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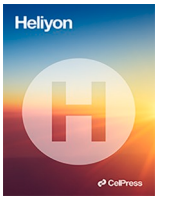

Review article

Micro-RNAs in breast cancer progression and metastasis: A chromatin and metabolic perspective

Sweta Sikder [a,1], Aditya Bhattacharya [a,1], Aayushi Agrawal [b,d], Gautam Sethi [c], Tapas K. Kundu [a,*]

[a] *Transcription and Disease Laboratory, Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, 560064, India*
[b] *Division of Cancer Biology, CSIR-Central Drug Research Institute, Sector-10, Jankipuram Extension, Sitapur Road, Lucknow, 226031, UP, India*
[c] *Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, 16 Medical Drive, 117600, Singapore*
[d] *Academy of Scientific and Innovative Research, Ghaziabad, Uttar Pradesh, 201002, India*

A B S T R A C T

Breast cancer is a highly complex disease with multiple subtypes. While many of the breast cancer cases are sporadic some can be familial or hereditary. Genomic integrity is closely monitored by several mechanisms, such as DNA damage machinery and mitotic checkpoints. Any defect in the key genes involved in the regulation of these mechanisms often results in genomic instability, predisposing the cells to malignancy. This results in altered expression of many coding and noncoding genes. The noncoding RNAs especially the long noncoding RNA (lncRNAs) and microRNA (miRNAs) act as key regulators of cancer gene networks. Some miRNAs repress the expression of the heterochromatin-associated proteins, inducing the formation of open chromatin, and promoting the expression of genes required for oncogenesis. Additionally, specific miRNAs may also favour cancer progression and metastasis by regulating the expression of genes that support the metabolic microenvironment essential for cancer cell growth and proliferation. Understanding how these noncoding RNAs contribute to breast cancer development opens potential avenues for therapeutic intervention, targeting their dysregulated activity.

1. Introduction

Breast cancer is the most prevalent form of non-cutaneous cancer affecting women all over the world [1]. Due to the inherent heterogeneity of breast tumours, there are ongoing concerns in terms of accurate diagnosis and effective therapeutics. In recent years, advancements in imaging techniques have allowed for earlier detection of breast cancer, which has led to a reduction in mortality rates and disease burden within the general population. However, despite these improvements, breast cancer remains a formidable threat due to its ability to progress to advanced stages and develop resistance to radiation therapy and chemotherapy. The development of malignant tumour in breast tissues, mainly the ducts and lobules responsible for milk secretion results in breast cancer. Although extensive research in the field has shed light on the molecular pathways and gene expression patterns in breast tumours, the exact cause of breast cancer in most patients remains an enigma. Various risk factors contribute to the development of breast carcinoma. These include age, family background, obesity, excessive alcohol consumption, exposure to estrogen, and inherited defects such as mutations in susceptibility genes like *BRCA1* and *BRCA2* [2]. Women harbouring the BRCA mutation in their genome are estimated to carry a 40 %–85 % risk of developing breast cancer, ovarian cancer as well as other primary cancers. *BRCA1* and *BRCA2*, located on chromosomes 17 and 13, respectively are inherited in an autosomal dominant fashion with high penetrance, thus increasing the

* Corresponding author.
E-mail address: tapas@jncasr.ac.in (T.K. Kundu).
[1] These authors contributed equally.

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incidence of BRCA-associated cancers in affected families [3]. *BRCA1* plays a predominant role in DNA damage repair response. Therefore the progression and generation of BRCA associated breast tumour rely on disruptions in functions of components involved in the DNA damage repair pathways [4].

Breast cancers are mostly epithelial in origin and are classified as carcinomas. They are considered as a heterogenous disease even though all kinds of breast tumours originate from the same organ i.e. breast. This inherent heterogeneity can be observed through various morphologic and molecular variations which serve as valuable diagnostic and therapeutic markers [5]. For instance, the presence of estrogen receptor (ER)/progesterone receptor (PR) indicates a subset of tumour that could be treated by hormone modulation therapy (e.g. tamoxifen and aromatase inhibitors). Likewise, *ERBB2* (*HER2*) amplification or overexpression is a feature of a definite subset that can be targeted with antagonists like trastuzumab [6]. Tumours that do not show positivity in ER, PR and HER2 amplification ("triple negative") are unlikely to respond to the above-mentioned therapeutics and are thus classified as tumours with poor prognosis i.e. difficulty in predicting the course of the cancer [7,8]. In recent times, a more in-depth molecular classification of breast cancer diversity has been carried out with newly mined information from genome scale analysis and microarray based gene expression profiling. Expression patterns of "intrinsic" genes (more variants between than within tumours) have led to further classification of breast cancer into at least six molecular subtypes [9–11]. As for example, luminal subtypes A and B both express markers (keratins 8/18) of the luminal epithelial layer of normal breast ducts and are ER positive, but luminal B tumours are more proliferative and have less favourable prognosis. Amplification and overexpression of *ERBB2* (*HER2*) and neighbouring genes at 17q12-q21 is associated with the *ERBB2* positive subtype. A basal-like subtype exhibits markers of the basal epithelial layer of normal breast ducts (e.g. keratins 5/6). They generally do not express ER, PR and HER2 and are associated with unfavourable prognosis. The triple negative class of breast tumours also exhibit low expression of cell adhesion proteins like Claudin, *E*-cadherin and high expression of mesenchymal markers like Vimentin, ADH1, Snai 1/2, along with other stem cell characteristics [11]. The mechanisms underlying origination of different molecular subtypes of a single carcinoma is very intriguing [12,13]. The different subtypes might arise because of distinct alterations in chromatin organization which consequently influence the gene expression.

The proliferation of malignant epithelial cells enclosed within mammary ducts leads to ductal carcinoma in situ (DCIS). They are characterised by their distinct cytological features and abnormal growth pattern. However, the malignant cells are still contained by the basement membrane of the ducts. The invasive ductal carcinoma (IDC), also known as infiltrating ductal carcinoma, is more aggressive in nature, characterised by cells invading through the breast tissue, lymphatics and blood vessels to the distant regional lymph nodes, or in later stages, throughout the body [14]. According to stages of differentiation, IDCs are classified majorly into three grades - grade 1 being well differentiated while grade 3 is poorly differentiated with clusters of neoplastic cells, absence of gland formation, a substantial amount of mitotic activity and nuclear atypia. Most of the IDCs express the hormone receptors for progesterone and estrogen, and are therefore susceptible to hormone mediated therapy. Approximately 15%–20 % of IDCs also express HER2, which contributes to the aggressive behaviour observed in these tumours. Infiltrating lobular carcinoma, the second most common type of invasive carcinoma, primarily affects older women and demonstrates better histological differentiation along with estrogen receptor positivity. ILC has been found to metastasize to different parts such as cerebrospinal fluid, leptomeninges, gastrointestinal tract, bone marrow, serosal surfaces, ovary and uterus (which resemble low-grade stromal sarcoma). These carcinomas occur mostly due to a lack of cellular cohesion because of mutation or loss of function of *E*-cadherin. However, types of breast cancer progression are associated with genomic instability and the consequent alteration of higher ordered chromatin structure. As cancer develops, cells change their metabolic status, a process known as metabolic reprogramming, to fulfil the nutritional requirements for continuously dividing cells. This is brought about by chromatin reorganization that alters the expression pattern of relevant metabolism-associated genes. One of the key players that regulate this gene expression is a class of non-coding RNAs called miRNAs.

In this review article we will extensively examine how various miRNAs can alter metabolism in breast cancer cells to suit their metabolic needs, and subsequently influence genome organization. The multi-omics and interdisciplinary approach to understanding cancer biology, reveals that the metabolism-miRNA/noncoding RNA-altered chromatin organization is the key axis for cancer initiation and progression. We would especially like to shed light on a possible interesting link between chromatin-associated proteins-PC4, HP1α and miRNA29a which could be critical players in the process of breast cancer manifestation through genome reorganization and alteration in metabolism. A comprehensive review, especially for early career students and post-doctoral researchers is not available. This review article should serve the purpose.

2. Key concept definitions

Tumour- An abnormal mass of tissue formed due to uncontrolled cell division and/or reduced cell death. The tumour may be benign if it does not grow further and spread. Otherwise, it will become malignant by spreading to other parts of the body through blood and lymph nodes.

Estrogen – A category of hormones responsible for development of the female reproductive system and their secondary sex characteristics.

Antagonist – A substance or ligand that interferes or competes with the physiological function of another.

Chromatin – A complex of DNA, histones and other proteins found in the nucleus of eukaryotic cells.

Literature review approach: We did a thorough literature search on miRNAs regulating chromatin-associated proteins and those regulating metabolic pathways. We primarily utilized PubMed to identify appropriate articles for our literature review. Most of the articles chosen for information collection were recent (post 2000 period) with the oldest being from 1979. While there may be a lot of findings on miRNAs and cancer, we primarily focused on miRNAs exclusively involved in breast cancer, its metabolism and underlying genome regulation.

3. Genomic instability: Fundamental cause of breast cancer progression

The systematic organization of chromatin by histones and non-histone proteins is the first line of defense to protect the genetic material. Additionally, cells rely on various epigenetic factors and non-histone proteins to modulate chromatin structure, along with regulating catabolic pathways such as autophagy and DNA repair processes. Disruption of these highly coordinated safeguard mechanisms might result in genomic instability. Genomic instability is one of the hallmarks of cancer and is believed to be necessary for cancer cells to accumulate multiple mutations required for its development and hence acts as a major driving force for cell heterogeneity and tumorigenesis [15,16]. It provides advantages to tumour cell populations by enabling them to shorten their cell cycle duration and evade intracellular and immunological control mechanisms. One hallmark characteristic of genomic instability is an increased frequency of small structural variations like base pair mutations, also known as microsatellite-instability (MSI), or significant variations such as changes in chromosome number and/or structure, which are collectively referred to as chromosome instability (CIN) [17,18]. Microsatellite instability has been commonly observed in many solid tumours. Chromosomal instability can result from an increased rate of chromosome mis-segregation during mitosis which results in inheritance of an incorrect number of chromosomes or abnormal chromosome structure [19]. Consequently, precise segregation of chromosomes is vital for preserving genomic stability and its failure can result either in cell death or the development of malignant tumours.

Telomere dysfunction has been proposed as one of the mechanisms underlying genomic instability [20]. Hyperproliferation of cells (hyperplasia) during the early stages of cancer progression could lead to telomere abrasion, which could further enhance the frequency of chromosome fusion and breakage-fusion-bridge (BFB) cycles resulting in complicated chromosomal rearrangements [21]. It has been reported that telomere length is shorter in more aggressive breast cancer subtype such as triple negative breast cancer (TNBC), luminal, and HER2+ tumours and hence can be used as a prognostic marker for chromosome instability in breast cancer [22]. The regulation of chromosome segregation relies heavily on various proteins associated with chromatin, underscoring their essential role in maintaining cellular homeostasis. Dysregulation of these proteins can potentially contribute to tumour formation. Hereditary breast cancers caused by germline mutations in BRCA1, BRCA2, CHEK2 and TP53 lead to defects in DNA repair and cell-cycle checkpoints [23,24]. Studies have shown that genomic alteration in TP53 gene can drive metabolic reprogramming in TNBC [25]. Most breast tumours linked to BRCA1 exhibit basal markers and gene-expression patterns and are typically triple-negative with highest frequency of chromosome instability among the breast cancer subtypes [26–28]. BRCA1 has a range of functions, but its tumour-suppressive role is most commonly associated with its involvement in repairing DNA double-strand breaks (DSBs) [29]. Mutation in BRCA1 have been associated with more aggressive receptor negative phenotype [30]. Both sporadic basal-like and BRCA1-associated breast tumours tend to lack markers of a normal inactive X chromosome [31].

Genomic instability can benefit tumours by introducing advantageous changes and can also create vulnerabilities that can be exploited. It can lead to "synthetic lethal" interactions by causing gene or pathway dependencies in tumour cells [32,33]. For instance, tumours with BRCA1 or BRCA2 deficiencies exhibit increased sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors [34]. PARP is involved in repairing DNA strand breaks, and its inhibition can result in the collapse of replication forks and the formation of double-strand breaks (DSBs) that rely on homologous recombination (HR) and non-homologous end-joining (NHEJ) pathways for repair [35]. Since BRCA mutations are present in tumours but not in normal tissues, PARP inhibitors are likely to be highly specific to tumours. Recent clinical trials have demonstrated the effectiveness of PARP inhibitors in tumours with BRCA mutation carriers [36,37].

4. miRNAs as modulators of gene expression: Role in breast cancer

Among the different factors that regulate chromatin dynamics and gene expression, microRNAs play a crucial role [38]. MicroRNAs are a subclass of non-coding RNA molecules that have been extensively studied due to their ability to modulate gene expression. These small RNAs are encoded by only about 1% of the genome in most species and are evolutionarily conserved [39]. The first miRNA to be discovered was lin 4 in *C. elegans* [40]. Since then, research in the field of miRNAs has gained a huge impetus due to the ability of miRNAs to modulate gene expression by diverse mechanisms. A primary microRNA is transcribed mainly by RNA polymerase II (some by RNA polymerase III), either from the intron of a coding gene or from the intergenic region like other regular mRNAs. The pri-miRNA undergoes several processing steps (capping, polyadenylation, etc.) by various enzymes or functional proteins, such as Drosha, Exportin 5 and Dicer, to yield the functional mature microRNA after being spliced from its precursor [41]. These miRNA molecules, which are approximately 22 nucleotides long, play a crucial role in post-transcriptional gene expression regulation by binding to their target mRNAs. This interaction occurs through incomplete base-pairing, primarily in the untranslated regions of the mRNA. As a result of this binding process and subsequent formation of the RNA-induced silencing complex, degradation of the mRNA takes place [42]. It is worth noting that unlike other forms of gene regulation that rely on high complementarity between molecules, miRNA-mRNA binding can occur with less stringent matching criteria. Interestingly, a single miRNA has been found to have multiple targets as it does not require exact sequence complementarity for regulatory effects [43]. One specific miRNA molecule can potentially impact several hundred different mRNAs simultaneously. Consequently, this molecular mechanism enables even subtle changes in miRNA expression levels to exert substantial influence over various cellular pathways including those related to cancer [44]. Microarray-based studies in various cancer cells and tumours have provided insights into the abnormal expression patterns of multiple miRNAs, particularly in breast, prostate, thyroid, and gastric cancers. However, predicting the prognosis or outcome of a specific type of cancer solely based on the expression pattern of a single miRNA is challenging due to the genetic heterogeneity observed among tumours and cell lines derived from different tumour types. It should be noted that miRNAs functionally interact with various factors such as protein kinases, cyclin proteins, growth suppressors and promoters to regulate cellular processes like cell proliferation and cell cycle

progression pathways. Thus, comprehending these complex interactions would allow for better understanding of how aberrant expression patterns may contribute to carcinogenesis [45]. A miRNA can play different roles in cancer, acting as an oncogene in certain types of cancer and as a tumour suppressor in others. The miRNAs acting as oncogenes are termed as oncomiRs and are often upregulated in cancer while those which show tumour suppressive functions are often downregulated. In breast cancer particularly, due to its heterogeneity and molecular subtypes, various miRNAs are deleted or undergo downregulation or upregulation. Aberrant expression of miRNAs occurs for several cancer-related genes resulting in cancer initiation, progression, metastasis, or drug resistance [46]. In breast cancer specifically, several key miRNAs have been identified that demonstrate altered expression levels depending on their respective roles as either oncogenes or tumour suppressors [47]. These dysregulated miRNA molecules exert their effects by targeting specific genes involved in breast tumorigenesis. Fig. 1 illustrates some carefully selected examples of differentially expressed miRNAs in breast cancer cells that contribute to the regulation of malignant processes.

It was found that one of the members of the miRNA29 family, miRNA29a is significantly upregulated in breast cancer cell lines and patient samples [48]. A study from our group revealed that this overexpression of miRNA29a led to the downregulation of nonhistone chromatin protein PC4 resulting in enhanced DNA damage, autophagy, and expression of genes required for malignancy [49].

The miR29 family in humans is composed of three mature microRNAs: hsa-miR-29a, hsa-miR-29b and hsa-miR-29c. The miR-29b group consists of two members miR-29b-1 and miR-29b-2 which share an identical mature sequence. These microRNAs are highly conserved across different species, with their mature sequences remaining the same. Specifically, the nucleotide positions from 2 to 7 (known as the seed region), which can bind to protein coding genes, exhibit exact matches among all mature miRNAs. The miR29 family genes have genomic localization in two different chromosomes. In humans, the gene encoding the precursors of miR- 29a and miR-29b-1 is located on chr. 7q32.3, whereas the gene encoding miR-29b-2 and miR-29c is on chr. 1q32 [50]. miR29, like other microRNAs (miRNAs), is transcribed by RNA pol II. Studies provide evidence that multiple transcription factors regulate the expression

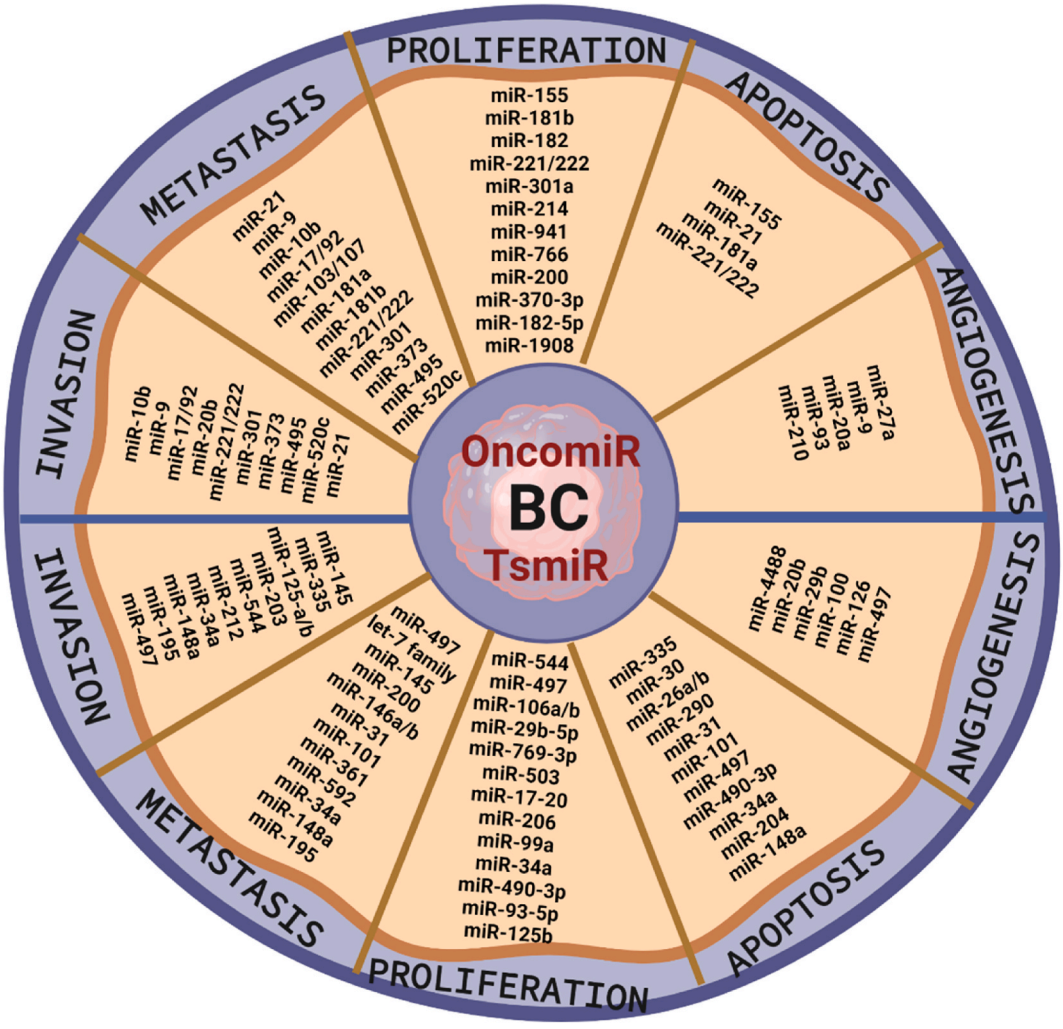

Fig. 1. Expression of miRNAs in Breast Cancer. This figure summarizes the miRNAs reported to be either upregulated (OncomiRs) or downregulated (tumour suppressor miRNAs) in Breast cancer.

of miR29 and subsequently influence the expression of its mRNA targets indirectly [50]. Analysis of miRNA expression patterns across tumour tissues and cancer cell lines indicates that there is a general downregulation of miR-29 in most cancers, while only a few show an upregulation. The contrasting levels of miR-29 expression have prompted an extensive investigation into their potential as oncogenes or tumour suppressors across various types of cancers [51].

miR-29 is downregulated in many solid tumours and hematologic neoplasms. miR-29 is also expressed at a lower level in lung cancer tissue compared to normal lung tissue. In non-small cell lung cancers, the entire miR29 family (miR-29a, miR-29b, and miR-29c) is downregulated [52]. Moreover, in the nervous system, miR-29 is expressed at low levels in neoplasms such as glioblastomas and neuroblastoma [53]. miR-29a was reported to induce osteoblastic cell apoptosis by inducing *E2F1* and *E2F3* expression and silencing *Bcl 2* and *Mcl 1* [51]. Even though miR29 is majorly downregulated in most cancers it was found to be upregulated in breast cancer tumour tissues and serum of patients mediating cell invasion and chemotherapy resistance [54,55]. This upregulation of miR29 family was also observed in several rare diseases such as diffuse large B cell lymphoma and malignant pleural mesothelioma [53]. miR-29a contributes to breast cancer EMT transition and invasion by repressing SUV420H2 mediated H4K20 trimethylation [48]. Thus, the expression pattern of miR29 is a critical factor in the context of the physiological state of the cell, the cancer cell type and its diverse mRNA targets which in turn regulate several cellular pathways. The target genes play a decisive role in determining the fate of the tumour, either its development, progression or its inhibition (Fig. 2).

A chromatin associated protein PC4 has been significantly downregulated both at the protein and transcript levels in most breast cancer samples, indicating its role in tumour suppression [49]. PC4 expression is significantly reduced in ZR-75-1 breast cancer cells, which are known for their high invasiveness. The restoration of PC4 expression in these cells resulted in a reversion of their invasive and migratory properties, suggesting the tumour-suppressive function of this protein. Interestingly, miR-29a was identified as a negative regulator of PC4 expression through direct binding to its 3′UTR region. Overexpression of miR29a led to downregulation not only of PC4 but also enhanced cell migration properties in MCF7 cells. This implicates the involvement of multiple regulatory factors impacting cellular behaviour through modulating key heterochromatin organizers like PC4. In agreement with our observation recently it has been reported that indeed in TNBC miR29a is overexpressed causing lung metastasis which could be efficiently inhibited by anti-miR29a treatment [56]. However, like PC4, another heterochromatin organizer, HP1 alpha has also been reported to be downregulated in breast cancer. The mechanisms behind this downregulation remain unclear. Further research is warranted to explore other potential microRNAs or molecular players involved. Overexpression of miRNA has been implicated in promoting malignancy through various mechanisms. One such mechanism involves its ability to alter the higher-ordered chromatin organization, resulting in a direct modulation of gene expression involved in cancer cell metabolism.

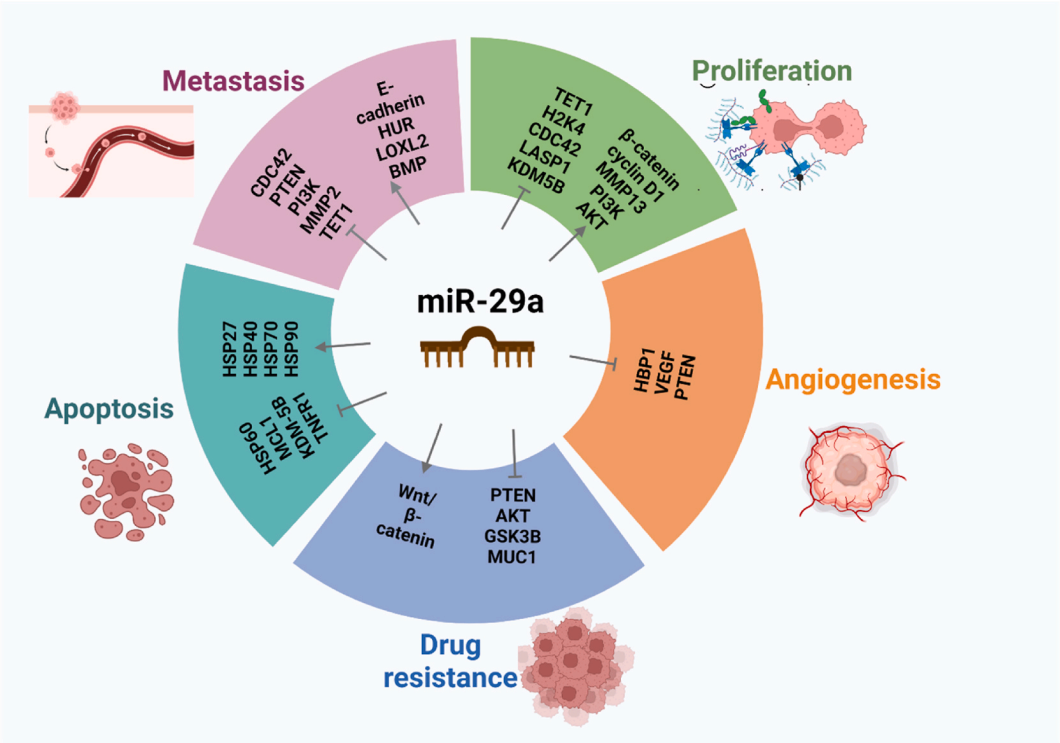

Fig. 2. Diverse roles of miR29a. Several cellular processes and genes that have been reported to be targeted by miR-29a. Some of their targets are shown above.

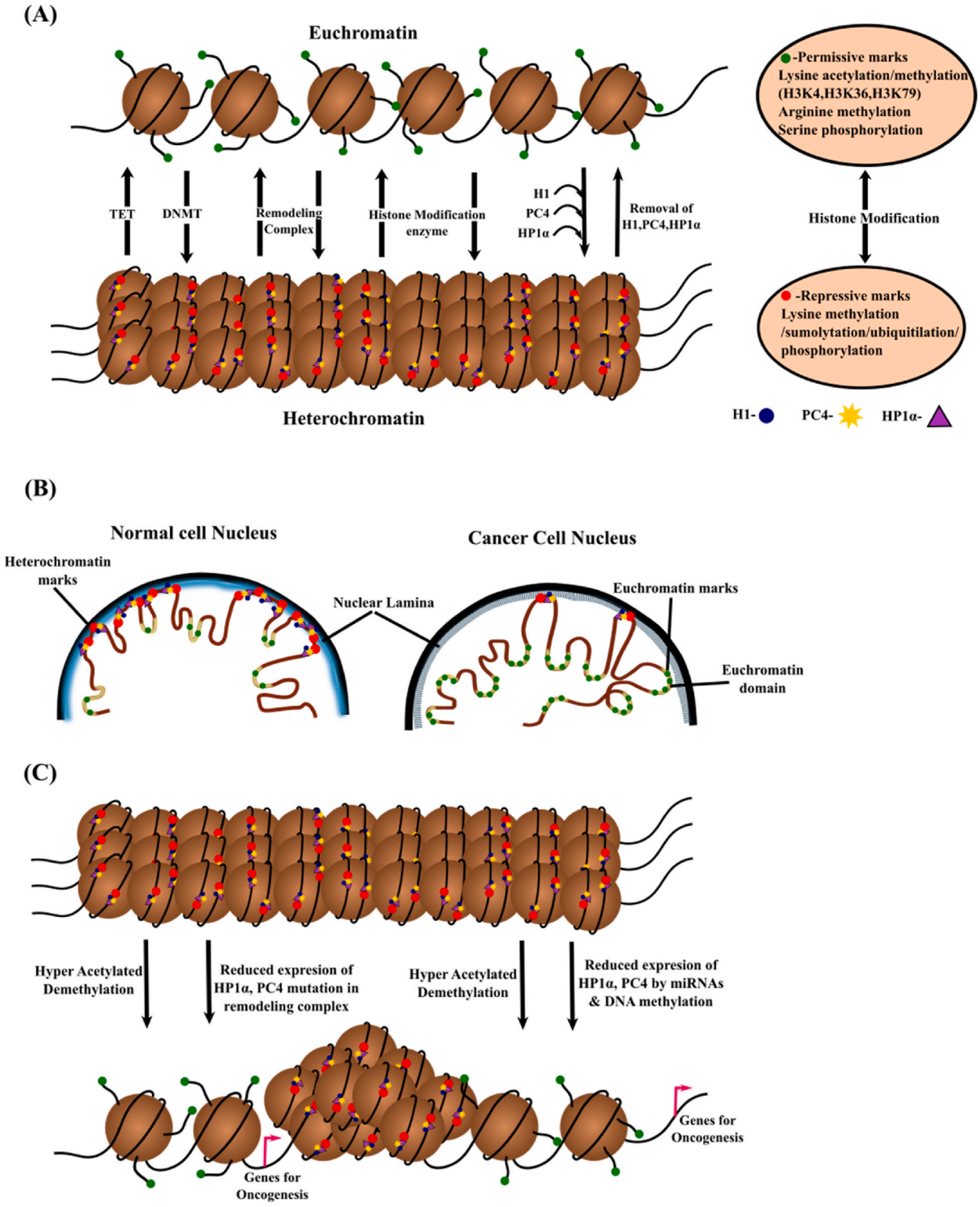

Fig. 3. Dynamic reorganization of heterochromatin facilitates oncomiR expression: (A) Besides Histone modifications and chromatin remodelling, heterochromatin organization is also regulated by nonhistone chromatin proteins (H1, HP1a and PC4). (B) Chromatin domain organization in normal cell and cancerous cell nuclei. Large segments of the genome in cancer cells become euchromatinized leading to increased expression of genes associated with cancer. (C) In cancer due to the loss of heterochromatin proteins and aberrant histone modifications, many euchromatin domains are formed which favour the expression of genes related to oncogenesis.

5. Dynamic euchromatin-heterochromatin landscape for cancer initiation and progression

In the interphase nucleus, each chromosome is present as an individual chromatin territory (CT) occupying a distinct place. The domains of CTs are in a dynamic state of folding (heterochromatin) and unfolding (euchromatin). Heterochromatin refers to the densely packed regions of DNA characterised by its condensed structure. These regions typically contain genes that are transcriptionally inactive or have restricted accessibility for gene expression machinery. On the other hand, euchromatin represents less compacted areas where active transcription occurs more frequently [57]. Each heterochromatin and euchromatin compartment comprises of numerous chromatin domains [58]. These domains put constraints on gene regulatory sequences, limiting their interaction. The nucleolus is a non-membrane-bound compartment consisting of perinucleolar heterochromatin which is enriched in H3K9me3, H3K27me3 and H4K20me3 marks [59]. It is also responsible for ribosome biogenesis and other cellular function including cell cycle, cell differentiation etc. [60,61]. Thus, the significant alteration of nucleolus structure and function is the signature of cancerous cells. These heterochromatin regions encompass a diverse range of genetic elements and can be found at distinct genomic regions. The region proximal to the centromere that assumes paramount importance in regulating transcription and ensuring accurate chromosome segregation is found to be heterochromatinized. This particular region primarily comprises repetitive DNA elements along with other associated chromosomal proteins [62]. Heterochromatin regions are found near telomeres and play a role in telomere protection from DNA damage [63]. In addition to these, heterochromatin marks are found near a subset of specific genes interspersed in the genome and are responsible for their differential gene expression [64]. The heterochromatin formation involves methylation of histones (H3K9me3) and the assembly of non-histone chromatin protein HP1 which recognises the above methylation marks and compacts the DNA [65]. H3K9me3 thus acts as a hallmark of heterochromatin formation.

The multifunctional chromatin associated protein PC4 directly and specifically interacts with HP1α [66]. The absence of PC4 leads to a drastic loss of heterochromatin and dramatic alteration in the epigenetic landscape of histone modifications with the induction of autophagy [67]. Recent findings suggest that HP1α, PC4 and histone H1 complex may play a central role, in heterochromatin transition and spread, which could be critical in cancer progression. It was found that indeed PC4 and HP1α are downregulated in breast cancer, where miRNA 29a is causally involved in the downregulation of PC4. The miRNA-mediated regulation of chromatin protein expression may directly affect the genome organization and thereby the gene regulation (Fig. 3A and B and C).

6. Epigenetic regulation of breast cancer metabolism

Cancer cells undergo various metabolic changes that significantly impact their fate, enabling them to acquire nutrients from both conventional and unconventional sources to produce biomass. This results in a reprogramming of cellular metabolism, promoting the utilization of the TCA cycle and glycolysis to generate NADPH as well as meet nitrogen requirements for nucleotide biosynthesis. In addition to genetic mutations, epigenetic alterations also contribute to this metabolic reprogramming in cancer cells. Notably, there exists a reciprocal relationship between cellular metabolites and the epigenome; these metabolites can act as chemical entities capable of modifying amino acid residues on histones, while at the same time, these epigenetic modifications can control gene expression responsible for various metabolic processes associated with cancer development [68]. The metabolites that promote tumorigenesis by altering the epigenome are termed as *oncometabolites*. The most widely studied epigenetic alterations associated with cancer include DNA methylation and post-translational modifications of histone and histone variants. In addition to this, miRNAs which are dynamically expressed, can control differential gene expression and are involved in maintaining genomic stability, impacting the metabolic pathways including glycolysis, glutaminolysis and the TCA cycle.

DNA methylation mostly occurs at the CpG sites within the gene promoters leading to transcriptional silencing. In normal cells, these CpG sites are mostly unmethylated whereas CpG-poor regions are highly methylated. In breast cancer, all the isoforms of DNA methyltransferases DNMT1, 3A and 3B are overexpressed [69]. Therefore, a noticeable alteration is noticed in cancer cells where there is an inclination towards hypermethylation of CpG islands at promoters of tumour suppressor genes like *BRCA1* and *MGMT*, which consequently promotes enhanced glycolytic metabolism, tumour advancement, and diminished methylation within gene bodies [70]. Several metabolites play key roles in regulating the patterns of histone and DNA methylation. One such metabolite is S-Adenosyl Methionine (SAM), the levels of which are drastically increased in breast cancer. The overproduction of SAM leads to hyperactivation of lysine methyltransferase Suv39h1 which in association with DNMT1, hypermethylates estrogen receptor alpha promoter, resulting in its silencing and non-responsiveness of breast cancer to receptor targeted therapy [71]. Suv39h1 can also increase the H3K9me3 mark and reduce the expression of *E*-cadherin to promote epithelial-to-mesenchymal transition [72]. Another metabolite that promotes breast cancer by regulating methylation is α-ketoglutarate, a cofactor for Jumonji C domain containing histone demethylases (JHDM) and Ten-eleven-translocation proteins (TET). α-ketogluarate levels are elevated in breast cancer which increases the activity of histone demethylases such as JMJD4 and JMJD5. JMJD4 is required for ensuring proper chromosomal segregation in breast cancer cell proliferation [73] while JMJD5 interacts with pyruvate kinase muscle isozyme and promotes glycolysis [74]. Glutamine is the third important metabolite associated with histone methylation regulation that plays critical regulatory role in breast cancer. In cells, glutamine gets converted to glutamate by glutaminase enzyme, the activity of which is positively correlated with breast cancer. Glutaminolysis i.e. conversion of glutamine to glutamate regulates the activity of JMJD3 and ubiquitously transcribed tetratricopeptide repeat X (UTX) which specifically demethylate H3K27me3 [75]. JMJD3 induces demethylation of promoters of *XIAP* and *survivin*, in a glutamine dependant manner and this leads to apoptosis resistance. Moreover, it has been shown in breast cancer cells that inhibition of glutamine synthetase leads to dysregulation of expression of anti-apoptotic and metastatic genes due to changes in H3K4me3 and H4K16 acetylation levels [76].

Multiple studies have indicated that histone acetylation is affected by glucose metabolism in cancer. Even in oxygen rich

conditions, cancer cells utilize glucose to produce lactate and this glucose availability is linked to histone acetylation and acetyl CoA abundance. Moreover, lactate by itself, can promote histone acetylation by inhibiting the activity of the antagonistic histone deacetylases [77]. Exogenous treatment of lactate could lead to hyperacetylation of histone H4 and increased expression of genes involved in cancer manifestation [78]. In breast cancer associated fibroblasts, it has been observed that lactate overproduction leads to tumour growth by promoting demethylation of HIF-1α [79]. There exists a positive correlation between histone acetylation and acetyl CoA level which is inversely associated with acetyl CoA/CoA ratio. Pyruvate dehydrogenase complex converts pyruvate to acetyl CoA and any perturbation within this complex induces the glycolytic shift resulting in ATP production via glycolysis rather than oxidative phosphorylation which occurs in cancer cells. In aggressively proliferating cancer cells, the excess pyruvate produced by glycolysis that does not get converted to lactate, will ultimately enter the TCA cycle by conversion to acetyl CoA. In breast cancer, a few enzymes of the TCA cycle, namely isocitrate dehydrogenase, succinate dehydrogenase and fumarate hydratase have been found to be deregulated which could affect acetyl-CoA generation and overall histone acetylation [80]. Several breast cancer cell lines have been reported to produce excess levels of pyruvate dehydrogenase complex and ATP citrate lyase which leads to increased histone acetylation consequently overexpressing genes required for therapy resistance [81,82]. The mTOR signalling complex, which plays an important role in promoting cancer cell growth, also promotes acetyl CoA production by phosphorylating ATP citrate lyase, an enzyme responsible for generating nucleocytosolic pool of acetyl CoA [83]. Another enzyme required for acetyl CoA generation is acetyl coenzyme A synthetase 2 (ACS2) which gets upregulated in breast cancer. An upregulation of H3K4 acetylation in the promoters of genes associated with estrogen resistance and epithelial-to-mesenchymal transition has been observed in the early stages of breast cancer [84]. In triple negative breast cancer, acetylation at H4K8, H4K12 and H4K16 positions is involved in the expression of genes required for maintenance of cell stemness under hypoxic conditions [85]. Cancer progression is also associated with a high rate of lipid biosynthesis which utilises acetyl CoA using the enzyme acetyl coenzyme A carboxylase [86].

2-ODDDs (2-oxoglutarate/Fe(II)-dependent dioxygenases) are enzymes that require oxygen to maintain the hypoxia and epigenetic modification and are important to reverse the methylation in histones and DNA. The dysregulation of O-GlcNAcylation contributes to several metabolic diseases including cancer. O-GlcNAcylation transferase (OGT) can modify all the core histones by interacting with chromatin remodelers. In cancer, OGT gets overexpressed and, as a result, various histone H3 modifications can be altered. In addition to O-GlcNAcylation, histones can also be phosphorylated at different serine and threonine residues. It has been found that H3 and H2B phosphorylation at S10 and S32 respectively are linked with the expression of oncogenes. Tyrosine and Serine/threonine kinases mediated signalling act as a regulatory switch for various histone modifications and connect gene transcription to chromatin remodelling complexes indicating the role of histone phosphorylation in cancer development [87]. One of the key glycolytic enzymes pyruvate kinase 2 gets upregulated in multiple cancers and results in protein kinase mediating histone phosphorylation [88]. In breast cancer, PKM2 directly interacts with H2AX and phosphorylates serine 139 under DNA-damaging conditions and promotes genomic instability [89].

7. Epigenetic regulation of miRNAs in breast cancer

There are growing evidence of miRNA expression being regulated by different epigenetic mechanisms and several of these findings have significant implications in breast cancer manifestation. miR-129-2 expression is downregulated by DNA hypermethylation in its promoter leading to increased cell proliferation and reduced apoptosis [90]. Another group of miRNAs- miRNA-124a-1, miRNA-124a-2 and miRNA-124a-3 are also hypermethylated at their promoters leading to enhanced cell proliferation [91]. Other examples of miRNAs whose expression is reduced by DNA hypermethylation in breast cancer are miR-200b, miR-200c and miR-141 [92,93]. These miRNAs probably serve as tumour suppressors and so DNA methylation is used as a mechanism to reduce their expression for promoting cancer. In contrast, there are miRNAs like miR-663, miR-375, miR-216a, miR-205 and miR-124-2 that can promote cancer and their promoters are found to be hypomethylated resulting in their overexpression [94–98]. There is also a negative feedback regulatory circuit between miRNAs and DNA methyltransferases, the dysregulation of which can lead to breast cancer. The promoters of miR-148a and miR-152 are hypermethylated due to overexpression of DNMT1, which is also targeted by these miRNAs [99]. These miRNAs function as tumour suppressors by targeting Insulin-like Growth Factor Receptor (IGF1-R) and Insulin Receptor Substrate 1 (IRS1) which are generally highly expressed in breast cancer tissues. miRNAs may also regulate the expression of downstream targets by regulating their promoter methylation indirectly. For example, in the invasive ductal carcinoma subtype of breast cancer, miR-646 gets upregulated which targets *TET1,* a dioxygenase that removes DNA methylation marks [100]. This leads to increased methylation at *IRX1* promoter and a concomitant upregulation of histone cluster H2B. There are also reports of reduced expression of miR-26 a/b, miR-29 a/b and miR-149 a/b, which leads to increased expression of their target DNMT3b resulting in aberrant DNA hypermethylation [101]. Besides DNA methylation, histone modifications may also regulate miRNA expression in breast cancer. miR-708, which is presumed to play a tumour suppressive role, is transcriptionally repressed by Polycomb Repressor Complex 2 induced H3K27 trimethylation of its promoter [102]. Another miRNA miR-9-3, which is involved in p53-related apoptotic pathways, is repressed by environmental estrogens in mammosphere derived epithelial cells through elevated trimethylation of H3K9 and H3K27, along with DNA hypermethylation at its promoter [103,104]. Collectively, both the DNA methylation and histone modifications seem to be fine-tuning the expression of miRNA. In coming years this regulatory network of miRNA expression will be unravelled further, encompassing other histone modifications and non-coding RNAs.

8. Metabolism, miRNA and breast cancer progression

Cancer cells possess unique characteristics such as rapid proliferation, insensitivity to contact inhibition, and the ability to spread to

other parts of the body. To fulfil their high energy requirements, these cells undergo metabolic reprogramming. For many years, researchers have attributed this process primarily to a phenomenon called the Warburg effect - named after Otto Warburg. In the Warburg effect, cancer cells shift from oxidative phosphorylation to lactic acid fermentation even in the presence of oxygen which should favour the former process over the latter for energy generation [105,106] This leads to faster production of ATP with a compromise on the net ATP yield that helps in quicker build-up of biomass to support cell proliferation. Moreover, lactic acidosis reduces the pH to maintain an acidic microenvironment and leads to ROS (reactive oxygen species) mediated signalling for homeostasis [107,108]. However, there is increasing evidence suggesting that in addition to the Warburg effect, a myriad of other catabolic and anabolic pathways may be altered by cancer cells to suit their specific demands in a context dependant manner. Interestingly, many miRNAs play direct or indirect roles in regulating these metabolic pathways by activating oncogenes or repressing tumour suppressor genes. In this review, we shall be discussing the regulatory roles played by miRNAs in altering metabolic pathways only in the context of breast cancer.

The principal source of energy in all the cells is carbohydrates, mainly in the form of glucose. Once glucose enters the cells, it undergoes glycolysis to generate ATP and pyruvate. The rate of glycolysis is higher in cancer cells because pyruvate predominantly undergoes reduction to form lactate instead of entering the longer TCA cycle, thereby increasing the glucose flux within the cells. The first step in glycolysis is a rate-determining irreversible step catalysed by hexokinase, which converts glucose to glucose-6-phosphate. There are four different isoforms of hexokinase (HK1-4) [109–111] among which HK2 is upregulated in a variety of cancers including breast cancer [112]. Increased expression of hexokinase leads to an accelerated rate of glycolysis that supports cell growth and proliferation. miR-155 is a miRNA that upregulates HK2 via repression of another miRNA-miR-143, a negative regulator of HK2 [113]. It does so by activating the transcription factor CCAAT/enhancer binding protein beta (C/EBPβ) and repressing the suppressor of cytokine signalling (SOCS1) expression, which is an inhibitor of Janus kinase/STAT signalling [113]. This results in STAT3-based pro-inflammatory response that is a characteristic feature of cancer progression. In fact, upregulation of miR-155 has not just been observed in breast cancer cells but also in the associated pro-angiogenic macrophages and neutrophils. The pro-inflammatory cytokines released by them further induce the expression of miR-155 in breast cancer cells [114]. Another reaction step in glycolysis, catalysed by glucose-6-phosphate isomerase or phosphoglucose isomerase (PGI), is regulated by a group of miRNAs collectively called miR-200s (comprised of miR-200a, miR-200b and miR 200-c). It has been demonstrated in the MDA-MB-231 breast cancer cell line that these miR-200s prevent cancer metastasis by repressing the PGI catalysed reaction which affects the NF-κB signalling pathway and reduces the expression of mesenchymal transition markers such as ZEB1/ZEB2 [115].

Following glycolysis, the reaction of pyruvate reduction to lactate is catalysed by lactate dehydrogenase. This reaction is negatively regulated by a group of miRNAs- miR-30a-5p, miR-30d-5p, miR-34a, miR-34c, miR-200c, miR-323a-3p, miR-369–3p, miR-374 and miR4524a/b [116]. An inhibition of this step reduces the glucose flux by slowing down glycolysis resulting in decreased ATP

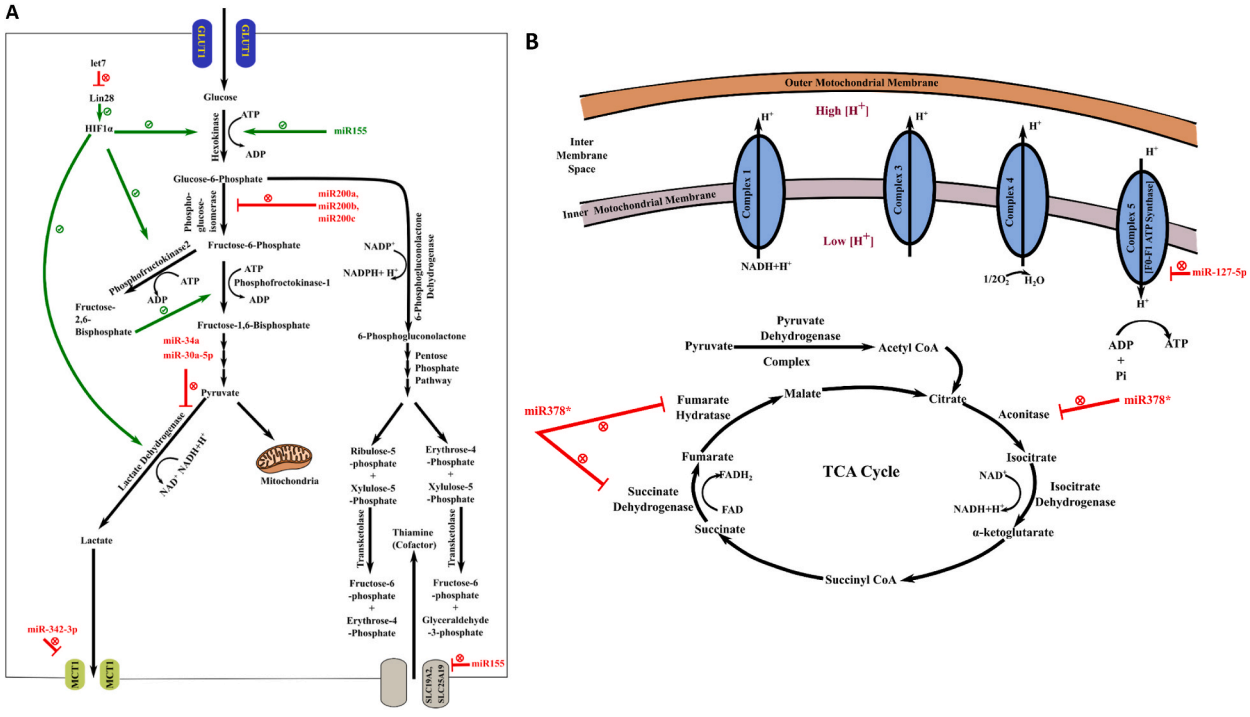

Fig. 4. The different metabolic pathways associated with breast cancer manifestation and controlled by miRNAs in (A) cytoplasm and (B) mitochondria. The miRNAs promoting the metabolic pathways suitable for breast cancer progression are shown in green. The miRNAs which negatively regulate cancer associated metabolic pathways are shown in red.

generation and cell proliferation. To ensure the continuation of glycolysis at a high rate, cancer cells from peripheral tissues efflux out lactate to the tumour microenvironment using monocarboxylate transporters (MCT), which are proton-linked plasma membrane transport proteins. This ensures that the excessive buildup of lactate in the cancer cells is avoided, thereby keeping the glycolytic flux high. There are several isoforms of MCT- MCT1, MCT2, MCT3 and MCT4, which have diverse expression patterns in different tissues. One such isoform MCT1 is negatively regulated by miR-342–3p which leads to reduced cell proliferation, migration and viability in breast cancer cells [117].

Oxidative phosphorylation is the more efficient method of generating ATP with a higher yield, compared to aerobic glycolysis. It consists of two stages. The first stage is the oxidative stage involving the oxidation of reduced electron carriers NADH and FADH2 by electron transport through a series of electron carriers with increasing order of reduction potential in the mitochondrial membrane and utilizing the released energy for creating a proton gradient across the membrane. This stage is regulated by several protein complexes with oxidoreductase functions (complex I, II, III and IV). The second stage is the phosphorylation stage in which the proton gradient is utilized by ATP synthase (complex V) to phosphorylate ADP to form ATP. Since cancer cells prefer a faster mode of ATP synthesis via aerobic glycolysis, there are miRNAs that serve this purpose by inhibiting or downregulating steps of the alternative pathway of oxidative phosphorylation. It has been reported in breast cancer cell line BT-549 that miR-127–5p downregulates the expression of the catalytic subunit of ATP synthase (β-F1 subunit) [118]. Another miRNA-miR-378* is regulated by Erb-B2 receptor tyrosine kinase, which brings about inhibition of expression of estrogen-related receptor-γ and GA binding protein transcription factor alpha subunit. These are binding partners of PGC-1b (the transcriptional coactivator for the gluconeogenic enzyme glucose-6-phosphatase) which is required for mitochondrial respiration and biogenesis. This results in decreased expression of important TCA cycle enzymes in the mitochondria viz. fumarate hydratase, succinate dehydrogenase and aconitase that further enables the cancer cells to rely more on anaerobic glycolysis instead of oxidative phosphorylation [119]. In addition to its designated role as an oncomiR, miR-378* has also been found to be a proangiomir because it promotes the expression of two transcription factors SuFu and Fus-1, that promote angiogenesis around the cancer cells, leading to metastasis [120]. (Fig. 4 B).

Several signalling pathways are closely associated with cancer manifestation. Among them, the PI3K/Akt/mTOR pathway is involved in regulating several metabolic reactions for reprogramming in breast cancer [116]. The serine-threonine protein kinase Akt increases ATP yield through a better coupling of glycolysis with oxidative phosphorylation, mediated by increased association between mitochondrial hexokinase (HKI and HKII) and voltage-dependant anion channel (VDAC) in mitochondria [121]. Akt also enhances glycolytic flux by increasing glucose permeability through induction of expression of lactate dehydrogenase isoform B (LDH- B), pyruvate kinase PKM2, glucose transporters GLUT1, GLUT2 and GLUT4 along with their translocation to the plasma membrane [122, 123]. The increased glycolytic flux causes more accumulation of citrate and ATP which is utilized by the enzyme ATP citrate lyase to generate acetyl CoA. This results in more acetylation of histones leading to increased expression of genes involved in cancer progression. The PI3K/Akt/mTOR signalling cascade is positively regulated by the Lin-28 which in turn gets suppressed by let-7, leading to attenuation of breast cancer progression [117].

With the growing knowledge of the different miRNA-regulated metabolic pathways utilized by breast cancer cells for survival (Fig. 4A and B), pharmacological drugs are being tested to target many of these steps.

One of the most prominent drugs used along these principles is metformin. The compound metformin can upregulate let-7 which in turn epigenetically downregulates the oncomiR miR-181a, thereby inhibiting epithelial-to-mesenchymal transition and reducing cancer cell proliferation [124]. Mechanistically, metformin can indirectly reduce mitochondrial oxidoreductase activity, prevent NADH reoxidation and maintain high enough AMP levels to affect the mTOR signalling pathway [125–127].

A positive correlation has been observed between obesity and breast cancer over a wide range of patient case studies. Therefore statins, which are cholesterol synthesis inhibitory drugs, have shown promise in breast cancer treatment. The drugs belonging to the class of statins, can bring about their antitumorigenic effect via modulation of expression of several miRNAs. Simvastatin downregulates miR-34a which in turn leads to reduced expression of NAD-dependent histone deacetylase SIRT1. It also upregulates miR-612 which reduces cancer stemness [128]. Another drug atorvastatin increases the expression of miR-140–5p which activates the transcription factor NRF1 that reduces breast cancer cell proliferation and induces apoptosis [129]. The isomiR-140–3p is downregulated by fluvastatin which leads to inhibition of the downstream mevalonic acid pathway and reduces cell growth in cell line models of triple negative breast cancer (TNBC) [130].

Since cancer manifestation also causes inflammation, non-steroidal anti-inflammatory drugs such as aspirin have been used for widespread applications in various types of cancer including breast cancer. Aspirin increases the abundance level of let-7 miRNA by reducing the levels of its sponge HC19. This affects the downstream PI3K/Akt/mTOR signalling pathway by decreasing levels of HIF1α and attenuates glycolysis, thereby lowering cell proliferation [131]. Another such anti-inflammatory drug sulindac downregulates miR 21 and reduces cell proliferation and invasion by inhibiting βcatenin/TCF4 signalling pathway.

Finally, small molecules that serve as antimetabolites by inhibiting enzymes required for nucleic acid biosynthesis have also been found to possess an antitumorigenic effect. Among them, 5-fluorouracil has attenuating effects on breast cancer cell proliferation by upregulating the expression of let-7 family miRNAs, miR-15b, miR-16, miR-23a, miR-23b and miR-200c [132].

9. Advantages and limitations of miRNA therapeutics in breast cancer prognosis and prediction

Over the decades, several research groups have explored the regulatory pathways of miRNA as a potential biomarker for the diagnosis, prognosis, and prediction of cancer. Their differential expression was used to explain the disease heterogeneity and pathology of different cancers. In addition, all this information on miRNA has started to find clinical applications using antagomirs for disrupting oncomiR functions and miRNA mimetics for restoring tumour suppressor miRNA functions. Antagomirs such as 2′-O-

methyl-modified oligonucleotides, locked nucleic acid (LNA) anti-miRs and cholesterol-conjugated oligonucleotides are being used to bind with the oncomiRs and prevent them from being processed by the RISC complex [133]. miRNA sponges can be used for interacting with multiple miRNAs that could act in a network for promoting carcinogenesis [134]. Simultaneously, the direct mRNA target could also be occluded from binding with miRNA using miRNA masks [135]. In cases where tumour suppressor miRNA levels are reduced in cancer, 2′-O′-methoxy RNA duplexes can be administered which biologically mimic the downregulated miRNAs and thus, after getting processed by RISC, can target the oncogenes and ameliorate cancer manifestation [136]. In the area of chemotherapeutics, miRNAs have certain advantages over small molecule modulators. They are relatively more target-specific and could have a more profound biological effect by specifically targeting mRNAs functioning in an interconnected network [137,138]. One obstacle for miRNA-based therapeutics is that these biomolecules have low physiological stability and tend to get degraded in the biological system upon administration for renal secretion [135]. Therefore, novel methods have been devised for efficient miRNA antagomir/mimetic delivery using viral vectors (adenovirus, retrovirus, lentivirus, adeno-associated virus) [139] and nanoparticles made with poly-ethylene glycol, iron, gold, carbon and silica [140]. To achieve specificity for directing the miRNA to tumour tissues, they can be conjugated with nanoparticles containing ligands, peptides or antibodies for cognate receptors of the corresponding targeted tissue [140]. miRNAs may also be encased in liposomes which can protect the molecules from degradation and pass through the plasma membrane easily through fusion before delivering them to specific sites [141]. For this purpose, polymers with high electrostatic affinity to membranes and biodegradability have also been used. These include materials like polyethyleneimine (PEI), poly (lactic-co-glycolic-acid) (PLGA) and other naturally cationic polymers such as chitosan and atelocollagen [142]. Another approach that could be taken to overcome the caveat of miRNA degradation upon delivery is directly editing out the oncomiRs using CRISPR-Cas9 based methods. Oncogenes implicated in breast cancer such as *HER2* [143] and *MIEN1* [144] have been selectively ablated by such methods, but these very same techniques are now starting to find applications in editing non-protein coding miRNAs as well. One promising result in this aspect has been seen with the use of CRISPR-Cas9 to knock out miR-23b and miR-27b which led to slower proliferation, colony formation, growth of breast cancer cells, both in vitro and in explanted tumours in mice [145]. These encouraging results indicate that miRNA therapeutics hold high prospects for breast cancer treatment.

In this review, we have focused on miRNAs whose involvement in breast cancer has been validated by several preclinical and clinical evidence. However, it is crucial to highlight that the validation of diagnostic, predictive, and prognostic miRNAs necessitates rigorous confirmation through independent cohorts or additional preclinical/clinical investigations. Moreover, incorporating multivariate testing is essential as the significance of numerous individual miRNAs diminishes when subjected to multiple testing. Each miRNA can potentially have several target mRNAs which further makes it difficult to have a comprehensive idea of which are the most critical miRNAs in breast cancer manifestation. It is important to note that miRNAs do not just function as individual entities but rather in a network to have a cooperative effect on the transcriptome. A number of interesting findings have been made in this regard, especially in recent times. miR-874–3p acts as a tumour suppressor by inhibiting cyclin E1 and preventing uncontrolled cell division. LINC02568 sequesters miR-874–3p and facilitates breast cancer malignancy by de-repressing cyclin E1 function [146]. Another miRNA miR-217–5p, which downregulates KLF5, gets adsorbed by the circular RNAs circEZH2 [147] and circROBO1 [148] that result in the upregulation of KLF5. This causes epithelial to mesenchymal transition in breast cancer leading to metastasis. So instead of targeting individual miRNAs, the entire "miRNome" should be taken into consideration when selecting potential targets for clinical therapeutics.

The establishment of a reliable panel of miRNA for breast cancer prognosis, diagnosis, and prediction poses challenges at each stage ranging from sample collection to data analysis. One major hurdle in utilizing miRNA as a biomarker lies in its low abundance which complicates detection efforts significantly. Most studies utilize plasma and serum samples which may introduce potential interference by white blood cells and platelets during sample preparation procedures. Some studies have also reported fluctuations in miRNA levels following chemotherapy treatment [149–151]. For normalization, reliable housekeeping miRNA is lacking which further changes the pathological and physiological status. The overlap between miRNA panels in different studies are very minimal reflecting the complex biology of miRNA expression in breast cancer patients. Breast cancer is heterogenous in nature with diverse biological behaviour and gene expression profile. This is one of the causes of discrepancy between miRNA signatures reported in different studies. Moreover, a miRNA serving as an oncomiR in breast cancer could contradictorily serve as a tumour suppressor in a different cancer, further confounding the picture. One such example is miR-498 which acts as an oncomiR by directly targeting the tumour suppressor gene *PTEN* [152] in breast cancer but acts as a tumour suppressor by targeting the oncogene *ZEB2* in liver cancer [153]. Despite this discrepancy, researchers continue to harness the potential of miRNA as a valuable tool for investigating cancer development and targeting malignant cells. The field of using miRNA in clinical research is still ripe with opportunities for further exploration.

10. Summary and future perspective

In this review, we have discussed the roles of miRNAs in breast cancer progression and metastasis. Based on the existing literature, various roles of oncomiRs in regulating chromatin organization through the downregulation of critical heterochromatin proteins have been hypothesized. Additionally, it has also been suggested that miRNAs could contribute to the development of an oncogenic microenvironment and altered metabolism in breast cancer. The metabolic characteristics observed in breast cancer cells may also be linked to epigenetic modifications such as acetylation, which can promote tumorigenic growth. Not only are miRNA profiles potential targets for anti-miRNA therapy, but they can also provide insights into drug resistance mechanisms and guide therapeutic interventions. Throughout the progression of cancer, unique patterns or signatures may emerge within miRNA profiles. These individualized signatures offer promise for predicting metastasis and tailoring personalized medicine approaches.

Data availability statement

No data from our side, associated with this study, has been deposited in any publicly available repository.

Publication ethics statement

The authors would like to mention that there was no plagiarism or data manipulation performed in this manuscript.

CRediT authorship contribution statement

Sweta Sikder: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Aditya Bhattacharya:** Writing – original draft. **Aayushi Agrawal:** Writing – original draft. **Gautam Sethi:** Writing – review & editing. **Tapas K. Kundu:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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