DNMT3A and DNMT3B in Breast Tumorigenesis and Potential Therapy

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Breast cancer has become a leading cause of cancer-related deaths in women worldwide. DNA methylation has been revealed to play an enormously important role in the development and progression of breast cancer. DNA methylation is regulated by DNA methyltransferases (DNMTs), including DNMT1, DNMT2, and DNMT3. DNMT3 family has three members: DNMT3A, DNMT3B, and DNMT3L. The roles and functions of DNMT1 in breast cancer have been well reviewed. In this article, the roles of DNMT3A and DNMT3B in breast tumorigenesis and development are reviewed. We also discuss the SNP and mutations of DNMT3A and DNMT3B in breast cancer. In addition, we summarize how DNMT3A and DNMT3B are regulated by non-coding RNAs and signaling pathways in breast cancer, and targeting the expression levels of DNMT3A and DNMT3B may be a promising therapeutic approach for breast cancer. This review will provide reference for further studies on the biological functions and molecular mechanisms of DNMT3A and DNMT3B in breast cancer.

Keywords: methylation, Dnmt3a, DNMT3B, breast cancer, inhibitors

INTRODUCTION

Breast cancer is a common malignant tumor among women and leads to cancer-related mortality in the world (Siegel et al., 2022). In 2020, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer with an estimated 2.3 million new cases (11.7%) followed by lung (11.4%) (Sung et al., 2021). Breast cancer is a highly heterogeneous disease that includes multiple intrinsic subtypes with heterogeneous molecular profiles, clinical representations, response to therapies and outcomes (Kerr et al., 2022). Although intensive chemotherapy, radiotherapy and targeted therapies have improved the outcomes of breast cancer patients, it is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths (Sung et al., 2021).

In general, DNA methylation is often regulated by DNMTs, which catalyzed methyl group attach to C-5 of the cytosine residue (Figure 1). Three canonical isofoms have been identified in human, including DNMT1, DNMT3A and DNMT3B (Liang et al., 2020; Zhu et al., 2021). Two non-canonical members are DNMT2 and DNMT3L. Among DNMTs isofoms, human tissues often express DNMT1, DNMT3A and...
DNMT3B isoforms (Liang et al., 2018; Hegde and Joshi, 2021). DNMT1 plays a critical role in maintenance methylation, while DNMT3A and DNMT3B function in de novo methylation to transfer a methyl group from S-adenyl methionine (SAM) to the C-5 position of cytosine residue (Okano et al., 1999; Lyko, 2018). However, several studies have confirmed that DNMT3A and DNMT3B also can maintain DNA methylation (Dodge et al., 2005; Feng et al., 2010). DNMT3C was identified in the male germ line and protected these germ cells from transposon activity (Barau et al., 2016).

Mounting evidence has indicated that DNA hypomethylation or hypermethylation and chromatin remodeling are critically involved in breast cancer development and malignant progression (Hinshelwood and Clark, 2008; Teschendorff et al., 2016; Pasculli et al., 2018). It has been reported that breast cancer patients have paradoxical gene-specific regional hypermethylation and global hypomethylation of the genome (Steeg et al., 2003). Regional hypermethylation leads to silence multiple genes involved in cell cycle and proliferation, while hypomethylation is required for tumor metastasis (Steeg et al., 2003). One group discovered the various roles of DNA methylation in different regulatory regions, which give rise to different breast cancer phenotypes (Fleischer et al., 2017). Higher expression of DNMT1 was displayed in the metastatic stage tissue samples, while higher expression of DNMT3A and DNMT3B was primarily exhibited in the primary stage, indicating that the expression of various DNMTs is tissue stage-dependent manner (Kar et al., 2014). Accumulated evidence suggests that DNMT3A and DNMT3B are pivotal in breast oncogenesis and progression.

Therefore, in this review, we described the latest findings of DNMT3A and DNMT3B in breast carcinogenesis, including their expression and clinical features, single-nucleotide polymorphisms (SNP), regulatory mechanisms, their biological functions. We also highlighted that targeting DNMT3A and DNMT3B could be useful for anti-breast cancer treatment. Hypomethylating agents and experimental DNMT inhibitors in breast cancer were also discussed.

Expression and Clinical Features of DNMT3A and DNMT3B

Emerging evidence has showed that the expression of DNMT3A and DNMT3B is linked to clinical features in breast cancer patients. The expression of DNMT3A is higher in mammary tumors than in fibroadenoma (Yu et al., 2015). One group also reported that DNMT3A was highly expressed in breast tumor tissues than the adjacent normal specimens (Liu et al., 2016). In addition, DNMT3A was discovered to be highly expressed in breast cancer with brain metastasis in comparison with primary breast cancer patients (Iwamoto et al., 2019). Breast cancer patients with advanced clinical stages often have high expression of DNMT3A and DNMT3B. Moreover, DNMT3A was correlated with a shorter DFS and OS in breast cancer patients (Yu et al., 2015). Another group indicated that higher expression of DNMT3A was observed in Grade III group and larger tumors in breast cancer patients (Kankava et al., 2016). Similarly, the mRNA levels of DNMT3A and DNMT3B were increased in tumor tissues compared with control groups (Jahangiri et al., 2018). These findings indicated that DNMT3A expression is linked to poor prognosis in breast cancer patients.

Interestingly, one study reported that DNMT3A expression was elevated in breast tumor subjects, but DNMT3A expression was not changed in breast cancer specimens in comparison to normal tissues, suggesting that deep exploration is necessary to determine the role of DNMT3A in breast cancer (Tavakolian et al., 2019). Another study reported that DNMT3B was highly expressed and predicted reduced survival in breast cancer patients (Shinden et al., 2021). Moreover, high expression of DNMT3B at mRNA level might be associated with lymph node diagnosis for breast cancer patients (Berger et al., 2006). By an array-based DNA methylation profiling, breast cancer patients with high methylation levels and upregulation of DNMT3B could have poor prognosis (Van der Auwera et al., 2010). Using differential high resolution melting analysis, one study revealed that DNMT3B promoter methylation was linked to cancer type, tumor size, histologic grade, suggesting that DNMT3B promoting methylation could predict diagnostic and prognostic biomarker for breast cancer (Naghtorabi et al., 2013). Therefore, DNMT3B overexpression is correlated with worse prognosis of breast cancer patients.

Role of DNMT3A and DNMT3B in Breast Cancer

Downstream Targets of DNMT3A in Breast Cancer

DNMT3A plays its biological functions via regulating its downstream targets. One study showed that high expression of DNMT3A was linked to promoter hypermethylation of ERα and BRCA1, and downregulation of ERα and BRCA1 in breast cancer patients (Yu et al., 2015). Stable silencing of SOX2 oncprotein via overexpression of DNMT3A in mice retarded the tumorigenic phenotype of breast cancer cells (Stolzenburg et al., 2015). DNMT3A can also enhance the methylation at non-CpGs and CpGs sites of HIF-1α in MDA-MB-231 cells (Li et al., 2019). Stilbenoid exposure resulted in SEMA 3A epigenetic activation via regulation of dynamic interactions of DNA with TF1C and DNMT3A in breast cancer cells (Beetch et al., 2019).

Downstream Targets of DNMT3B in Breast Cancer

Accumulating evidence has uncovered multiple downstream targets of DNMT3B. DNMT3B overexpression is responsible for hypermethylation phenotype in multiple breast cancer cell
Single Nucleotide Polymorphisms (SNPs) of DNMT3A and DNMT3B

DNMT gene polymorphisms are associated with breast oncogenesis (Table 1). One study identified 16 SNPs in DNMTs, including 5 SNPs in DNMT1, 6 SNPs in DNMT3A, 3 SNPs in DNMT3B, 1 SNP in DNMT3L and 1 SNP in DNMT2 in 408 breast cancer patients and 469 controls. Moreover, the heterozygous genotypes of rs2424908 in DNMT3B was linked to decreased risk of breast cancer in Han Chinese women (Sun et al., 2012). In a British population, the C46359T polymorphism in the DNMT3B promoter in breast cancer cases was reported by investigation of 352 breast cancer patients and 258 controls, indicating that individuals with T allele in DNMT3B have a high risk of breast cancer development (Montgomery et al., 2004). Interestingly, there is no relationship between DNMT3B polymorphisms and the risk of breast cancer in Chinese women (Ye et al., 2010). It is necessary to mention that DNMT3A and DNMT3B have mutation and amplification in breast cancer patients. DNMT3B gene amplification was observed in breast cancer cells and was associated with resistance to DNA demethylating drugs, including Decitabine, 5-aza-2cytidine (Vidaza), and SGI-1027 (Simo-Riudalbas et al., 2011). By a mutational analysis, 10% DNMT3A was found to have frequent high mutational in metastatic breast cancer patients (Rong et al., 2021).

Regulation of DNA Methylation in Breast Cancer

miRNAs Regulate DNA Methylation

Several noncoding RNAs have been reported to affect DNA methylation in breast cancer cells (Pronina et al., 2017) (Table 2; Figure 2). One study analyzed the association between multiple miRNAs expression and DNMT3B-induced DNA hypermethylation, and concluded that dysregulation of miRNAs led to aberrant DNA hypermethylation via suppressing post-transcriptional level of DNMT3B in basal-like breast tumor (Sandhu et al., 2014). This group also reported several miRNAs such as miR-26b, miR-29c and miR-148b regulated the expression of DNMT3B in multiple breast cancer cells (Sandhu et al., 2012). Another group showed that microRNA-29b (miR-29b) can bind with 3′-UTR of DNMT3A and DNMT3B and inhibit the mRNA level of DNMT3A and DNMT3B, leading to multiple gene promoter methylation in breast cancer cells and suppression of cell proliferation (Starlard-Davenport et al., 2013). This study suggested that miR-29b could regulate DNMT3A and DNMT3B and suppress proliferation of breast cancer cells (Starlard-Davenport et al., 2013).

Moreover, low expression of miR-29b was observed and negatively associated with the expression of DNMT3A in primary ER-positive breast cancer patients (Shinden et al., 2015). Similarly, overexpression of miR-29b-1-5p repressed the
expression of DNMT1, DNMT3A and DNMT3B and elevated the expression of RASSF1A, CCND2 and HIN1 in breast cancer cells (De Blasio et al., 2020). In consistent, miR-29c-5p was revealed to negatively target the DNMT3A in ER-positive breast cancer (Aure et al., 2021). In line with this report, miR-29c inhibited the expression of DNMT3B and subsequently reduced the expression of TIMP3 and affected STAT1/FOXO1 signaling pathway in breast cancer cells (Li et al., 2018).

Another group clarified that miR-143 decreased the expression of DNMT3A at mRNA and protein levels, and subsequently decreased the PTEN hypermethylation and enhanced TNFRSF10C methylation, leading to suppression of proliferation of breast cancer cells (Ng et al., 2014). Similarly, miR-124a-3 hypermethylation was associated with high expression of DNMT3B and linked to aggressive and advanced stages in breast cancer patients (Ben Gacem et al., 2014). Kindlin 2, a focal adhesion protein to govern Wnt signaling pathway, can bind with DNMT3A and co-occupy the miR-200b promoter, leading to downregulation of miR-200b and promotion of invasion of breast cancer cells (Yu et al., 2013). In addition, another study revealed that MYC can recruit DNMT3A to bind with miR-200b promoter and caused CpG island hypermethylation, leading to miR-200b suppression in MDA-MB-231 cells and upregulation of SOX2, CD133 and ZEB1 (Pang et al., 2018). Interestingly, miR-200b also directly reduced the expression of DNMT3A in TNBC cells (Pang et al., 2018). Moreover, miR-200b, miR-200c and miR-221 target DNMT3B expression, while DNMT3B can also stimulate the DNA methylation of miR-200s in CAFs and further indicated that TGF-β1/miR-200s/miR-221/DNMT3B axis governed CAF status to stimulate proliferation of breast cancer cells (Tang et al., 2019).

In keeping with this finding, another investigation also confirmed miR-221 maintained CSCs via suppressing DNMT3B and increasing the expression of stemness genes in breast cancer, such as Nanog and Oct3/4 genes (Roscigno et al., 2016). FEN1 was reported to elevate the expression of DNMT3A and promote their interaction among FEN1/PCNA/DNMT3A and suppressed the expression of miR-200a-5p, leading to upregulation of miR-200a-5p targets, MET and EGFR, which contribute to enhancement of growth of breast cancer cells (Zeng et al., 2019). Overexpression of miR-101 caused the downregulation of DNMT3A and subsequent upregulation of E-cadherin expression in MDA-MB-231 cells, which is

| TABLE 2 | miRNAs regulate DNMTs in breast cancer. |
| Noncoding RNAs | DNMTs | Targets | Functions | Ref |
| miR-29b | DNMT3A, DNMT3B | N/A | Suppresses proliferation | Starlard-Davenport et al. (2013) |
| miR-29b-1-5p | DNMT1, DNMT3A, DNMT3B | RASSF1A, CCND2, HIN1 | Increases ROS generation, reduces cell proliferation | De Blasio et al. (2020) |
| miR-29c | DNMT3A, DNMT3B | TIMP3, STAT1, FOXO1 | Reduces the proliferation, migration, and invasion | Li et al. (2018) |
| miR-143 | DNMT3A | PTEN, TNFRSF10C, SOX2, CD133, ZEB1 | Performs antitumor activity | Ng et al. (2014) |
| miR-200b | DNMT3A, DNMT3B | SOX2, CD133, ZEB1 | Inhibits proliferation, migration | (Yu et al., 2013; Pang et al., 2018) |
| miR-101 | DNMT3A | E-cadherin | Promotes tumorigenesis | Liu et al. (2016) |
| miR-203 | DNMT3A, DNMT3B | CD44, Oct3/4, SOX2, ALDH1A3 | Cancer stem cell development | El-Osaily et al. (2021) |
| miR-150 | DNMT3A, DNMT3B | CD44, Oct3/4, SOX2, ALDH1A3 | Cancer stem cell development | El-Osaily et al. (2021) |
| miR-770-5p | DNMT3A | E-cadherin | Inhibits EMT and invasion | Noyan et al. (2021) |

| FIGURE 2 | miRNAs regulate DNA methylation in breast cancer. |
suppressed DLG3 expression, which caused inactivation of the three DNMTs and increased DLG3 promoter methylation and progression (Wang et al., 2021). LncRNA MIAT bound to activation of Wnt signaling pathway and breast cancer methylation and repress its expression, contributing to three DNMTs in the NKD2 promoter to trigger NKD2 targets (Gamez et al., 2020; Xu et al., 2021). There is evidence that with argonaute proteins, leading to regulation of downstream targets (Li et al., 2020). piRNA (piRNA) is a class of small noncoding RNA, which can interact (Li Y. et al., 2020). Recently, piR-823 increased the expression of DNMTs, including DNMT1, DNMT3A and DNMT3B, enhanced APC DNA methylation and subsequently activated Wnt pathway, leading to induction of CSCs in luminal breast cancer (Ding et al., 2021).

**LncRNAs and piRNA Regulate DNA Methylation**

LncRNA is a type of long noncoding RNA, which plays an essential role in diseases, including tumors (Li et al., 2019; Jiang et al., 2020a; Liu and Shang, 2022). Piwi-interacting RNA (piRNA) is a class of small noncoding RNA, which can interact with argonaute proteins, leading to regulation of downstream targets (Gamez et al., 2020; Xu et al., 2021). There is evidence that LncRNAs and piRNAs can regulate DNA methylation in breast cancer (Table 3). For example, lncRNA 01638 downregulation repressed the expression of DNMT1, DNMT3A and DNMT3B, and increased the expression of PTEN and BRCA1, resulting in inhibition of proliferation and invasion in HER2-positive breast cancer cells (Liu et al., 2019). Similarly, lncRNA 00922 recruited three DNMTs in the NKD2 promoter to trigger NKD2 methylation and repress its expression, contributing to activation of Wnt signaling pathway and breast cancer progression (Wang et al., 2021). LncRNA MIAT bound to three DNMTs and increased DLG3 promoter methylation and suppressed DLG3 expression, which caused inactivation of the Hippo pathway and promotion of breast cancer progression (Li D. et al., 2020).

LncRNA MALAT1 increased the expression of DNMT1, DNMT3A and DNMT3B and inhibited the BRCA1 and PTEN expression, leading to regulating of herceptin sensitivity in HER2-positive breast cancer (Yang et al., 2021). LncRNA H19 depletion promoted the interaction between DNMT3B and Beclin 1 promoter, causing the Beclin 1 DNA methylation, decreasing tamoxifen resistance due to autophagy inhibition in breast cancer (Wang et al., 2019). Li and others identified that circRNA circIQCH (hsa_circ_0,104,345) facilitated breast cancer progression via sponging miR-145 and increasing DNMT3A expression (Li Y. et al., 2020). Recently, piR-823 increased the expression of DNMTs, including DNMT1, DNMT3A and DNMT3B, enhanced APC DNA methylation and subsequently activated Wnt pathway, leading to induction of CSCs in luminal breast cancer (Ding et al., 2021).

**Signaling Pathways Regulate DNA Methylation**

Multiple signaling pathways are validated to govern DNA methylation in breast cancer and some of these pathways are related to DNMT3a/DNMT3b. FEN1-mediated DNMT3a upregulation, released the suppression of its targeting MET and EGFR, and promoted breast cancer cell proliferation by activating PI3K/AKT and MAPK/ERK pathways in MCF-7 cells (Zeng et al., 2019). In addition, Wang et al. showed that DNMT3a interacts with p53 signaling in maintaining genome and represses p53-mediated transactivation of the p21 gene (Wang et al., 2005). DNMT3B affected many signaling pathways, such as STAT3, PI3K/Akt, β-catenin, NF-kB and Notch pathways (So et al., 2020).

The Oxidative DNA Damage might also be related to DNMT3b. One study in the 2020 revealed a novel mechanism underlying the modulation of DNA methylation patterns induced by oxidative DNA damage at the tumor suppressor BRCA1 gene through the coordination between pol β and DNMT3b (Jiang Z. et al., 2020). Furthermore, one study determined a molecular mechanism by which DNMT3b7 (aberrant DNMT3b transcripts) promotes tumor progression in breast cancer cells through hypermethylation and loss of CDH1/E-cadherin expression, altered β-catenin localization, and subsequent changes in cell adhesion, proliferation, and growth in soft agar (Brambert et al., 2015). Therefore, targeting these signaling pathways could be helpful for regulation of DNA methylation in breast cancer.

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**Table 3 | LncRNAs and circRNAs regulate DNMTs in breast cancer.**

| Noncoding RNAs | DNMTs | Targets | Functions | Ref |
|----------------|--------|---------|-----------|-----|
| Linc01638      | DNMT1, DNMT3A, DNMT3B | PTEN, BRCA1 | Inhibits proliferation, invasion | Liu et al. (2019) |
| Linc00922      | DNMTs | NKD2, Wnt | Promotes tumor progression | Wang et al. (2021) |
| LncRNA MIAT    | DNMTs | DLG3, Hippo | Promotes tumor progression | Li et al. (2020a) |
| MALAT1         | DNMTs | BRCA1, PTEN | Regulates Herceptin resistance | Yang et al. (2021) |
| LncRNA H19     | DNMT3B | Beclin 1 | Decreases tamoxifen resistance | Wang et al. (2019) |
| CircIQCH       | DNMT3A | miR-145 | Facilitates tumor progression | Li et al. (2020c) |
| piR-823        | DNMTs | APC, Wnt | Induces CSCs | Ding et al. (2021) |

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Targeting DNA Methylation in Breast Cancer

DNA methylation is a reverse process, suggesting that DNA methylation is a promising therapeutic target (Wu and Zhang, 2014; Pechalrieu et al., 2017). Several pre-clinical or clinical observations in our laboratory demonstrated that 6-TG blocked DNMT1 activity markedly, leading to inhibition of MDA-MB-231 cell growth and induction of apoptosis through reactivating methylation-silenced genes in the apoptosis pathway and PI3K–AKT signaling pathways, and also inducing FAS-mediated exogenous apoptosis and p21-dependent G2/M arrest in MCF-7 breast cancer cells (Li H. et al., 2020; Zhang et al., 2020; Chu et al., 2022).

A variety of breast cancer-related preclinical studies indicated the anti-tumor potential for the nucleoside analogues azacitidine and decitabine. For instance, one study showed that protein levels of DNMTs were associated with response to decitabine in TNBC cells as examined in TNBC patient-derived xenograft organoids, and all three DNMTs (DNMT1, DNMT3A and DNMT3B) were degraded by decitabine treatment in vitro and in vivo (Yu et al., 2018). Several breast cancer-related clinical trials by DNMT inhibitors (NCT01349959, NCT00978250, NCT03295552, NCT00748553) are ongoing. Although some patients may respond to these DNMT inhibitors, in most patients they are ineffective in part due to drug administration, drug distribution and selection of DNMT isoforms. Using DNMT inhibitors still faces enormous challenges. We believe that targeting DNMTs remains an attractive approach for the development of novel therapies for breast cancer patients.

CONCLUSION AND PROSPECTS

In conclusion, DNMT3A and DNMT3B play an enormously critical role in the occurrence and development of breast cancer. There are several issues that need to be addressed regarding the role of DNMTs in breast cancer. For example, DNMTs target numerous genes for their DNA methylations. Which gene methylation is the key driver to trigger breast cancer development? All DNMT1, DNMT3A and DNMT3B are involved in breast carcinogenesis. Which DNMT is critical to participate in breast oncogenesis? Since noncoding RNAs and signaling pathways regulate the expression of DNMT3A and DNMT3B, targeting these noncoding RNAs and pathways is an alternative approach to control the DNMT3A and DNMT3B expression. Due to the critical role of DNMTs in breast tumorigenesis, targeting DNMTs might be a potential approach for breast cancer therapy. Many compounds are validated to target several DNMTs in breast cancer cells. It is better to discover the potentially specific inhibitors for individual DNMT for breast cancer treatment. Moreover, whether these inhibitors of DNMTs can be used clinically for treating breast cancer needs to be answered. Therefore, further investigation of roles of DNMTs in breast tumorigenesis will help us to design novel therapeutic strategy via targeting DNMTs for breast cancer.

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AUTHOR CONTRIBUTIONS

XM designed this study and draft the manuscript. QL, BW, and HZ searched the literature and edited the manuscript. SZ and ZL revised the manuscript, and supervised this work. All authors approved the final version of manuscript.

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