and Analysis of Findings

The results of this review highlight the complex nature of the role played by both genetic and epigenetic factors in the progression of breast cancer. Genetic changes including mutation in RAD51C and dysfunction in BAF chromatin reorganizing complex illustrate how the disturbances in DNA mending and chromatin framework integration cause tumor development, progression, and dissemination. The mutations in RAD51C affect homologous recombination and cause genomic instability, chromosomal aberration and tumor progression in mice. On the same note, the mutation of the BAF complex affects chromatin remodeling, thereby affecting aberrant transcription of oncogenes and tumor suppressor genes, facilitating unregulated cell proliferation and metastatic potential[38].

At the epigenetic level, DNA methylation, histone alterations, and microRNAs all play a role in regulating the pattern of gene expression essential in the homeostasis of cells. It has aberrant patterns of DNA methylation which include hypermethylation of tumor suppressor genes and hypomethylation of oncogenes which have a direct effect on tumor initiation and progression. The additional modification of the histone's changes chromatin accessibility, which regulates the transcription of genes associated with proliferation, apoptosis, and metastasis. The deregulation of the histone acetylation or methylation in animal models causes the gene expression and increase in tumor aggressiveness. MicroRNAs are fine regulators of post-transcriptional gene regulation, oncogenic miRNAs enhancing tumorigenesis and tumor suppressor miRNAs suppressing malignancy. In studies involving animals, it is always demonstrated that therapeutic alterations in miRNAs (either suppression of OncomiRs or reinstatement of tumor suppressor miRNAs) can substantially reduce tumor growth and metastasis.

The combination of these results highlights the synergistic relationship between the action of genes and the action of epigenetics. Where genetic defects are amplified by epigenetic alterations, genetic mutations interfere with DNA repair pathways and chromatin architecture, and in general, genetic defects exert their effects. In vivo models have especially been used to elucidate such interactions in animal models which can be controlled in an in vivo environment and then give mechanistic information that would otherwise be hard to receive in human experiments alone.

4.2.Implications and Significance

These results have important implications on both fundamental studies and therapy development. To begin with, the elucidation of the functions of RAD51C and BAF complex modifications demonstrates the possibilities of the therapeutic approach based on the targeting of DNA repair and chromatin remodeling's processes. As an example, homologous recombination-deficient tumors can be specifically vulnerable to DNA damage-targeting agents or synthetic lethality strategies, including PARP inhibitors. On the same note, interventions focused on the restoration of the correct dynamics of chromatin in BAF-deficient tumors can possibly inhibit abnormal transcriptional programs that facilitate tumor growth[39].

Dynamic and reversible targets of epigenetic modifications are therapeutic. The ability to modulate DNA and histone modifications and miRNA expression in animal models successfully demonstrates that it is possible to design therapies that could be used to restore normal gene expression patterns. The interventions aimed at those epigenetic mechanisms, as

a therapeutic tool, would be complementary to the already existing genetic-based therapy, and the multi-pronged treatment of breast cancer development.

Also, the results highlight the possible value of the genetic and epigenetic changes in biomarkers. RAD51C mutations, dysregulation of BAF complex, signature patterns of DNA methylation, histone modification, and miRNA expression might all be used as predictive/prognostic biomarkers and help to detect disease early, stratify risks and tailor treatment plans.

4.3.Gaps in Current Research

Although numerous things can be learned through animal research, there are a number of gaps. To begin with, it is still difficult to translate the results of animal models to the clinical setting in humans since interspecies variations of the breast tissue structure, the tumor microenvironment and gene expression patterns differ. Second, much of the literature deals with single-gene or single-pathway studies which might not be fully representative of the complexity and interrelationship of genetic and epigenetic networks in human breast cancer.

The other knowledge gap is the long-term consequences and safety of epigenetic therapies. Although animal research demonstrates their promising tumor suppression, the off-target effect, the reprogramming of normal tissues at an epigenetic level, and long-term effects are not fully researched[40]. Also, miRNA-based therapies are effective in preclinical models but delivery, stability, tissue specificity and miRNA-based therapies are problematic, which must be resolved prior to clinical use.

Lastly, the existing studies tend to be insufficient in incorporating multi-omics data such as genomic, epigenomic, transcriptomic and proteomic data. There is still a need of a more holistic view of the interactions between genetic and epigenetic changes in the progression and heterogeneity of tumors and resistance to therapy.

4.4.Future Research Directions

In order to fill the current gaps, the further research should concentrate on the following directions:

- **Creation of improved animal models:** The use of patient-derived xenografts (PDX) and genetically engineered models that are highly similar to human subtypes of breast cancer will enhance the transparency of preclinical results. Tumor heterogeneity could be better represented with models that combine several genetic and epigenetic changes at the same time.
- **Multi-omics integration:** Integration of genomic, epigenomic, transcriptomic and proteomic data in animals will also give the systems-level picture of breast cancer development and offer new potential therapeutic targets.
- **Combination therapies:** Future researches should consider a combination approach that would simultaneously address genetic defects (e.g., RAD51C deficiencies) and epigenetic dysregulation (e.g., DNA methylation, histone modifications, miRNAs) to increase the efficacy of therapeutic approaches and to lower resistance.
- **Translational studies:** It is important to bridge the animal model to the clinical application. The pharmacokinetics, biodistribution, and safety of new epigenetic

modulators and miRNA-based therapies should be evaluated through preclinical investigations to help ease clinical translation.

- **Biomarker development:** Future studies need to confirm the predictive and prognostic biomarkers that are genetic and epigenetic biomarkers predicting breast cancer progression and response to treatment. Animal models and human cohort longitudinal studies will be significant in order to establish the reliability and clinical significance of these markers.
- **Mechanistic studies:** Intensive studies should be done on the interaction between genetic mutations and epigenetic changes to gain a deeper insight into the biology of breast cancer, especially how such interactions contribute to metastasis and resistance to therapies.

It has been discussed that breast cancer development is a complex interaction of genetic and epigenetic changes, with RAD51C and BAF complex mutations, DNA methylation changes, histone modifications, and miRNA disruption playing key roles. Animal models are useful to give invaluable critical mechanistic understanding and preclinical validation of potential therapeutic strategies. The proposed research will seal the existing gaps by applying sophisticated models, multi-omics studies, and translational studies that will eventually guide precise treatment of breast cancer considering both genetic and epigenetic pathways, and eventually improve patient outcome.

5. CONCLUSION

The complex interaction of genetic and epigenetic events contributes to the development of breast cancer and the progression of tumor cells, which have a significant impact on tumor formation, tumor growth, and tumor metastasis. The genetic mutations, which include mutation of RAD51C and disruption of the BAF chromatin remodeling complex, disrupt DNA repair and stability of the chromatin, whereas epigenetic changes, including DNA methylation, histone alteration, and microRNA dysregulation, dynamically control the expression of genes, which favor tumor aggressiveness and metastatic ability. The present review indicates the role of genetic and epigenetic approaches in understanding the overall biology of breast cancer and the potential of the translation of the studies into a clinical practice through targeting of these processes. The animal model experiments are important in preclinical information but there still exist challenges in extrapolating the findings to clinical human trials. The next round of research ought to be on the development of advanced models, the use of multi-omics and precision medicine programs including combining genetic and epigenetic markers. Through this, it is possible to achieve new therapeutic opportunities, including the manipulation of DNA repair processes, repair of the chromatin remodeling processes, and efficacy of epigenetic regulators or microRNAs. Eventually, the further development of this area leads to a better patient-specific treatment approach, increased survival rates, and decreased mortality rates of breast cancer.

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