REVIEW
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Diseases & Research

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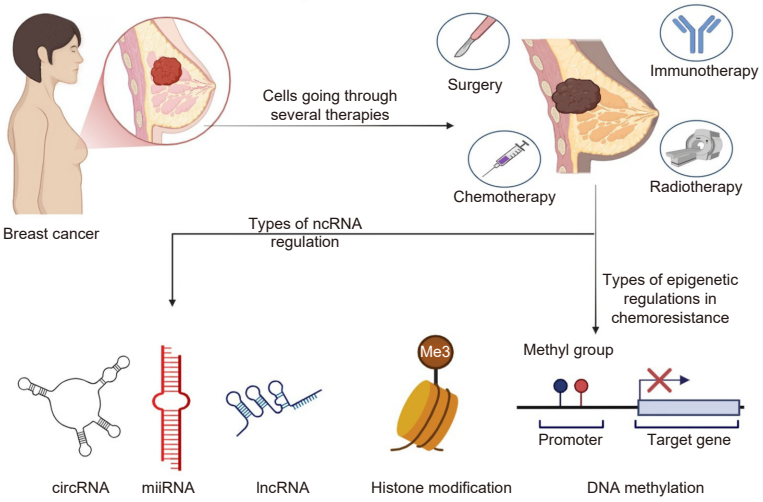
Graphical abstract



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Epigenetic Regulation in Chemotherapy Resistance of Breast Cancer: Role of Chromatin Modifications and Non-Coding RNAs in Chemotherapeutic Resistance

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Abstract: Chemotherapy is the main systemic treatment approach to breast cancer. But chemotherapy resistance is one of the main drawbacks in breast cancer treatment nowadays. In this respect, the role of epigenetic control and non-coding RNAs leading to the development of chemoresistance will be presented here. The information about epigenetic changes in each cell, particularly concerning drug metabolism, DNA repair, apoptotic gene expression, and drug efflux, enhances the effectiveness of drugs by increasing chemosensitivity. This is achieved through mechanisms such as DNA methylation, histone modifications, and chromatin remodeling. At the same time, non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), also regulate these pathways by targeting key genes of the chemosensitivity network. In this review, epigenetic and non-coding RNA-based chemoresistance mechanisms are described with a specific focus on chromatin-based mechanisms and miRNAs, lncRNAs, and circular RNA. Like, overexpression of miR-34a and miR-125b shows reduced resistance in breast cancer cells, with the association of different drugs like docetaxel and paclitaxel. Additionally, upregulation of miR-125 targets the UTR (Untranslated region) of the *p53* gene to inhibit translation. In the EMT pathway, overexpression of miR-21 and miR-155 resulted in suppression of different genes, promoting tumorigenesis, metastasis, etc. On the other hand, lncRNAs like H19 induce autophagy and inhibit breast cancer cells from undergoing the EMT (Epithelial-to-mesenchymal transition) pathway. Another lncRNA, HOTAIR expression helps to promote tumor growth, invasion, and other processes. It also suggests therapeutic methodologies directed at the epigenetic regulators and non-coding RNAs to overcome chemoresistance. Perseverant research on these regulatory mechanisms might help come out with personalized and streamlined treatment protocols in the management of breast cancer.

Keywords: Cancer; Chemotherapy resistance; Chromatin modifications; Epigenetic regulation; Non-Coding RNAs.

Introduction

The World Health Organization (WHO) describes breast cancer as one of the most common solid tumor malignancies; cases of breast cancer, which are newly reported, are more than one million annually, and approximately 40,000 deaths related to breast cancer are reported each year worldwide, thus making it a serious public health problem. The prevalence of the disease in its lifetime has gradually been on the rise. Despite the considerable progress, metastatic breast cancer (MBC) is still not curable, and the level of mortality remains substantial. The growing burden of MBC emphasizes the need to continue research and design better treatment plans to increase the quality of life of patients with advanced MBC[1].

To date, chemotherapy remains the main systemic treatment approach to breast cancer. The opposition to this treatment is a significant barrier, and it occurs in two ways: primary (or innate) resistance, which occurs before exposure to drugs, and acquired resistance, which occurs after the administration of chemotherapy. Relapses in patients treated using first-line anthracycline-based or taxane-based therapies often display cross-resistance to both drugs and thus cease further treatment options. When the resistance to anthracyclines or taxanes is established, the treatment options are limited even further. Commonly used as a mono therapy or in combination therapy, capecitabine can lead to only a 25% response, as well as it can also lead to resistance at the same time[2,3].

Epigenetic alteration is an essential element in the development and advancement of breast cancer. The science of studying non-genomic variability in gene expression is called epigenetics. These alterations can switch off gene transcriptional activity and thus change cell behavior, a trait of special relevance to cancer biology. There are three major regulatory processes of the epigenome, including DNA methylation, histone regulation, and non-coding RNA (ncRNA) activity. Such processes are the key to controlling the expression of genes by controlling the pathways of cellular signals, the cell cycle, and apoptosis. Moreover, they affect the expression of genes that play a role in the immune re-

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Received 1 June 2025; Revised 23 June 2025; Accepted 13 August 2025; Available Online 5 September 2025
DOI: 10.54457/DR.202503004

sponse, thus, cellular immunity[4–6].

Recent studies have emphasized the importance of DNA methylation, modification of histone, and ncRNAs in breast cancer treatment. The current review thus provides an in-depth explanation of these mechanisms, clarifies their action, and outlines their process.

Literature Selection Methodology

To carry out an electronic searching of the database, a generalized electronic database search in PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar was conducted, and the date retrieval was between the inception of each study to December 2024. The combination of predefined searches using Medical Subject Headings (MeSH) and free-text keywords were used, i.e., a combination of the following keywords and terms such as chemotherapy, cancer, resistance, epigenetic regulation, and noncoding RNAs connected with the use of the Boolean operators AND, OR, and NOT to achieve maximum coverage without compromising on specificity. Title and abstracts were screened at first by two independent reviewers based on their expertise in this field of study and experience. Methodological rigor, relevance, and reporting completeness were then appraised in full text; any disagreement was solved by consensus or by referring to a third reviewer whenever necessary. Further search was done in high-impact journals, well-designed experiments, sufficient sample size, and sufficient statistical analogy to complete the research on that matter, along with a manual search of article references lists of related articles to add to the previously unidentified articles that did not pop up in the research using the database searches.

Mechanism of Resistance to Chemotherapy Agents Utilized in Breast Cancer

Drug resistance, otherwise known as chemoresistance, is the inability of a tumor to respond to a treatment procedure following exposure to a chemotherapy agent. The condition has been an essential contributing factor to chemotherapy failure in various oncologic settings. Numerous exogenous factors and endogenous factors can trigger chemoresistance. Among the external determinants are pH, hypoxia, paracrine signaling, and cancer-adjacent cell-cell interactions, and among the internal determinants, heterogeneity within tumors, cancer stem-cell subpopulations, and epigenetic alterations. Chemoresistance phenomenon in breast cancer cells involves varied mechanisms that include disruptions to drug absorption, transport, and ejection across the cell membrane; overexpression or elevation of drug transporter proteins; triggering of DNA repair pathways; the continued presence of cancer stem-cell phenotypes; engagement with the tumor microenvironment; and epithelial-mesenchymal transition (EMT). Although attempts to re-sensitize established, classic chemotherapeutic agents and to address chemoresistance in breast cancer have been made repeatedly, the present results are modest. Greater knowledge of resistance pathways, together with the optimization of treatment strategies, thus becomes fundamental to promote clinical efficacy, as well as to manage the outstanding issue of chemoresistance[7].

Multidrug Resistance (MDR) in Chemotherapy

Multidrug resistance (MDR) is a clinical phenomenon where cancer cells fail to die completely after successful chemotherapy, hence developing the ability to resist cancerous drugs. The phenomenon is regulated by the functional mechanism of the membrane transporter proteins, especially the ones in the superfamily of ATP-binding cassette cation-coupled transporter (ABC transporter). The classic, P-glycoprotein (or MDR1), produces a protein that can bind cytotoxic chemotherapy agents directly and move these substances to the extracellular environment via ATP-driven processes. Several studies have proved that the 7q11.2-21 chromosome becomes amplified and that the P-glycoprotein (P-gp) in the *abcb1* gene is fused with the expression of *slc25a40*, the upstream gene, thus leading to hyperexpression of P-glycoprotein and eventual drug resistance of cancer cells in breast cancer. The up-regulation of the ABC transporter family genes is one of the outstanding forms of acquired drug resistance in cancer chemotherapy. Indicatively, in breast cancer, the P-glycoprotein efflux pump channels against cytotoxic chemotherapy and is further linked to aberrant DNA methylation[8,9].

DNA Damage Response (DDR) in Chemotherapy

DNA damage response (DDR) is a cascade signal reaction that activates the sensor molecular system to repair DNA damage. It can reverse neoadjuvant chemotherapy drug-induced damage, leading to drug resistance. *tdp1* is a significant gene in breast cancer cells and participates in DDR repair. Overexpression of miR-211 can inhibit *tdp1* expression. The DDR pathway is closely related to PARP-1 inhibitors have been used in clinical applications. The combination of PARP-1 inhibitors and neoadjuvant chemotherapy drugs can enhance drug efficacy and prevent drug resistance in breast cancer patients. Topoisomerase inhibitors are another group of neoadjuvant chemotherapeutic drugs that induce drug resistance via DNA damage repair. Topoisomerases belong to two classes, Topo I and Topo II, which are vital in DNA replication. Topoisomerase inhibitors have a potent clinical effect, although drugs that target a single topoisomerase are susceptible to resistance. Research has implicated drug resistance through the overexpression of a second DNA topoisomerase. DDR helps to maintain genomic stability in cancer treatment, which is why we need to continue investigating to create specific DDR inhibitors in case we are to reduce the resultant cytotoxic effects on normal tissues and cells[2,10].

Multidrug resistance occurs when tumor cells can circumvent therapeutic agents, and a number of cellular detoxification enzymes help in this process, e.g., Aldehyde dehydrogenase (ALDH), DNA topoisomerase, protein kinase C, dihydrofolate reductase, glutathione, and glutathione S-transferases (GST). The negative effects of GST on drugs are stated to harm drugs both directly and indirectly; directly by inactivating the mitogen-activated protein kinase (MAPK) gene in the RAS-MAPK signaling pathway, and indirectly inactivating other antitumor agents like cyclophosphamide, melphalan, cisplatin, and adriamycin. GST-pi also enhances the pace of transformation and metabolism of antineoplastic drugs, and it reduces the cellular effective drug concentrations and efficacy. Moreover, consistent with m9sf3, a

transmembrane-9 superfamily protein, another one, tm9sf3, is found upregulated in paclitaxel-resistant breast cancer cells and contributes to adhesion, phagocytosis, and innate immunity. An anti-apoptotic inhibitor, survivin, is also overexpressed in such cells and mediates tumor recurrence, thus contributing to the multidrug resistance. Moreover, there are other proteins like kinase C (PKC), DNA polymerase, and O^6-Alkylguanine-DNA alkyltransferase (AGT) associated with MDR of cancer cells through changing the inherent resistance of tumor cells with a mechanism that involves changing the membrane transport, DNA repairing, and transcription of genes[11].

Epithelial-Mesenchymal Transition in Chemotherapy

Potentially, epithelial-mesenchymal transition (EMT) is the process of converting epithelial cells into a more mesenchymal structure involving the loss of cell-cell attachment, loss of cell polarity, and gaining migrating and invasive phenotypes. This process is initiated by changes in proteins and transcriptional reactions to extracellular signals. Excess interstitial proteins like N-cadherin and vimentin can lower the intercellular adhesion, exhibiting high migration and invasive potential of breast cancer cells, which are associated with drug resistance. This process, whereby epithelial cells are converted to have the characteristics of mesenchymal cells, a key feature of EMT, is controlled by two interdependent pathways that is the MAPK/ERK cascade and the TGFβ-SMAD system. These two pathways contribute to resistance to anticancer agents in clinical terms. The simultaneous inhibition of both cancer-inducing pathways has also been reported upon pharmacological targeting of the CDK4/6 kinase complex, which stalled tumorigenic progression and reversed resistance in breast cancer cell lines. The e-cadherin gene (*cdh1*) is extremely elevated in the epithelial cells and extremely reduced in the mesenchymal ones, hence serving as the most critical constituent of the epithelial-mesenchymal transformation (EMT) process. The downregulation of *cdh1* expression helps to drive the phenotypic switch of the non-invasive to invasive tumour cells, which asserts the pivotal involvement of *cdh1* in tumour invasion and metastasis. Mesenchymal cancer cells, with their increased resistance to chemotherapy drugs, often appear in breast tumors and are closely linked to the cancer stem cells (CSCs). It can be concluded that the combination of EMT-related inhibitors with neoadjuvant chemotherapeutic regimes in the adjuvant treatment of breast cancer is likely to help avoid the EMT-based chemo-resistance effect and enhance patient outcomes[2,8].

Microenvironment of Tumors (TME) in Chemotherapy

The tumor microenvironment (TME), as a complex system, is comprised of neoplastic cells, elements of the extracellular matrix, stromal cells, immune cells, and cytokines. Most tumor cells exist in hypoxic and acidic environments due to their metabolic features, not just distinctive structural characteristics. TME plays a core role in resistance to breast cancer cells, primarily since the cancer cells frequently have poor access to oxygen, thus rendering them unresponsive to drugs. The stem cell features of cancer stem cells usually rely on hypoxia and hypoxia-induced factor (HIF). Hypoxia is a characteristic of the tumor microenvironment, and it also plays a critical role as a determinant in cancer development. It stimulates cell signaling pathways, giving the CSC phenotype, angiogenesis, drug efflux, senescence/apoptosis, metastasis, and genomic instability. Hypoxia also makes drugs ineffective because it causes the inversion of the extracellular PH gradient. The extracellular acidity (pH 6.5) is a characteristic of cancer cells that traps the weak-base anticancer agents and distorts the distribution of drugs. Proton pump inhibitors are, therefore, established as an indisputable treatment intervention capable of returning extracellular pH and countering hypoxia-induced drug resistance. Antitumor drugs, cell growth, metastasis, and drug resistance are impacted by the microenvironmental pH. In breast cancer, drug resistance is completely mediated by TME, and it is one of the most difficult clinical challenges. Whereas they showed promising outcomes in several tumors in current clinical trials, they remain unpopular in the neoadjuvant chemotherapy treatment of breast cancer. As an acidic milieu in TME has been declared as a treatment target, researchers have presented strategies seeking to modify such microenvironment through interventions, hence providing an interesting, risk-free way of avoiding drug resistance[10,12].

Epigenetic Modifications in Drug Resistance

Epigenetic alterations are the main etiology of breast cancer. Epigenetics is a term that is used to describe the epigenetic aspect of the study of proteins and reactions capable of maintaining different levels of gene expression within identical DNA sequences. The epigenetic mechanisms include gene transcription control, genomic stability, regulation of proper cell growth, development, and differentiation. The fact that epigenetic modifications do not alter the genetic material or rewire the genetic information is their most important feature. DNA methylation, Histone modification, and non-coding RNAs are the three main processes that are understood. In the cellular and tissue environment, epigenetic processes have a significant impact on gene transcription and expression. Epigenetic changes take on special importance in tumour installment and development in the oncological context. Several epigenetic alterations have also been observed in carcinogenesis; among them are genome-wide hypomethylation, global change in historically patterned histone deposition, and non-coding RNA impairment. The changes in epigenetics, which are reversible compared to genetic mutations, have also emerged as a very powerful modality in re-instituting acquired drug response through reprogramming of the epigenomics that is specific to cancer. The disparities in patient response to therapeutic doses could also be explained by the differences in the epigenetic processes that are the basis of oncogenic development and tumour progression[4,5].

Methylation and Demethylation of DNA in Drug Resistance

DNA methylation is a type of epigenetic modification that is common in bacteria and plants. DNA methylation is one of the

processes to permanently silence genes, and this is done during DNA replication. DNA methylation is a covalent process in eukaryotic cells that results in modification at the 5' end of the CpG dinucleotide in the cytosine ring. The donor of the methyl group is S-adenosyl-methionine, which results in 5-methylcytosine (5mc). DNA methylation is a process that is carried out by enzymes known as DNA methyltransferase or DNMTs (Fig.1). There are three currently active DNMTs: DNMT1, DNMT3A, and DNMT3B. Although the two DNMTs, DNMT3A and DNMT3B, play the role of establishing the methylation of DNA, DNMT1 is estimated to be the one in charge of maintaining the existing level of methylation[12,13].

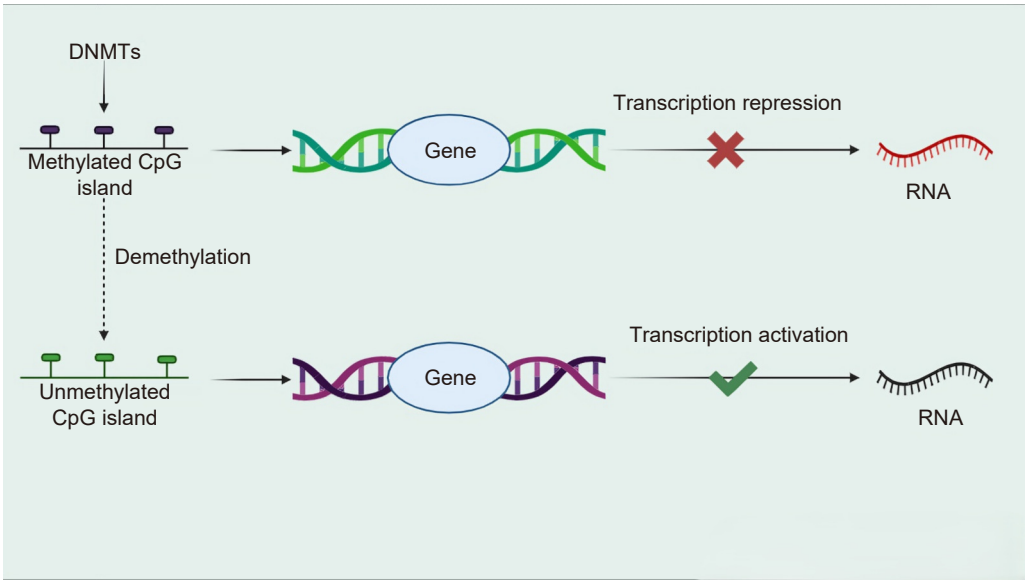

Fig. 1. Process of DNA methylation and demethylation.
In this illustration, it is shown that if the CpG islands get methylated, the gene transcription will be affected, and if the islands get demethylated, the transcription will go on further. DNMTs help in DNA methylation, and TET enzymes help in the DNA demethylation process. This illustration was created using BioRender software (https://BioRender.com). Source: [14,15].

The alteration can either inhibit the binding of a transcription factor and the binding sites or bind to the methylation-binding domain proteins, which contribute to gene repression. This change has the potential to reduce gene transcription activity. In the context of mammalian cells, the most prevalent of all the DNA methylated forms is the CpG dinucleotide. Nevertheless, CpG sites do not occur evenly distributed within the genome; instead, CpG-rich sites are usually found in compact groups in short stretches of CpG-rich DNA or long repetitive stretches of DNA, and these are usually called "CpG Islands". The CpG islands are usually not methylated, while the cytosines in the islands remain unchanged during the normal development and differentiation of tissues, unlike most CpG sites on the genome, which are normally methylated in normal cells. The process of forming a pattern of DNA methylation occurs during the process of differentiating cells. The process, however, renders these cells with possess lesser ability to proliferate partially or totally. DNA methylation patterns are unique to tissues, and their functional meaning varies across cell types. Gene promoters that have CpG islands are typically not methylated in normal cells and thus maintain the euchromatic structure, i.e., transcriptionally active form, in which it facilitates gene expression. Conversely, in the process of cancer formation, a large number of genes become hypermethylated on their CpG island-bearing promoters, and this leads to transcriptional silencing of the corresponding genes as an open euchromatic conformation is altered to a compact heterochromatic conformation. Hypermethylation of DNA is able to differentiate cancerous and non-cancerous tissue. CIMP or CpG island methylator phenotype is a type of tumor that has intense DNA methylation. The CIMP tumors can be individual subtypes of the tumor that harbor minimal genetic changes, and therefore, working on the epigenetic machinery can introduce new therapies. DNA methylation can be reversed, and three members of the ten-eleven translocation (TET) family, namely TET1, TET2, and TET3, carry out this process. TET enzymes operate on the 5mC to 5-hydroxylmethylcytosine (5hmC) conversion, which in turn is converted to cytosine by a cascade of oxidations, to generate 5-formylcytosine (5fC) and 5-carboxyl-cytosine (5caC) intermediates. 5fC and 5caC are, in turn, cleared by DNA glycosylases and the base excision repair machinery to generate cytosines at TET. Thus, the image indicates that TET enzymes modulate chromatin morphology and expression of genes. The activity of DNA methylation does not operate alone, but rather collaborates with other epigenetic regulatory equipment, as demonstrated by synergistic regulation of chromatin structure by histone change and nucleosome placement[5,16,17].

Histone Methylation and Demethylation in Drug Resistance

The histone octamer, which consists of H2A, H2B, H3, and H4 histone proteins, is the basic building block of a nucleosome. The histone tails are N-terminal of the nucleosome core, and some of their amino acids could be subject to several covalent modifications, i.e., methylation, acetylation, phosphorylation, and ubiquit-

ination. Collectively or singly, such changes are believed to transmit heritable epigenetic information needed to control a wide range of nucleosome processes, including replication and repair of DNA, inactivation of the X chromosome, expression of genes, the formation of heterochromatin, and the process of mitosis[6].

Histone methyltransferases (HMTs) and histone demethylases (HMDs) are in primary positions in the regulation of the process of histone methylation, which involves the addition of a single methyl group, a duo of methyl groups, or a triplet of methyl groups on the arginine or lysine residues of the histone protein (Fig.2). Transcription activation is associated with histone 3 methylation at lysine positions 4, 36, or 79 (H3K4, H3K36, H3K79), while transcriptional suppression is associated with methylation of histone 3 at lysine positions 9, 20, or 27 (H3K9, H3K20, H3K27). There are three HMT families described, each specific to the lysine or arginine residue on which it acts: the set domain containing protein family, the non-set domain protein family, and the protein arginine methyltransferases (PRMT1) family[18,19].

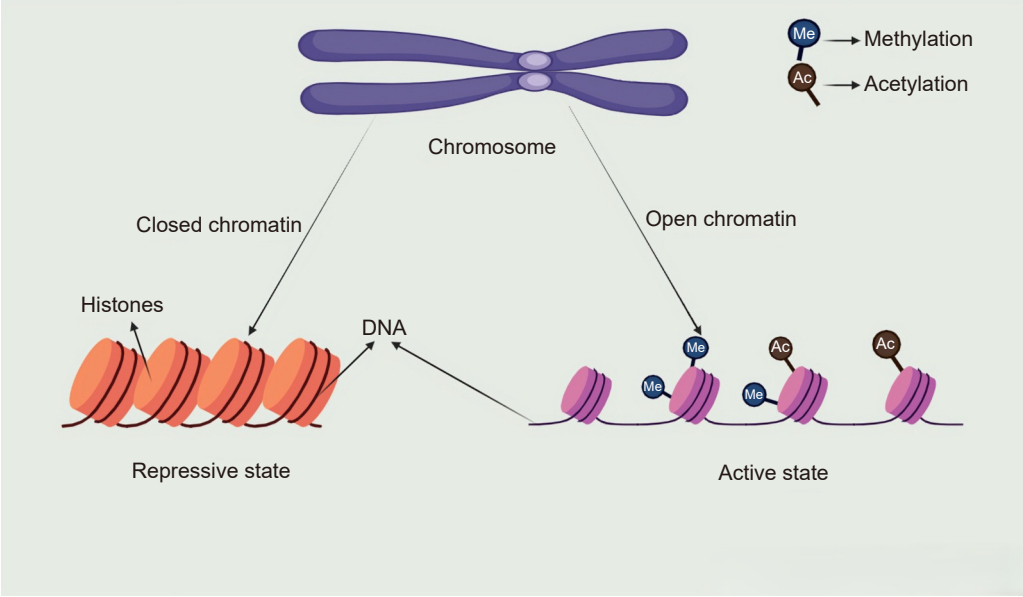

Fig. 2. Process of Histone methylation and demethylation.
Here, two types of chromatin states are shown. A repressive state means no transcription, and an active state means active transcription. HAT is a histone acetyltransferase. This illustration was created using BioRender software (https://BioRender.com). Source: [20,21].

Several histone demethylases will maintain the methylation balance by demethylating certain residues; this action operates in opposition to that of methyltransferases, which act on other residues of histones. Demethylation is done by two distinct families of histone demethylases (HDMs) that use different metabolic pathways. Lysine-specific demethylase 1 (LSD1) is the first enzyme described in this class. The enzyme performs an amine oxidation reaction using flavin adenine dinucleotide (FAD), which demethylates its substrates by LSD1. Another very promising protein is LSD 1, which can attach to a very broad spectrum of proteins, and it is capable of processing a large number of biological processes. The second class of demethylases contains some proteins that bear a catalytic JumonjiC (JMJC) domain. The malonic acid removal of histone residues is catalyzed by these enzymes using Fe (II) and a-ketoglutarate as their cofactors in a dioxygenase mechanism. Detection of the histone code or histone language by some cellular machinery, e.g., the transcription apparatus, will demonstrate the roles of histone modifications. Epigenetic changes, particularly histone methylation and demethylation, have been the most significant mechanisms in drug resistance. In that regard, histone demethylases have been known to be central regulatory factors and have been directly implicated in resistance phenotypes. Therefore, pharmacological inhibition of these enzymes would constitute a new evidence-based medical approach to addressing chemical insensitivity in several malignancies[6,22].

Role of Noncoding RNAs (ncRNAs) in Chemoresistance and Epigenetic Regulation

Based on their size, non-coding RNAs, which comprise 98% of the human genome, are divided into many categories. They include circular RNAs (circRNAs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and others like small nuclear RNAs (snRNAs), short nucleolar RNAs (snoRNAs), piwi-interacting RNAs (piRNAs), and small interfering RNAs (siRNAs). The cataloging norms in the ncRNA community are changing profoundly and persistently[13].

Recent studies have confirmed that certain ncRNA transcripts can encode micro-peptides, which are proteins with less than 100 amino acids, involved in many processes, both health and disease, including cancer. Discoveries propose that at least a part of the non-coding RNAs function either as coding transcripts of non-canonical peptides or do both coding and non-coding functional actions[16].

Role of miRNA in Epigenetic Regulation

MicroRNAs (miRNAs) are a family of non-coding single-stranded RNAs of 19-22 bases, of which the functional part is a guide strand that binds (anneals) with (partially or completely) complementary areas of the target transcripts. miRNA has been linked to the post-transcriptional regulation of oncogenes, tumor suppressors, as well as the repression of numerous mRNAs. Their process of operation follows through a number of steps: pri-miRNAs are cleaved within the nuclear compartment into pre-miRNAs that are then exported to the cytoplasm, where they are cut into a miRNA/miRNA duplex. Of these two strands, one acts as an inhibitor and the other is destined to be degraded (Fig.3).

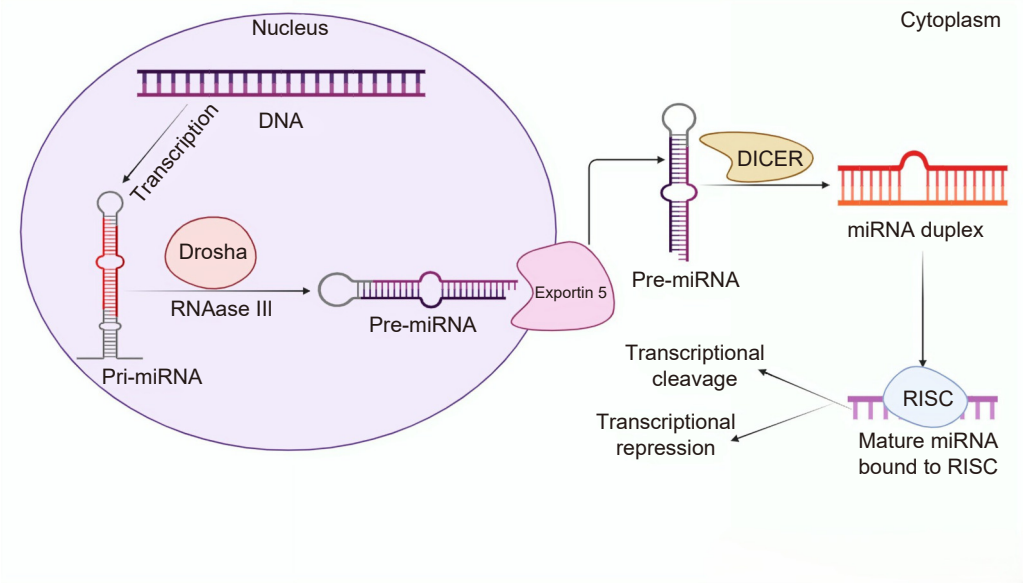

Fig. 3. Biogenesis of miRNA.
Here, Drosha is an RNAse III enzyme that helps to cleave long Pri-miRNA into shorter Pre-miRNA. DICER, another RNAse III enzyme, cleaves the pre-miRNA into a miRNA duplex. RISC or RNA-induced is a multi-protein complex that acts as a guide for miRNA silencing. This illustration was created using BioRender software (https://BioRender.com). Source: [23,24].

Besides these canonical pathways, miRNAs display multidimensional functions which comprise affinity to proteins, stimulation of toll-like receptors, encoding of peptides, promotion of translation of mRNAs, deterrence of mitochondrial mRNAs, induction of transcription, and repression of nuclear non-coding RNAs. Although they are rather complicated and involved in terms of target coverage, the translation of the basic knowledge into clinical practice is an unsolved issue. Enhanced clarification of the role played by miRNA in oncology is thus in order[17,25,26]. A short mechanical flowchart is shown in Fig.4.

Gene silencing and tumor suppression revolve around DNA methylation, which is largely at the cytosine site of CpG Islands. In miRNA promoters, a hypermethylation of CpG islands represses transcription factors and RNA polymerase, resulting in miRNA gene silencing. Hypomethylation, on the other hand, contributes to the enhanced development of cancer and expression of genes. To give an example of this process, in glioma, silencing of miR-424, where miR-424 hypermethylation inhibited its expression, may increase cell invasion and the migration of cells. In addition, miR-29 familial secluded DNA epigenetic as miR-29 b modulated metabolism through the DNMTs and TETs[27].

MiRNA also affects histone modification; based on prediction by bioinformatics, miRNAs were found to be involved in the regulation of histone marks during mammalian spermatogenesis, namely H3K4me1, H3K27me3, H3K27ac, H3K9ac, H3K4me3, and H2AZ. MicroRNA-34a transcriptionally represses HDAC1 in foam cells and targets the 30 UTR of HDAC1 in those cells. The elevated miR-34a enhanced an inappropriate intracellular lipid aggregation coupled with an increment in histone H3 acetylation at lysine 9, and consequently dimming of HDAC1. Simultaneously, the microRNA-138 represses KDM5B histone demethylase in breast cancer cells, where the reduced expression of miR-138 was accompanied by an increased expression of KDM5B mRNA and protein[28,29].

Role of miRNA in Chemotherapy Resistance

Cytotoxic drugs in association with miRNAs

High-risk recurrent breast cancer patients are generally recommended to receive adjuvant chemotherapy after definitive surgery. Doxorubicin (Adriamycin) was the initial line anti-cancer drug to be used to treat breast cancer because it suppressed DNA replication. Similarly, miR-505, miR-128, and miR-145 are tumor suppressors that are downregulated in doxorubicin-resistant breast cancer. Nevertheless, overexpression of the above miRNAs reversed doxorubicin resistance. Downregulation of miR-663, miR-181a, and miR-106b ~ 25 clusters enhanced the susceptibility of doxorubicin-resistant cells, suggestive of their role in carcinogenesis.

Cisplatin is used in the treatment of malignancies of many types through the process of inhibiting DNA replication. A microarray study to explore the miRNA expression profile in cisplatin-resistant versus sensitive breast cancer cells revealed 46

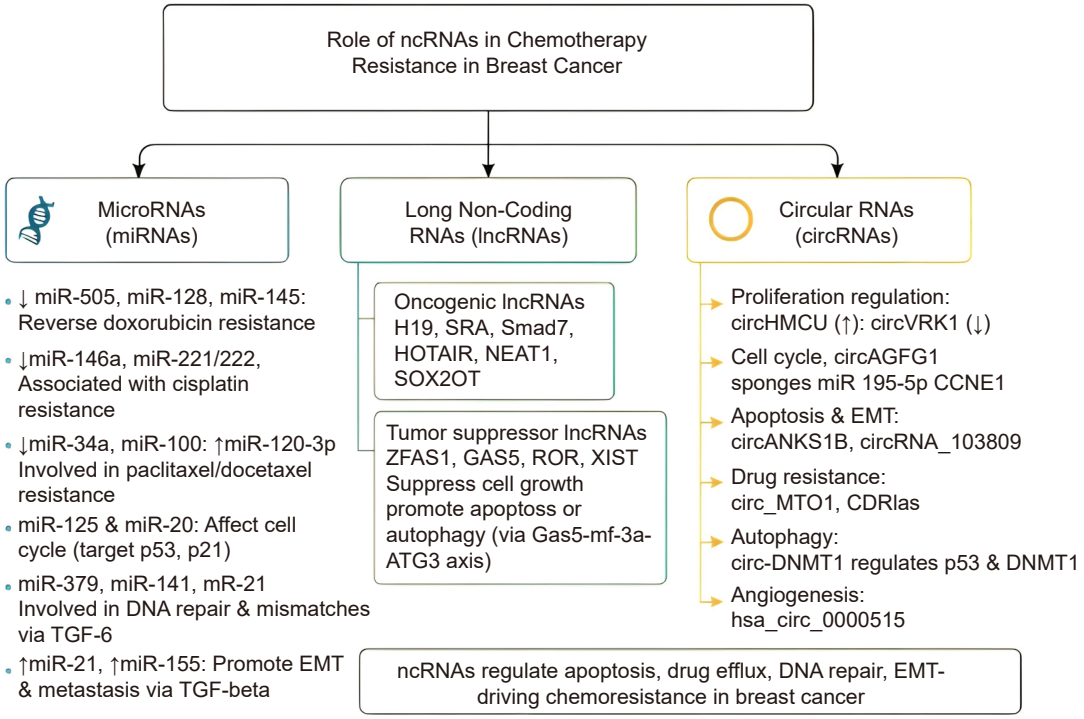

Fig. 4. Mechanical Flowchart of the role of ncRNAs in chemotherapy resistance in Breast Cancer.
This flowchart was created on the Canva software (https://www.canva.com/).

miRNAs overexpressed and 57 miRNAs downregulation. Of note, miR-146a, miR-10a, miR-221/222, miR-345, miR-200b, and miR-200c showed downregulation with significant effects in the resistant cell line. According to functional validation investigations, breast cancer cells' susceptibility to cisplatin is caused by miR-302b, while cisplatin resistance is caused by miR-345 and miR-7.

Docetaxel and paclitaxel are commonly used in cancer treatment because they prevent microtubule dynamics during cell division. Research has indicated that the levels of miR-34a, miR-100, and miR-30c are reduced in breast cancer cells that are resistant to paclitaxel. On the other hand, an overexpression of the level of miR-129-3p was found in docetaxel-resistant breast cancer cells. However, two studies have yielded conflicting results on the involvement of miR-125b in the modulation of paclitaxel-resistant breast cancer. The first observation revealed that miR-125b, which was identified as an oncogenic microRNA, was overexpressed in paclitaxel-resistant cells; however, later studies revealed that miR-125b can also function as a tumor suppressor gene[30,31].

Arrest of the cell cycle

DNA damage is sensed by Sensor proteins, such as *p53* detect DNA damage, setting up checkpoint pathways that prevent the cyclin-dependent kinases (CDKs) from acting and obstruct cell cycle progression. Reduced sensitivity to DNA damage and higher resistance to therapy are associated with *p53* impairment. This is brought about by the upregulation of miR-125, which targets the 3'-UTR of the *p53* gene to inhibit translation. This reaction results in the activation of a number of important regulatory genes in the cell, such as the cyclin-dependent kinase inhibitor p21 (*cdkn1a*). miR-20, targeting p21, is also upregulated in drug-resistant cell lines and therefore decreases the levels of this cell cycle-negative regulator. The reduction in p21 may encourage the cell cycle progression of cancer cells even when there is DNA damage[32].

DNA repair pathways

DNA repair pathways, critical for the maintenance of genetic integrity, are involved in resistance to genotoxic agents. To safeguard cells from drug-induced DNA damage, the nucleotide excision repair (NER) pathway is activated. DNA repair and the enhancement of survival of drug-resistant cell models may be improved by downregulation of miR-373, a microRNA that suppresses the NER repair protein RAD23B. MMR-deficient tumors exhibit resistance to anticancer drugs that form substrates for the MMR system. Dysregulation of miR-141 and miR-21, both targeting essential members of the MMR machinery, is observed in drug-resistant breast cancer cell lines[30,32].

EMT pathway and miRNA regulation

Transforming growth factor beta (TGF-β) promotes epithelial-mesenchymal transition (EMT) through the Ras and Wnt pathways, resulting in dysregulation of critical mRNAs that can lead to aberrant patterns of gene expression. TGF-β increases the levels of miR-21 and miR-155, which suppress the expression of *reck, maspin, tpm1*, and Ras homolog *rhoa genes*, thus promoting tumorigenesis, metastasis, and drug resistance. Through the process of cell viability and invasive capacities, suppression of

these miRNAs made breast cancer cells more sensitive to Taxol by blocking the TGF-β-induced EMT process. The miRNAs TGF-β pathway is modulated by miR-15, miR-128, miR-141, and miR-211[33].

Role of lncRNA in Epigenetic Regulation

Transcripts longer than 200 nucleotides, and in general not translated into protein, are known as long non-coding RNAs (lncRNAs) and form the most complex known category of ncRNA. Since lncRNAs are the longest ncRNAs as well as have the highest ability to encode peptides, the majority of primary miRNAs have been accepted as lncRNAs when they are not interacting. Similar to mRNAs, lncRNAs are subject to the process of biogenesis, most of which are polyadenylated, spliced, and capped. These unique 3-dimensional designs enable them to perform various functions simultaneously. It is possible to categorize these functions as cis (those that work near the site of transcription) or trans functions (those that operate far away from the site of transcription). One of the Cis functions is chromatin modification, chromosomal looping, and regulating transcription of DNA, whereas trans functions are mRNA binding and control of mRNA stability, binding and modulating protein product, and interaction with other ncRNAs (Fig.5).

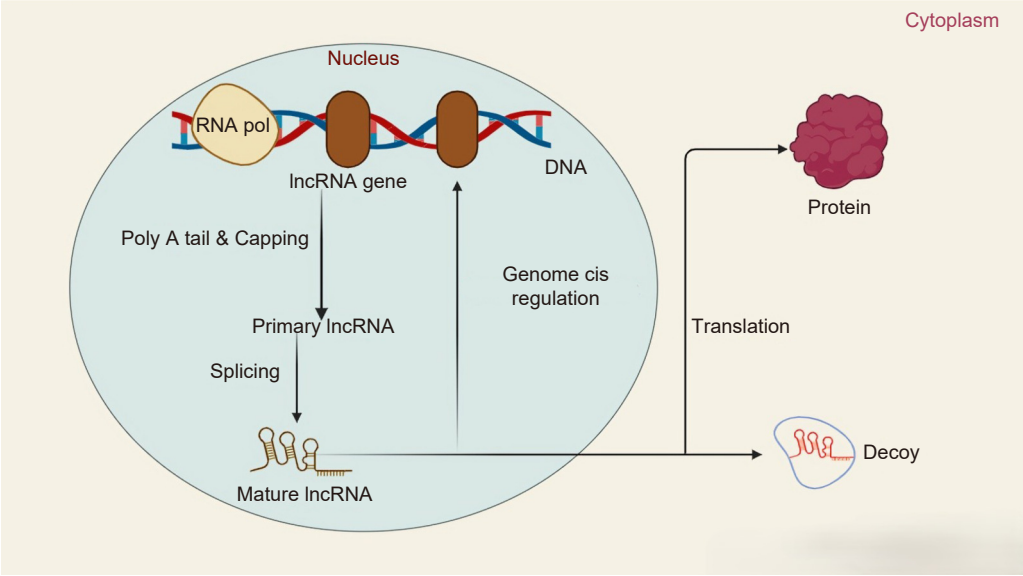

Fig. 5. Biogenesis of lncRNA.
This illustration shows the processing of lncRNA, and after producing the mature lncRNA, it serves 2 types of regulation: cis and trans. In cis regulation, it involves chromatin modification, chromosome looping, and other processes, while in trans regulation, it can involve protein modulation, binding with other non-coding RNAs, and other mechanisms. This illustration was created using BioRender software (https://BioRender.com). Source: [34,35].

The building blocks of multiple biological functions of lncRNAs are these features of lncRNAs (i.e., diverseness, structural variability, conserved motifs, and plasticity). The lncRNAs, because of their variety of structures, are involved in the main epigenetic regulation. An expanding literature base clearly shows that three central systems of epigenetic regulation are spawned via the structural elements of the lncRNAs. The former acts via allostery, and lncRNAs can bind to many protein regulators. Their second consideration is due to their capacity to serve as molecular scaffolds, and this allows them to attract chromatin-modifying proteins. The third is the interface that unites the ability to use repeat elements in lncRNAs to achieve the role of regulating the expression of the neighboring genes, and together, these data incline to the fundamental role of lncRNA structure in epigenetic regulation. Allostery is a dynamical property on the basis of relatively active chemical properties, and this is the primary role of epigenetic regulation of long non-coding RNA (lncRNA). The spatiotemporal aspect of the lncRNA structural structures is functionalized through this characteristic, thereby forming or destroying certain protein-binding sites in the genome. Besides, lncRNAs have a plastic nature to adopt various common structural folds, and this leads to an increased molecular switch and the subsequent activation or repression of a given genomic locus. As a scaffold at the molecular level, two structural motifs are present in lncRNA that could bind multiple proteins to attain stable complexes of ribonucleoprotein. The other mechanism by which the lncRNA can alter the epigenetic processes, in its turn, is connected with the repeat components of the regions of functions, which can form the network, interacting with the proteins and the elongated RNAs of the silencing of the genes and the chromatin[16,36].

LncRNAs can bind to protein complexes recognized as histone writers, erasers, and readers of histone modifications to guide them into specific subnuclear compartments and genomic loci. They serve as a decoding signal of chromatin changes and as a molecular scaffold of dedicated chromatin regulatory complexes that assemble by combining and integrating the molecular functions of groups of histone modifiers, inducing chromatin remodeling at a particular target locus. Because of miRNA sponge potential, lncRNAs most frequently control histone modification through their miRNA targets, which creates regulatory circuits. Alternatively, the regulation of miRNAs as well as lncRNAs is synonymous with the regulation of histone modification, such as methylation and overexpression of HDAC[37].

Role of LncRNA in Chemotherapeutic Resistance

Long non-coding RNAs (lncRNAs), which are crucial for the promotion or suppression of tumorigenesis, have also been found to be epigenetic, transcriptional, and post-transcriptional regulators. Based on their role in the development of breast cancer, lncRNAs have been divided into two categories: (1) those that promote the development of breast cancer and (2) those that hinder the development of breast cancer. Certain lncRNAs, like H19 and MEG3, are imprinting genes controlled by DNA methylation of the paternal or maternal allele. H19, a differentially methylated region, is overexpressed in the majority of human cancers by DNA methylation regulation, including esophageal, lung, breast, and bladder carcinoma. Other tumor suppressor lncRNAs like MEG3 and LOC554202 are suppressed in the majority of cancers with high promoter CpG methylation[38,39]. A short mechanical flowchart is shown in Fig.4.

Oncogenic LncRNAs in Breast Cancer

H19 expression in ER + /- Breast Cancer

LncRNA H19 is a 2.3kb non-coding RNA that is imprinted. Compared to ER-positive breast cancer, ER-negative breast cancer was reported to have lower levels of LncRNA H19 expression. When lncRNA H19 is overexpressed, hormone receptor-positive breast cancer cells undergo autophagy. H19, via the H19/Let-7/Lin28 pathway, induces autophagy and inhibits breast cancer cells from causing EMT. H19 can induce autophagy via the H19/SAHH/DNMT3B pathway, which promotes tamoxifen resistance in breast cancer. It is noteworthy that H19 was found to suppress let-7 microRNA, which suppresses breast cancer stem-like cell self-renewal and breast cancer carcinogenicity. H19 regulated endogenous let-7 target expression and acted as a let-7 molecular sponge. H19 is also referred to as the precursor of the oncogenic miRNA miR-675, which suppresses pRB production[39,40].

Role of SRA in Breast Cancer Progression

Steroid receptor RNA activator (SRA) is the first long non-coding RNA (lncRNA) that has been identified to act without the need for chemical reactions or DNA modifications. SRA helps to activate steroid receptor-dependent genes and acts largely in response to hormone receptors. The nuclear receptor controls the composition and stability of a group that helps to trigger the copying of a gene upon the presence of steroids. SRA also works with many other proteins, such as SRC-1, which helps to stimulate the copying of steroid-responsive genes. SRA levels are described to be elevated in breast cancers, which might suggest a cancer function. The mouse mammary tumor virus (MMTV) promoter controls the MMTV-SRA mouse, which bears a human non-coding SRA sequence. In the mouse model, the female mammary gland cells are producing SRA, and female mice with such a mutation in their genome were shown to develop abnormally formed mammary glands. SRA overexpression also helped to boost cell division and growth[41].

Smad7 in association with the TGF-β pathway

It was recently discovered that lncRNA-Smad is located adjacent to the mouse *smad7* gene. All mammary epithelial cells and breast cancer cell lines were induced by TGF-β to express LncRNA-Smad7. Loss of TGF-β's anti-apoptotic effect was caused by inhibiting this LncRNA. But apoptosis caused by a TGF-β receptor inhibitor was inhibited by ectopic LncRNA-Smad7 expression. But because its knockdown did not affect TGF-β-induced EMT, Smad2 phosphorylation, or *smad7* gene expression. Though a complete mechanism must be established, this data implies a tumorigenic role for this LncRNA[39,41].

LncRNA HOTAIR as Epigenetic Regulator

The *hoxc* gene cluster encodes the 2.2kb HOX transcript antisense RNA (HOTAIR). The mechanism and function of HOTAIR, a known epigenetic regulator, are well documented. HOTAIR is the first lncRNA to have been demonstrated to act in trans. The PRC2 complex has been found to bind the 5' end of HOTAIR, and the histone demethylase LSD1 has been found to bind the 3' end of the RNA. The PRC2 and LSD1 in the target genes are guided and scaffolded by HOTAIR. HOTAIR suppresses transcription in trans over 40 kilobases of the *hoxd* gene by enlisting the PRC2 complex, which is in charge of the histone H3 lysine-27 trimethylation of the locus. The *hox* genes of breast cancer include tumor suppressive and oncogenic genes. HOTAIR is an oncogenic lncRNA and a global regulatory phenomenon. It is highly expressed in metastatic breast cancer tissues. It is a favorable predictor of metastasis and survival in primary breast cancer. HOTAIR expression promotes colony formation, invasion, tumor growth, and lung colonization. Depletion of HOTAIR reduces matrix invasiveness. It triggers localization of PRC2 and H3K27me3 on 854 genes, predominantly downregulated by HOTAIR. Because HOTAIR reprograms the PRC binding pattern in breast cancer to embryonic fibroblasts, the pattern of PRC2 expression in HOTAIR-overexpressing cells resembles that of embryonic fibroblast expression[39,41].

Role of Neat1 in Breast Cancer Development

A crucial part of paraspeckle nuclear bodies that regulate gene expression, transcription factors, and hyper-editing of mRNAs is Nuclear Paraspeckle Assembly Transcript 1 (NEAT1). Their biological importance and physiological status are not yet known. They are assembled in luminal epithelial cells of the developing mammary gland. Mammary gland morphogenesis and defects in lactation result from Neat1 abrogation because Neat1 mutant cells' ability to sustain high levels of proliferation is impaired during lobular-alveolar development, as a result of which a lactation defect arises[40].

Oncogenic Role of SOX2OT

The large multi-exon LncRNA SOX2 overlapping transcript (SOX2OT) has the *sox* gene coding region within its intron. *sox2* and *sox2ot* expression are both positively correlated with breast cancer, and ER-positive and ER-negative breast cancers express SOX2OT differently. *sox2* is a pluripotency maintenance key gene, and *sox2* and *sox2ot* are both elevated in cancer stem-like cells. In addition, ectopic *sox2ot* expression leads to a remarkable upregulation of *sox2* expression, which further enhances anchorage-independent development of breast cancer. Enhancing or

maintaining *sox2* expression can play an oncogenic role in breast cancer[40].

Tumor Suppressive LncRNAs in Breast Cancer

Role of Zfas1 in Mammary Epithelial Differentiation and Ribosome Biogenesis

Recently, it has been revealed that Zfas1, which is antisense to the 5' end of the protein-coding gene *znfx1*, is a new regulator of mammary development in mice. The duct and alveoli of the mammary gland include Zfas1, which encodes three snoRNAs (SNORDs), Snord12, Snord12b, and Snord12c. In addition, Zfas1 transcripts are highly stable, and their decrease enhances cellular proliferation and differentiation without altering overall levels of SNORDs. Like Zfas1, its human orthologue ZFAS1 is decreased in tumor conditions but increased in mammary tissues. The finding suggests that ZFAS1 might be a tumor suppressor gene that controls alveolar formation and epithelial cell differentiation processes. ZFAS1 was also shown to be associated with ribosomal components and could be crucial in the regulation of their biosynthesis or assembly. There is a high correlation between the expression of ZFAS1 and mRNAs for ribosomal proteins, which are crucial for the assembly, synthesis, and maturation of the ribosome[41].

Role of Gas5 as Molecular Sponge

As a tumor suppressor, growth arrest-specific 5 (Gas5) hinders the malignancy and survival of most types of cancer cells. Their mechanism may collectively be the foundation of their tumor suppression, as different tumor types undergo apoptosis, which is induced and inhibited by Gas5 lncRNA. Through the Gas5-miR-23a-ATG pathway, the LncRNA Gas5 regulates autophagy in breast cancer, and Gas5 is reduced in this. Gas5 can induce the suppression of tumor cells through autophagy by functioning as a "molecular sponge", which inhibits and sequesters miR-23a and positively regulates miR-23a-targeted autophagy-related gene *atg3*[41,42].

Regulatory Role of ROR in Breast Cancer

LncRNA ROR (reprogramming regulator of reprogramming) is upregulated in nasopharyngeal carcinoma, hepatocellular carcinoma, and breast cancer, and it can help maintain embryonic and pluripotent stem cells. Tamoxifen was discovered to reverse the function of luminal B breast cancer cells, and LncRNA ROR downregulation inhibited the proliferation, invasion, and migration of luminal B breast cancer cells. Targeting the autophagy-related proteins LC3 and beclin1, LncRNA induces autophagy and further promotes breast cancer progression as well as tamoxifen resistance. It was found that LncRNA ROR interacted with miR-205 in modulating the process of breast cancer EMT. Interacting with miR-145, ROR can regulate triple-negative mammary gland growth and metastasis[41].

Controversial Functions of XIST in Breast Cancer

XIST (X inactive specific transcript) is the one lncRNA that, during embryonic development, inactivates the X chromosome. To maintain the X chromosome in a silenced state, the 17kb long LncRNA recruits PRC as it moves along the chromosome. It has been shown that in early X chromosomal inactivation, YY1 is responsible for directing XIST loading and spreading. Over 1000 genes on one X chromosome were silenced due to this dosage correction. The function of XIST in breast cancer is currently being investigated, but its function is controversial and not clear. XIST RNA builds accumulated on the dormant X chromosome through the action of the breast cancer tumor suppressor *brca1*, which is important for the maintenance of X chromosome inactivation markers. *brca1* loss in female cells could result in destabilization of the X chromosome. XIST is *brca1*-independent in X inactivation. Breast cancer subtypes differ in how XIST is expressed, and it is linked to *brca1* status. *brca1* only controls XIST from the inactive X chromosome, but XIST is ectopically expressed from an active X chromosome, and the mechanism of XIST expression in breast cancer cells may differ from normal cells[41,42].

Role of Circular RNA in Epigenetic Regulation

CircRNAs (also known as circular RNAs) are a novel family of non-coding RNAs that have been known since 1976 in RNA viruses. Such RNAs are created after ligation of exons of a piece of DNA, leaving a single-chained molecule that is covalently secured and stable. Early literature had dismissed circRNAs as a sequestration breakdown of bad splicing or random processing in pre-mRNA, and they were supposed to be available in low quantities. This was followed by the advent of high-throughput RNA sequencing with circRNA identification and quantification dedicated algorithms, leading to awareness that the group of non-coding RNAs is its unique population. It is known that there are three other abundant subtypes, which are exonic circRNAs (EcRNAs), circular intronic RNAs (ciRNAs), and exon-intron circRNAs (ElciRNAs). A short mechanical flowchart is shown in Fig.4. Besides, circRNAs have been implicated in regulating DNA methylation and N6-methyladenosine (m6A) modification. It was recently pointed out that m6A RNA methylation in circRNAs can also be caused by associated binding to miRNA molecules: e.g., CircBACH2 works as a miR-944 sponge, alleviating repression of the m6A regulator HNRNPC, promoting its upregulation, which promotes BC cell growth and proliferation. A culmination of these findings shows that circRNAs play a major role in gene regulation based on their potential to sequester miRNA to m6A modifications[43–45].

Role of circRNAs in Chemotherapeutic Resistance

Proliferation of Breast Tumor Cells

The G2/M accumulation of breast cancer cells is correlated with a decrease in the formation of the CDK1/cyclin B1 complex in eukaryotic organisms. The mitotic regulator P21 can arrest growth and proliferation at the G2/M stage by blocking the activation of CDK1. CircHMCU increases the proliferation of breast tumor cells by regulating the checkpoint at the G1 stage of the cell cycle, whereas CircDDX17 and CircRNA 103809 regulate cell cycle-related parameters. Overexpression of circHMCU promotes aggressive cellular proliferation. In cell lines of breast can-

cer cell lines, Circ-VRK1 expression is decreased, thereby inhibiting tumor cell growth. In BT549 and MDA-MB-468 cell lines, studies show that co-transfection of the hsa-miR-2682 repressor and si-hsa_circ_0131242 eliminates both cell migration and proliferation, whereas hsa_circ_0131242 silencing inhibits the growth of breast cancer cells. These findings point to the importance of determining how cell cycle-related variables influence the growth and spread of breast cancer cells[46,47].

Cell Cycle Progression

Atypical cell formation is a prevalent characteristic of cancer. Oncogenic signal transduction occurs in the cell cycle. As a competitive endogenous RNA (ceRNA), CircAGFG1 blocks the inhibitory effect of miR-195-5p on cyclin E1 (CCNE). Through the regulation of RB phosphorylation by *ccne1*, inhibition of CircAGFG1 could hinder the release of E2F1 from RB, which causes decreased transcription activity of E2F1 and G1/S stage cell cycle arrest. CircAGFG1 enhances *ccne1*-induced cell proliferation by inducing miR-195-5p in the TNBC. Decreased hsa_circ_0008039 results in decreased cellular motility, suppressed proliferation, and blocked cell cycle progression. As a miR-33a ceRNA, CircEIF3M increases the production of *ccnd1*, which works with cyclin-dependent kinase 4 (CDK4) to control cell cycle progression. Dysregulation of the process occurs in several cancers, such as melanoma and breast cancer[46,47].

Apoptosis

Apoptosis is gene-programmed cell death that leads to DNA breakage, wrinkling, nuclear enrichment, and membrane foaming. Induction of tumour cell apoptosis is critical because tumours are mainly generated by uncontrolled growth and suppression of apoptosis. Human circRNA was significantly up-regulated in TNBC tissues. It targets miRNA, a target gene of miRNAs and miRNA sponges, and is knocked out in three cell lines[46,47].

Invasion and Metastasis

Breast cancer metastases are a major cause of cancer patients' deaths. An essential stage in the metastases of breast cancer cells is EMT transformation, in which epithelial cells lose their polarity and adhesion ability and acquire mesenchymal traits through the upregulation of mesenchymal biomarkers and the downregulation of epithelial markers. The major inducer of EMT is TGF- signaling, which can be regulated by circRNA. CircANKS1B promotes USF1 expression by upregulating TGF-β1 and activates the TGF-β1/Smad signal via the utilization of miR-152-3p and miR-148a-3p. Functional studies show that hsa_circ_001569 downregulation significantly inhibits BC cell proliferation and metastatic ability. Circ_0006528, by elevating Raf1 expression, can facilitate breast cancer growth, infiltration, and migration by inducing endogenous miR-7-5p[46,47].

Autophagy

Lysosomes receive damaged organelles, misfolded proteins, and intracellular structures that are degraded via autophagy, an important process in the energy cycle. This results in eukaryotic cells exhibiting dysregulated pathogenic behaviors, thus hastening the progression of diseases like cancer. Under stress, autophagy supplies cancer cells with energy and keeps them alive. Growth of GC cells is promoted by the established signaling pathway AKT/mTOR, which suppresses catabolic processes, including autophagy, and promotes anabolic processes. By suppressing catabolic processes like autophagy and ULK1 phosphorylation to block AMPK from activating it, mTORC1 veritably slows the process of ageing. Ectopically expressed Circ-DNMT1 can bind and interact with AUF1 and *p53*, promoting their nuclear migration. Nuclear migration of AUF1 reduces the instability of DNMT1 mRNA, leading to increased translation of DNMT1, while nuclear migration of *p53* induces cellular autophagy. By attaching to and controlling cancer-causing proteins in breast cancer cells, ectopic circ-DNMT1 promotes autophagy, which enhances cell survival and proliferation[46,47].

Angiogenesis

Tumor development and metastasis depend on angiogenesis, which sustains a continuous blood supply for aberrant cell proliferation. The Hypoxia-inducible factor (HIF) family, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), TGF-β, TNF-α, interleukin, fibroblast growth factor (FGF), αvβ3 integrins, Eph-B4/ephrinB2, VE-cadherin, plasminogen activator/plasmin, matrix metalloproteinases (MMPs), the three untranslated regions (UTRs) of CYP4Z2P, and the CYP4Z1-3′UTR pseudogenes are some of the signaling pathways linked to tumor angiogenesis. Through the sequestration of microRNAs and the activation of the PI3K and ERK1/2 pathways, these pseudogenes facilitate the angiogenesis of breast tumors. Experimental data have shown that hsa_circRNA_002178 downregulation may suppress aggressive malignant behaviors, while the modulation of CXCL10-induced breast cancer cell angiogenesis involves hsa_circ_0000515 and miR-296-5p[46,47].

Drug resistance and circRNA involvement

CircRNA can be involved in the induction or reversal of breast cancer chemotherapy resistance, as indicated by studies. Chemotherapy and endocrine drugs are essential for advanced metastatic breast cancer treatment, although drug resistance normally makes treatment difficult. Drug resistance development is largely controlled by a series of genes, such as MRPS and MDR1. Drug-resistant enzymes include Glutathione S-transferase (GST) and O6-methylguanine DNA methyltransferase (MGMT), and the multidrug efflux pump ATP-binding cassette (ABC) superfamily includes breast cancer resistance protein (BCRP). Intracellular drug accumulation of chemotherapy agents suppresses the monastrol drug-resistant cell lines by the downregulation of circ_MTO1, which increases monastrol-induced cytotoxicity. The 5-FU-resistant BC cells' susceptibility to chemicals can be enhanced by the upregulation of miR-7, which suggests that CDR1as can be an effective tool in enhancing chemotherapeutic approaches to BC[47,48].

Tumor immunity

The immune reaction to cancer can defend the host by triggering cell death or cancer cell proliferation. It can also be favored to in-

duce tumor-specific immunity through the selection of tumor escape mutants or by generating particular microenvironments within the tumor. CircRNA facilitates the immune response. CircRNA CDR1as is thought to have a unique role in the invasion of immunological and stromal cells, including endothelial cells, $CD8^+$ T cells, activated NK cells, M2 macrophages, and cancer-associated fibroblasts (CAFs) in breast cancer tumor tissue, according to research[48].

Exosomes in Breast Cancer

Numerous cells secrete exosomes, extracellular membrane vesicles that exhibit a diameter of 40-100 nm. The biogenesis of exosomes is shown in Fig.6, where different internal processes have been shown. They can move all kinds of payloads, such as proteins (cytoskeletal, Transmembrane, and heat shock proteins), enzymes (GAPDH, ATPase, and much more), and nucleic acids (DNA, mRNA, miRNA, and long and short non-coding RNA). In most situations, the contents of the exosomes can reflect the nature and state of the donor cell. The selective sorting at a cellular level could be assumed through the enhancement of some proteins and nucleic acids into some form of exosome. Conversely, exosomes can control biological processes in their target cells through genetic information transfer[49].

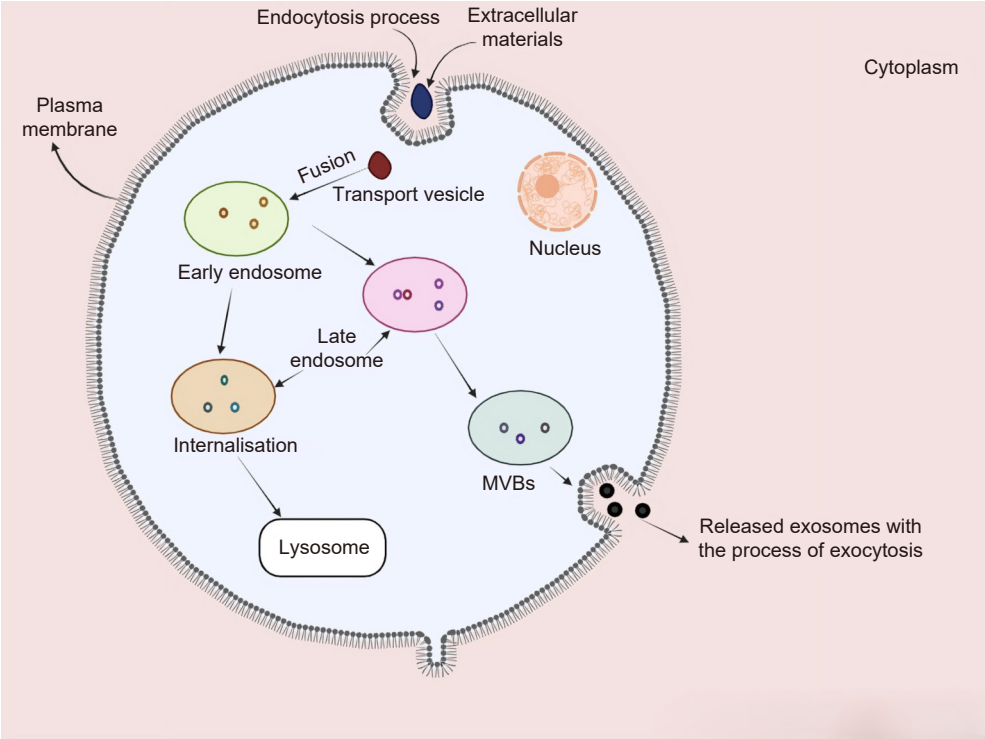

Fig. 6. Biogenesis of exosome.
The 'MVB' in the figures refers to 'multivesicular body'. This illustration shows a process called 'endocytosis' where cells engulf external materials into the cell membrane and, by going through some processes, release them as exosomes with the help of a process called 'exocytosis'. This illustration was created in BioRender software (https://BioRender.com). Source: [50,51].

Role of Exosomes in Chemotherapy Resistance

Invasion and metastasis

Metastasis in neoplastic cells involves reorganization of the surrounding microenvironment to support invasion and proliferation, such as loss of cellular adhesion, increased motility, and invasive potential. Adhesion is an important attribute in many clinical conditions, e.g., in the context of cancer biology. Detachment of mammary cancer cells leads to the release of exosomes, which accumulate on the cell surface and increase extracellular matrix protein binding. Fetuin-A, a glycoprotein of fetal bovine serum, increases cell attachment by mediating the recruitment of exosomes. These exosomes increase cell migration as well as induce cell migration in synchrony with the metastatic potential of the cells. Exosomes released by breast cancer cells under hypoxic conditions have been implicated in increased invasive and metastatic properties. Experiments using human breast cancer cell lines (MCF-7, MDA-MB-231, and MDA-MB-435) identified that hypoxia-inducible factors regulate the expression of RAB22A and thus mediate the release of microvesicles. Fibroblast exosomes also increase breast cancer metastasis and motility through the Wnt pathway, which is pivotal in cell migration, adhesion, stem cell maintenance, tissue patterning, and carcinogenicity[52,53].

Modulation of stem cells

Mesenchymal stem cells (MSCs) have the ability for self-renewal and generation of tumour stroma-like myofibroblasts, which is crucial for tumour angiogenesis. Adipose tissue-MSCs can be transformed into tumor-associated myofibroblasts by tumor-secreted exosomes, which can promote the progression of breast cancer. Exosome treatment can augment tumor-stimulating chemical expression. MSC-released exosomes promote MCF-7 migration and control the formation of breast cancer stem cells (CSCs).

Exosomes generated from MCF-7 activate the activation markers CD44, IL6, and ApoE, as well as the stem cell regulating gene *notch3*[52].

Angiogenesis

Through a SMAD-dependent pathway, exosomes released by breast cancer cells can induce MSMs to differentiate into myofibroblasts. Myofibroblasts are a significant cell type of tumour stroma and are crucial in tumour angiogenesis. From breast cancer cells, the release of exosomal miR-16 downregulates VEGF expression, suppresses angiogenesis, and can act against anti-tumor therapy as an anti-angiogenetic agent. The synthesis of exosomal miRNA is regulated by Neutral sphingomyelinase 2 (nSMase2) and induces cancer cell dissemination in the tumour microenvironment via angiogenesis. MiR-210, exosomal angiogenic miRNAs released by metastatic breast cancer cells, induce endothelial cell migration and capillary formation and may impact tumour angiogenesis and brain metastases. Overexpression of miR-210 can cause poor prognosis in patients with breast cancer and brain metastases[52,53].

Immune system regulation

Through altering their immunogenicity and releasing immunosuppressive mediators, cancer cells can elude the host immune system. Exosomes in breast cancer transmit negative signals that diminish anti-tumor immunological reactions, especially T cell immunity, and rewire the immune cells to exhibit characteristics that promote cancer growth. Exosomes from tumour cells express functional CD39 and CD73, which dephosphorylate ATP and 5'AMP and suppress T cell activity. DC-released exosomes trigger apoptosis, stimulate natural killer cells, and induce tumor cell killing. Exosomes from breast tumours also promote tumour growth by suppressing IL-2-induced NK cell activation and immunological response to tumour cells. Exosomes released by breast cancer stimulate macrophage activity and induce pro-inflammatory activity[53].

Chemotherapy Resistance

Breast cancer cells can resist treatment by various mechanisms, leading to resistance to chemotherapy drugs. As information carriers, exosomes aid cancer cells in exporting chemotherapy medications, which may accelerate the emergence of chemo-resistance. Exosomal miRNA transfer allows drug-resistant breast cancer cells to transmit resistance and change chemosensitivity in recipient-sensitive cells. Drug resistance includes P-glycoprotein (P-gp), by drug efflux through the membrane. Regulatory miRNAs found in the exosomes of doxorubicin-resistant breast cancer cells can impart resistance to recipient cells. Additionally, exosomal miRNAs can give susceptible cells drug resistance. By boosting therapy-resistant tumor-initiating cells, stromal fibroblast exosomes deliver non-coding RNA to breast cancer cells, making them more resistant to treatment[52,53].

Radiotherapy resistance

Radiotherapy is an essential therapy for breast cancer. Oxygen supply is typically necessary to cause DNA damage in radiation-induced cytotoxicity. Thus, breast cancer can acquire increased resistance to radiation therapy under hypoxia, and hypoxia is also associated with increased exosome secretion. Furthermore, exosomes transported from stroma to breast cancer cells boost the native tumor's resistance to radiation and facilitate antiviral signaling. Additionally, another study found that the oxygenation status of the breast tumors could be predicted using the proteomic profiles of exosomes generated by tumors[53].

Endocrine and Targeted Therapy Resistance

Tamoxifen resistance is a major obstacle in the treatment of ER-positive breast cancer. Tamoxifen-resistant cell-secreted exosomes stimulate tamoxifen-sensitive cell growth and colony formation, inducing growing tamoxifen resistance in recipient cells. Exosomal miRNAs suppress target genes, leading to tamoxifen resistance. The most effective medications for HER2+ breast cancer are HER2-targeted therapies, such as trastuzumab and lapatinib. Exosomal miRNA-155 suppresses SOCS6, activates STAT3, and increases gene expression, leading to tamoxifen resistance in BC cells. MiRNA-27a/b suppresses TFPIa expression in MCF-7 cells, leading to apoptosis. Suppression of exosomal miRNA-449a enhances ADAM22 expression, leading to tamoxifen resistance[52,53].

Therapeutic Implications and Future Directions in Epigenetic Regulation

DNA-Modifying Drugs

DNMT1 inhibitors (DNMTi) are further categorized into two groups: nucleoside and non-nucleoside analogs. Nucleoside analogues replicate to the DNA as a cytosine proxy, resulting in a proteasomal degradation of DNMTs there, upon developing DNA hypomethylation. Non-nucleoside analogues, on the other hand, do not embed within the DNA; they simply attach to definite target proteins and thus, they capture their activities. The Food and Drug Administration (FDA) has approved 5-azacytidine (5-AzaC (Vidaza)) and 5-aza-20-deoxycytidine 5-AzaDC, (decitabine) as nucleoside analogues that are used in the treatment of hematological malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). 5-AzaC was reported to suppress DNMTs, causing DNA hypomethylation and the resultant silencing. In particular, in vitro experiments point out that DNA hypermethylation inhibition is one of the mechanisms through which azacitidine regulates the process of EMT. However, the first-generation DNMTis have a cytotoxic effect at high doses, and thus, low doses and a long duration are required. This is why the second stage of the DNMT study will be related to the production of second-generation reagents that will be more biostable and effective.

A second-generation DNMT is guadecitabine, which is more biostable and active than decitabine or azacitidine. In animal cancer models of breast cancer, guadecitabine therapy regulates the TME to include activation of cytotoxic T cells and a decrease of myeloid-derived suppressor cells (MDSCs). The two-fold immunomodulatory effect implies that guadecitabine could support a more permissive TME to anti-tumor responses. The existing research on DNMTi aims at DNA-methylation inhibitors side by

side with gene-reactivation approaches to cancer treatment[4,54,55].

HDAC and HAT Enzymes

Histone acetyltransferases (HAT) and Histone deacetylases (HDAC) are the critical enzymes controlling chromatin architecture and gene expression. HATs acetylate lysine residues by transferring acetyl groups, while HDACs remove the acetyl groups, leading to a more stable chromatin architecture and suppressing transcription. Carnosol, garcinol, curcumin, and anacardic acid are naturally occurring HATs that promote the treatment of breast cancer. Carnosol inhibits p300 by blocking its acetyl-CoA site of binding, which causes cell lines of breast cancer cell lines to have hypoacetylated histones. Garcinol efficiently inhibits the acetylation of *p53* in MCF-7 cell lines of breast cancer, which is mediated by CBP/p300. Additionally, curcumin also inhibits the activity of p300/CBP, which causes MCF-7 cell arrest at the G2/M stage of breast cancer. HDAC inhibitors are divided into three categories: hydroxyamides, benzamides, and carboxylic-acid-based inhibitors. Targeting the class I and class II HDAC families, vorinostat is a first-generation HDAC inhibitor that reduces ERα expression, which in turn reduces cell proliferation, migration, and invasion. By inducing histone H1 production, quisinostat, a next-generation HDAC inhibitor, can prevent cancer stem cell self-renewal without endangering healthy stem cells. Tacedinaline is a class I and II HDAC inhibitor with the ability to inhibit the *birc5* gene and decrease apoptotic protein expression. When combined with capecitabine, mocetinostat, an HDAC I and IV inhibitor, causes apoptosis in breast cancer cell lines. When used with exemestane, chidamide, an HDAC inhibitor of the benzamide family, has demonstrated promise and shown potential in patients with HER^{+} breast cancer[4,55].

HMT and HDMT inhibitors

Enzymes known as Histone methyltransferases (HMTs) provide methyl groups to certain amino acid residues on histone proteins. S-adenosyl-L-methionine (SAM) acts as a methyl group donor for the two classes of enzymes: Lysine methyltransferases (KMTs) and arginine methyltransferases (RMTs). Current clinical trials involve GSK3326595, a PRMT5 inhibitor, and JNJ-64619178, a highly potent PRMT5 inhibitor for early HR + cancer. An experimental oral small molecule inhibitor called pemrametostat blocks PRMT5 by preventing the arginine methylation of histones H4, H3, and H2A, which stops the growth of tumor cells. The compounds sinefungin, isolated from *Streptomyces incamatus* and *S. griseolus*, are natural EHMT1/2 inhibitors. Flavin-adenine-dependent (FADs) and iron-oxygen-dependent 2-oxoglutarate demethylases are the two classes of histone demethylases (HDMTs). Phenelzine, an antidepressant with monoamine oxidase (MAO) inhibitory activity, reduces LSD1 activity and reduces mesenchymal markers in metastatic breast cancer patients. Pargyline is an LSD1 inhibitor, which reduces cellular growth in a dose-dependent manner along with an increase in apoptotic protein production. ORY-1001, a discovered LSD1 inhibitor, inhibits androgen receptor expression in breast cancer cell lines, inhibits cell proliferation, and induces apoptosis[4,6].

Therapy of Chromatin Modification

Because of their specificity, Histone lysine methylases (HMTs) are possible therapeutic targets. Therapeutically approved inhibitor drugs target EZH2, G9a/GLP, DOT-1L, and SUV39h1. However, with a short plasma half-life, 3-Deazaneplanocin (DZNep) is extremely toxic in animal models. The development of EZH2 inhibitors results in to lower down the toxicity and improving the antitumor activity. The growth and metastasis of breast cancer are suppressed by an EZH2 inhibitor, ZLD1039. BIX-01294, a selective G9a inhibitor, suppresses G9a function in a model of breast cancer with apoptosis, cell migration, cell cycle, and anchorage-dependent growth inhibition. Even under normoxic settings, pro-tumorigenic pathways, including the Hypoxia-induced pathway (HIF), were boosted by G9a inhibition. This necessitates the vital aspect of HMTs in the development of drug therapy and establishing drugs that target HMT. There are currently no HMTs being used to treat breast cancer in clinical studies[6].

Combination Therapy

Combination therapy in cancer therapy and drug resistance plays an important role. Poly (ADP-ribose) polymerase inhibitors (PARPi) are potent anticancer drugs; nevertheless, resistance ensues due to compensatory networks and intersections of gene and effector proteins. Epigenetic drugs, e.g., DNMT inhibitors (DNMTi), cross-talk with PARPi on different platforms. For example, DNMTi + PARPi causes DNA damage and double-strand breaks, and hence increases the cytotoxicity in triple-negative breast cancer (TNBC) stem cell-like cell lines. Furthermore, DNMTi helps to promote the DNA damage response and PARP trapping, resulting in homologous recombination deficiency (HRD) and improving BRCA-proficient cancer cell sensitivity to PARPi. A phase I/II clinical study in TNBC will assess the combination approach. Including both PARP and EZH2 is a promising treatment approach for breast cancer. Lastly, Histone deacetylase inhibitors (HDACi) increase PD-L1 expression in TNBC cells, which is a call for appreciation as it intersects the epigenetic therapies and immunotherapy. Additionally, the proliferation of tamoxifen-resistant cells was inhibited by Bromodomain and Extra Terminal motif (BET) inhibitor (JQ1), together with or without the inclusion of selective ER downregulation-promoting molecules. Also, the synergistic effect of combination therapy is available in TNBC. As an example, the study showed the potential of synergistic efficacy of HDACi and anti-HER2 treatment with trastuzumab in a clinical trial. In this way, oncogenic mechanisms can be addressed through an adequate combination of the drugs. This opens up a new, potentially synergistic approach for the breast cancer stem cells with issues of resistance and recurrence[4,56].

Limitations

Heredity and disturbed epigenetics lead to tumors in humans; because of this, epigenetic cancer treatment has been developed. Treatment Epigenetic treatment is an attempt to counter these changes and recover the epigenome to its original state. Despite DNA methylation and histone modification being deemed as improved, the place of epigenetic mechanisms in cancer is not well

understood. The drugs that have FDA approval for cancer therapy are DNMT and HDAC inhibitors. More powerful and more selective inhibitors are, however, required to reduce side effects. Research on accurate epigenetic changes in cancer and long-term tumors is bound to improve the detection and treatment of cancer. The combination of HDACi, romidexin, cisplatin, and nivolumab shed fantastic light on the refractory cases of metastatic TNBC. However, a combination of more than one drug is not always effective, and new approaches to treating epidrugs with other drugs should be sought to increase the antitumor effect.

Conclusion

This review study highlights the most important roles of epigenetic regulation and non-coding RNA expression in the expression of chemotherapy resistance in breast cancer. In particular, chromatin remodeling, mainly DNA methylation and histone modification, can adapt the gene expression pattern leading to drug-resistance mechanisms, e.g., high levels of efflux transporter protein, high DNA repair function, and attenuated apoptotic responses. At the same time, non-coding RNAs, specifically miRNAs and lncRNAs, additionally regulate the processes to organize significant genes involved in pathways of chemotherapy sensitivity. As far as miRNA is concerned, we have identified some potential miRNAs which can be correlated with many of the processes or pathways and can be treated in chemoresistance in the future, e.g., miR-128 is a tumor suppressor, and doxorubicin is a type of anti-cancer drug which inhibits the replication of DNA. However, the miR-128 gene is downregulated in doxorubicin-resistant cells. In case we could somehow increase the expression of this miRNA, then we could reverse the doxorubicin resistance. There is another miRNA that is controversial in its effects with regard to the paclitaxel-resistant cells (miR-125b). One study indicated miR-125b was an oncogenic RNA, and the other indicated it as a tumor suppressor RNA. Therefore, since we are able to be in a better position to examine the role of this miRNA, we are then in a position to hopefully have a successful target in a number of these drug-resistant cells. Inhibition of translation was also observed to be mediated by a miR-125b that is upregulated and targets the 3'UTR of the *p53* gene. In the same manner, miR-128 has also been identified in the process of correcting the TGF-beta-induced EMT process. In the case of lncRNA, we have made two categories of it, and when it is oncogenic, we believe that H19 and HOTAIR may be a good option. Overexpression of H19 may lead to autophagy, which leads to multiple drug resistance in breast cancer cells. It also contributes to suppressing the role of let-7 miR, which contributes to the deduction of the self-renewal process of breast cancer. It could be possible to obtain a more specific role of H19 in breast cancer resistance; we may be able to develop a drug against it, which would be able to stop its functioning. Likewise, HOTAIR favors invasion, the growth of tumors, and colonies of cancerous cells. Therefore, the epigenetic reprogramming of such oncogenic lncRNAs must be undertaken before they impose some dire consequences on our bodies. Speaking of circRNAs, we did not locate any specific circRNA that interacts with many processes or influences the chemotherapy resistance too much, and could not identify any possible targets in relation to circRNAs. Added together, epigenetic variations with dysregulation of ncRNA establish a complex network that regulates chemosensitivity in breast cancer cells through synergistic effects. Examination of these complex regulatory mechanisms gives us the means to develop new approaches to therapies. Inhibitors of epigenetic modulators and ncRNAs, with or without conventional chemotherapy, are an attractive approach in re-sensitizing the resistant tumors.

Possible clinical uses consist of:

1: Establishment of epigenetic biomarkers to allow the prediction of chemotherapy response and inform the use of individualized approaches.

2: Development of specific epigenetic treatment based on DNMT inhibitors or HDAC inhibitors to overcome resistance-related epigenetic changes.

3: miRNA mimics or inhibitors that allow one to silence leading resistance mechanisms.

4: Development of engineering exosomes as delivery systems of epigenetic drugs or ncRNA-based therapeutics.

5: Combination regimens where epigenetic agents are used with conventional chemotherapy to increase the effectiveness of the therapy.

6: Inquiring about methylation patterns of the circulating tumor DNA as liquid biopsy indicators to monitor treatment.

7: Understanding the lncRNA-based therapeutics as a way of disturbing the gene regulatory networks that promote resistance.

With studies gaining more traction on the epigenetic and ncRNA of chemo-resistant breast cancer, the strategies present high potential in clinical applications in transforming the discouraging drug resistance issue. Further exploration of the mechanistic and translation aspects of the epigenetic control of the resistance to treatment of breast cancer is necessary to see these advantages and develop more efficient patterns of treatment.

Abbreviation

AKT, Ak strain transforming; ALDH, Aldehyde Dehydrogenase; AMPK, AMP-activated protein kinase; APOE, Apolipoprotein E; CDK, Cyclin Dependent Kinase; CpG, Cytosine-Phosphate-Guanine; CSC, Cancer Stem Cell; DDR, DNA Damage Response; EMT, Epithelial-Mesenchymal Transition; ERK, Extracellular Signal-Regulated Kinase; EZH2, Enhancer of zeste homolog 2; FDA, Food and Drug Administration; GADPH, Glyceraldehyde 3-phosphate dehydrogenase; HER2, Human Epidermal Growth Factor Receptor 2; IL6, Interleukin 6; MAPK, Mitogen-Activated Protein Kinase; MDR1, Multi-Drug Resistance 1; MTOR, Mechanistic Target of Rapamycin; P13K, Phosphoinositide 3-kinase; PARP1, Poly ADP-Ribose Polymerase 1; RasMAPK, Rat Sarcoma/ Mitogen-Activated Protein Kinase; SMAD, Suppressor of Mothers Against Decapentaplegic; SOCS6, Suppressor of Cytokine Signaling 6; STAT3, Signal Transducer and Activator of Transcription 3; TDP1, Tyrosyl-DNA Phosphodiesterase 1; TFPI, Tissue Factor Pathway Inhibitor; TGF, Transforming Growth Factor; TNBC, Triple Negative Breast Cancer.

Conflicts of Interest

The author declares no conflicts of interest.

Authors' contribution

This review topic was conceptualized and designed by SH and SG. SD: Literature Reading and Writing – original draft. SG and SH: Writing – review & editing.

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