



Review Article

Non-coding RNAs Affect Breast Cancer Development Through the Notch Signaling Pathway: An Overview



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Abstract

Breast cancer is the most prevalent malignancy and the leading cause of cancer-related death in women. Breast cancer is still an extremely difficult cancer to treat due to its significant metastasis. Mis-regulation of Notch signaling components such as Notch receptors/ligands and their interaction in breast cancer sparks tumor initiation, maintenance, and progression through induction of abnormal tumorigenesis while modulating vascular integrity, drug resistance, invasion, and migration. Numerous studies have shown that non-coding RNAs can regulate Notch signaling and accordingly impact breast cancer pathobiology. MiRNAs could regulate Notch signaling components directly or indirectly via sponging or suppressing other genes involved in the pathway. Further, lncRNAs interact with miRNAs and mRNAs, and lncRNA-miRNA-mRNA interaction networks function as substantial mediators in various pathways, including the Notch signaling pathway. Also, by targeting and sponging other genes, circRNAs could induce tumorigenic properties via the Notch signaling pathway. Due to the intricacy of human physiology, it is challenging for standard drugs to be effective, and cancer cells can develop resistance to treatment and have a significant self-renewal capacity. Moreover, because non-specific Notch signaling intervention targets both tumor cells and immune cells, it may have the reverse effect of regulating the formation of tumors. Thus, an in-depth understanding of the mechanisms could be useful in diagnosis, prognosis, and the development of novel medications that specifically target Notch signaling, improving the efficacy of cancer immunotherapy in the treatment of breast cancer. This review will discuss and clarify the mechanisms by which miRNAs, lncRNAs, and circRNAs affect the Notch signaling pathway leading to BC development.

Keywords: Breast cancer; Circular RNAs; Long non-coding RNAs; MicroRNAs; Notch signaling pathway.

Abbreviations: 3'UTR, 3'-untranslated regions; BC, breast cancer; CircRNA, circular RNA; CoA, Coenzyme A; CSC, cancer stem cells; CSL, CBF1 Suppressor of Hairless Lag-1; Dll, Delta-like; EMT, epithelial-to-mesenchymal transition; ESR, estrogen receptor; EYA1, Eyes absent homolog 1; FAT1, FAT Atypical Cadherin 1; HIF, Hypoxia-Inducible Factor; KLF8, Kruppel-like Factor 8; Linc, long intergenic non-coding RNA; lncRNA, long non-coding RNA; MAML, mastermind-like transcriptional coactivator; miRNA, micro-RNA; MMP, Matrix metalloproteinases; ncRNA, non-coding RNA; NICD, Notch intracellular domain; NICD1, Notch1 intracellular domain; NTM, Notch transmembrane subunit; NUMB, NUMB endocytic adaptor protein; OIP5, Opa interacting protein 5; OIP5, Opa interacting protein 5; OX, oxaliplatin; Pyk2, Proline-Rich Tyrosine Kinase 2; RNAi, RNA interference; SKA1, spindle and kinetochore associated complex subunit 1; STAT3, signal transducer and activator of transcription 3; TIC, tumor-initiating cell; TNBC, triple-negative breast cancer; UBR5, Ubiquitin Protein Ligase E3 Component N-Recognin 5; VEGF, Vascular endothelial growth factor.

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Introduction

Breast cancer (BC) is the most commonly reported cancer and the main cause of cancer-related death in women worldwide.¹ Epidemiological data show that diverse communities have varying sensitivity to BC.² In 2020, more than 2.3 million new cases of BC and 685,000 deaths were recorded, with incidence rates ranging from less than 40 per 100,000 women in some African and Asian countries to more than 80 per 100,000 in Northern America, New Zealand/Australia, and some parts of Europe, implying a pattern of global geographic distribution. BC-related mortality shows less geographic variation, as it is disproportionately more prevalent in developing countries.³ International panels have introduced molecular subtypes for BC including duct A, duct B, HER2-enriched, and triple-negative breast cancer (TNBC), emphasizing the importance of choosing therapies based on fundamental molecular subtypes.^{4,5} According to recent findings, BC is a molecularly heterogeneous malignancy that requires treatment specific to each subtype. For example, for individuals with advanced hormone receptor-positive BC, chemotherapy was linked to a worse prognosis compared with endocrine therapy. In contrast, immunotherapy has a higher likelihood of being

beneficial in patients with early stage TNBC.⁶ Epithelial to mesenchymal transition (EMT) plays an essential role in metastatic cell invasion and tumor formation based on its prominent functions in wound healing, regeneration, and embryonic development. EMT in BC enhances the ability of tumor cells to migrate and invade, as well as their capability to evade the immune system. These factors are implicated in increased metastasis and tumor growth, which makes treatment options more challenging.⁷ To prevent drug resistance, a greater understanding of the molecular components and pathways that characterize the response to treatment is required. Additionally, the availability of targeted therapy is limited. Overall, these variables underlie the importance of identifying optimal molecular targets for various BC subtypes to provide valuable and alternative approaches to enhance treatment strategies.

Mammals have four Notch receptors (Notch1-Notch4) and at least five ligands, including Jagged (JAG)1, JAG2, Delta-like (Dll)-1, Dll-3, and Dll-4, which are derived from the Delta and JAG/Serrate families.⁸⁻¹¹ Notch has an extracellular domain and an Notch intracellular domain (NICD). These are joined by a transmembrane domain in mature Notch receptors.¹² The cleaved NICD, which activates the signaling response, is released upon ligand binding to the Notch receptor.¹³ Ligand-induced activation of the signaling cascade is straightforward. The NICD is released from the membrane by two consecutive proteolytic cleavages of the Notch receptor. Most of the Notch extracellular domain is cleaved by ADAM metalloproteases (a disintegrin and metalloprotease). S2 cleavage is the term used to describe this process.¹⁴ The residual Notch receptor (NICD) is then released from the cell through an intramembrane cleavage known as S3 cleavage, catalyzed by the γ -secretase complex.¹⁵ Mastermind-like transcriptional coactivator (MAML) proteins are essential cofactors in the RBPJ/NICD complex and are necessary for the proper functioning of the complex during transcriptional switching.¹⁶ In the case of aberrant expression of upstream and downstream Notch effectors, Notch signaling components control differentiation of the mammary epithelial cell during normal development, which are essential underlying factors in BC.¹⁷ Dysregulation of Notch family members promotes BC progression via several routes, including cell proliferation, metastasis, migration, stem cell maintenance, and chemoresistance. The severe clinicopathological features of TNBC are strongly linked to Notch1 upregulation.¹⁸⁻²⁰ A high level of Notch ligands and receptors has been associated with a poor prognosis in BC patients.²¹ Multiple studies have shown that aberrant expression of Notch1, Notch2, and Notch4 can lead to cancer development. On the other hand, Notch3 has been shown to have tumor suppressor functions in BC, which plays roles via tumor growth, EMT, angiogenesis, invasion, and self-renewal of BC stem-like cells caused by its mutation.²²⁻²⁹ Other research has demonstrated that increased expression of Notch1, Notch3, and JAG1 is directly related to an increased mortality rate.²² Collectively, there is ample evidence demonstrating that the Notch pathway has various crucial functions in the advancement of BC, and deregulation of the Notch signaling pathway can lead to different outcomes depending on the subtype of BC. This is due to the unique gene expression patterns and prognosis associated with each subtype. For instance, Notch3 expression is increased in ductal A, and higher levels of Notch4 were observed in ductal A and B.^{30,31} In contrast, there have been reports of increased levels of Notch1, Notch3, Notch4, and JAG1 in the basal-like/TNBC subtype, leading to enhanced angiogenesis and poor survival of patients.³²⁻³⁴ In summary, tumor development, viability, and induced BC stem cell phenotypes are regulated by the Notch signaling pathway.³⁵

BC is still an extremely difficult cancer to treat due to its significant metastasis. Notch signaling could either accelerate or inhibit the spread of primary tumor cells by interacting with downstream

effectors that regulate the invasion of BC cells via the mesenchyme and basement membrane.³⁶ Furthermore, because non-specific Notch signaling intervention targets both tumor cells and immune cells, it may have the reverse effect of regulating the formation of tumors. In the meantime, immune cells involved in pro- or anti-tumor responses and tumor immunogenicity can be modulated by Notch signaling.³⁷ Thus, an in-depth understanding of the mechanisms could be useful in the development of novel medications that specifically target Notch signaling, improving the efficacy of cancer immunotherapy in the treatment of breast cancer.

Current advances in high-throughput technologies have demonstrated that most of the human genome is transcribed to non-translating transcripts referred to as non-coding RNAs (ncRNAs). These ncRNAs can function as tumor-suppressor genes and proto-oncogenes, and contain functional elements that affect the expression of protein-coding genes.^{38,39} ncRNAs consist of long non-coding RNAs (lncRNAs), PIWI-interacting RNAs, small interfering RNAs (siRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs).^{40,41} Multiple studies have delved into the involvement of various ncRNAs in the molecular pathways and progression of BC.^{42,43} It has been shown that ncRNAs modulate intracellular and/or intercellular signaling by controlling different cellular functions, including estrogen receptor (ESR) levels and activity, proliferation, apoptosis, invasion, migration, and stemness.⁴⁴ Additionally, ncRNAs have the potential to function like competitive endogenous RNAs and might represent an essential molecular target for the classification of various subtypes, age categories, prognosis, therapy, and diagnosis of BC patients.⁴⁵ Multiple functional and experimental studies have been conducted recently that support the involvement of different ncRNAs in the modulation of the Notch signaling pathway.⁴⁶ We will discuss this research in the following sections and clarify the mechanisms by which miRNAs, lncRNAs, and circRNAs affect the Notch signaling pathway leading to BC pathobiology.

MiRNAs impact BC through Notch signaling

MiRNAs, which are 22 nucleotides in length, primarily control mRNA expression through binding to complementary sequences located in the 3'-untranslated regions of genes that they target.⁴⁷ Although the effects of miRNAs as repressors and destabilizers of the translation of mRNA transcripts have been widely explored, the impact of miRNAs on the function of lncRNAs is still not entirely clear.⁴⁸ The control of miRNA metabolism and function by various processes, including diverse protein-protein and protein-RNA interactions, has been the focus of numerous reports in the past few years.⁴⁹ Because they control cell cycle progression, metastasis development, apoptosis, metabolism, and angiogenesis, miRNAs have attracted attention for their significant role in tumorigenesis.⁵⁰ For example, in colorectal cancer cell lines miR-100 and miR-143 recovery may efficiently inhibit invasion, proliferation, and migration and trigger cell death, suggesting that miR-100 and miR-143 could be developed as therapeutic targets.⁵¹ Similarly, miRNAs have recently been increasingly linked to the regulation of BC initiation and progression, both positively and negatively, as discussed below.⁵²⁻⁵⁴

MiRNAs positively regulate BC through Notch signaling

Multiple studies have revealed that miRNAs are upregulated and act as oncogenes in BC through regulating the Notch signaling pathway (Table 1).⁵⁵⁻⁹³ Gao *et al.* provided evidence that

Table 1. Outline of miRNA mechanisms of action through the Notch signaling pathway in BC

miRNAs	Target(s)	Function(s)	Expression	Model (<i>in vitro</i> , <i>in vivo</i>)	Mechanism of action	Reference(s)
miR-150	Notch1 and Notch3	Promoted apoptosis, migration, and invasion	Upregulated	<i>in vitro</i>	Upregulates Notch1 and Notch3	55
miR-378d and miR-378a-3p	NUMB	Enrolled in Doxorubicin and Paclitaxel resistance	Upregulated	<i>in vitro/in vivo</i>	Activate Notch stem cell and Wnt pathways by targeting NUMB and DKK3	56
miR-449a	Notch1	Increased migration and cell growth	Upregulated	<i>in vitro</i>	Decreases Notch1	57,93
miR-106b-25 cluster	Notch1	Caused tumor initiating and TIC phenotypes	Upregulated	<i>in vitro</i>	Upregulate Notch1 by targeting NEDD4L	58
miR-221/222	Notch3	Induced migration and invasion	Upregulated	<i>in vitro</i>	Target Notch3	59
miR-146a	NUMB	Induced stemness	Upregulated	<i>in vitro/in vivo</i>	Targets the 3'UTR of NUMB	60
miR-21	PTEN, Notch1, HES1	Blocked cell migration, invasion, and growth	Upregulated	<i>in vitro/in vivo</i>	Activates the Notch and PI3K pathways by increasing Notch1 and HES1 and decreasing PTEN	61
let-7	NUMB	Declined stem-like cells proportion and inhibited regrowth of tumors	Upregulated	<i>in vitro/in vivo</i>	Degrades NUMB	64
miR-182	Notch oncoprotein	Promoted proliferation and invasion	Upregulated	<i>in vitro</i>	Increases Notch oncoprotein and cyclin E by targeting FBXW7	66
miR-34a	Notch1, Notch3, JAG1, HES1, and PTEN	Blocked cell migration, invasion, and growth	Downregulated	<i>in vitro/in vivo</i>	Inhibits the Notch and PI3K pathways by decreasing Notch1 and HES1 and increasing PTEN/Targets Notch1, Notch3, and JAG1	61,78–80,82,85,89
miR-206	Notch3 and Notch2	Triggered apoptosis and suppressed proliferation, stemness, and metastasis	Downregulated	<i>in vitro/in vivo</i>	Targets Notch3 and Notch2	62,63
miR-129	NUMB	Declined stem-like cell proportion and inhibited regrowth of tumors	Downregulated	<i>in vitro/in vivo</i>	Inhibits ESR1 and stops cyclin D1/DICER1 from maintaining let-7	64
miR-526b-3p	HIF-2 α , Nanog, ALDH1, Notch1, and HEY2	Hindered cell viability, CSC properties, and paclitaxel resistance	Downregulated	<i>in vitro/in vivo</i>	Downregulates HIF-2 α , Nanog, ALDH1, Notch1, and HEY2	65
miR-205	HES1, HEY1, and Notch2	Increased cell viability, migration, Stemness, and EMT	Downregulated	<i>in vitro/in vivo</i>	Inhibits MFNG (which upregulates HES1 and HEY1) along with GATA3 in a feed-forward loop/Targets Notch2 and is a target of HES1, setting up a feedback loop/Targets ZEB1 (regulate EMT)	67,68,88
miR-27-3p	Notch oncoprotein and NTM	Hindered cleavage of the Notch protein and declined Olaparib resistance	Downregulated	<i>in vitro/in vivo</i>	Prevents Notch oncoprotein cleavage by γ -secretase and activation of the Notch pathway	69

(continued)

Table 1. (continued)

miRNAs	Target(s)	Function(s)	Expression	Model (in vitro, in vivo)	Mechanism of action	Reference(s)
miR-133a-3p	MAML1	Played a role in migration, invasion, proliferation, and EMT process	Downregulated	<i>in vitro/in vivo</i>	Targets MAML1, and in a positive feedback loop, MAML1 upregulates DNMT3A, which silences miR-133a-3p by hypermethylation	70
miR-1179	HES1, Notch4, Notch1	Inhibited invasion, migration, and proliferation	Downregulated	<i>in vitro/in vivo</i>	Inhibits Notch4, Notch1, and HES1	71,92
miR-3178	Notch1	Promoted proliferation, metastasis, and EMT	Downregulated	<i>in vitro/in vivo</i>	Targets Notch1	72
miR-130b-3p	Dll-1	Blocked cell migration and invasiveness	Downregulated	<i>in vitro/in vivo</i>	Targets Dll-1	73
miR-139-5p	Notch1	Mediated drug resistance, proliferation, invasion, and metastasis	Downregulated	<i>in vitro</i>	Targets Notch1	74,75
miR-30a	Notch1	Increased cell viability, migration, and invasion	Downregulated	<i>in vitro/in vivo</i>	Targets Notch1	76
miR-101	JAG1, HEY1, HES1 and EYA1	Induced apoptosis and blocked proliferation	Downregulated	<i>in vitro</i>	Downregulates JAG1, HEY1, and HES1 by targeting EYA1	77
miR-9	Notch1	Induced metastasis	Downregulated	<i>in vitro</i>	Targets Notch1	81
miR-224	Notch1	Increased cell survival, migration, and angiogenesis	Downregulated	<i>in vitro/in vivo</i>	Targets Notch1	82
miR-200 family	MAML2, MAML3 and JAG1	Promoted stemness, EMT, and proliferation	Downregulated	<i>in vitro/in vivo</i>	Target ZEB1, MAML2, MAML3, JAG1, which in a mutual feedback loop, ZEB1 and miR-200 family can suppress each other	83,84
miR-154-3p	Notch2	Increased metastasis and cell growth	Downregulated	<i>in vitro/in vivo</i>	Targets Notch2	86
miR-548p	Notch2	Induced metastasis, invasion, proliferation, and migration	Downregulated	<i>in vitro/in vivo</i>	Targets Notch2	87
miR-140-5p	JAG1	Induced angiogenesis	Downregulated	<i>in vitro/in vivo</i>	Targets JAG1	90
miR-525-5p	Notch2	Induced metastasis, proliferation, and drug resistance	Downregulated	<i>in vitro</i>	Targets SKA1 (which stimulates Wnt and Notch pathways by upregulating β -catenin, GSK-3, and Notch2)	91
miR-449a	Notch1	Decreased migration and cell growth	Downregulated	<i>in vitro</i>	Targets Notch1	93

CSC, cancer stem cells; Dll, Delta-like; EMT, epithelial-to-mesenchymal transition; ESR, estrogen receptor; FBXW7: F-box and WD repeat domain-containing 7; HES: Hairy and Enhancer of Split; JAG, jagged; MAML, mastermind-like transcriptional coactivator; miRNA, micro-RNA; NTM, Notch transmembrane subunit; TIC, tumor-initiating cell.

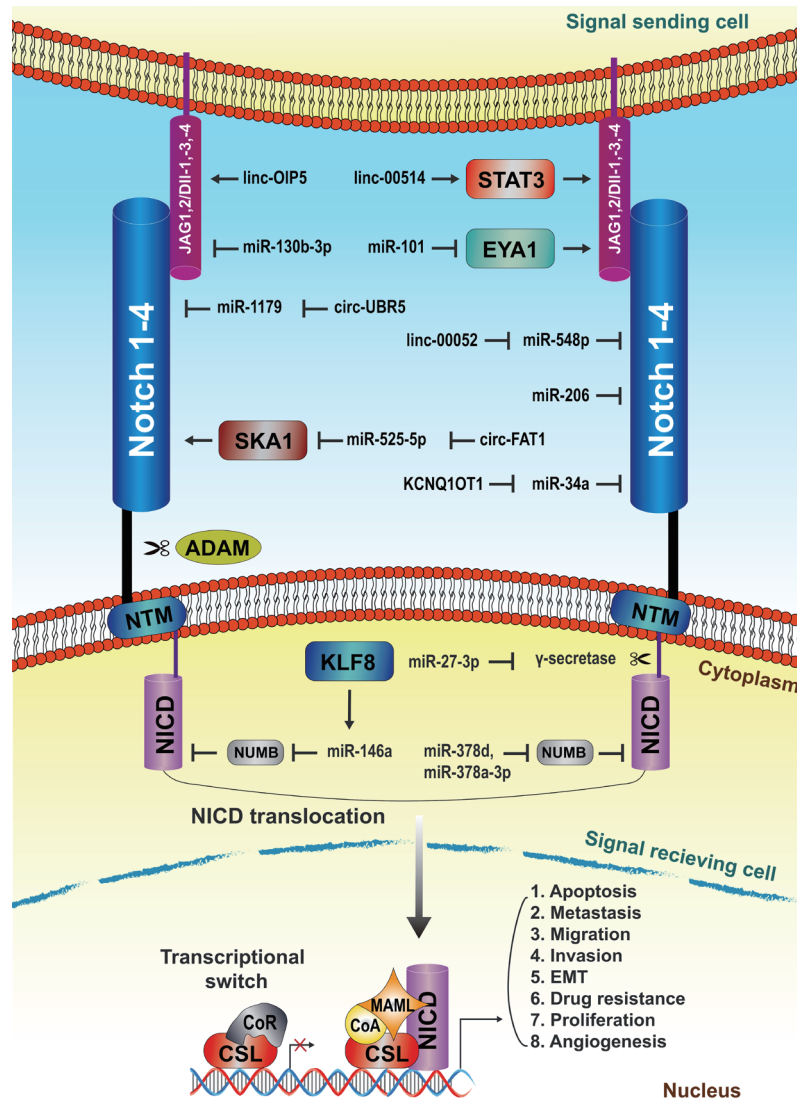


Fig. 1. NcRNAs interfere with diverse components of the Notch signaling pathway. The development and characteristics of BC are substantially influenced by Notch signaling. This includes modulating angiogenesis, drug resistance, migration, metastasis, and apoptosis. ADAM, a disintegrin and metalloprotease; CoA, Coenzyme A; CoR, corepressor; CSL, CBF1 Suppressor of Hairless Lag-1; Dll, Delta-like; EYA1 Eyes absent homolog 1; EMT, epithelial-to-mesenchymal transition; FAT1, FAT Atypical Cadherin 1; JAG, jagged; KLF8, Kruppel-like Factor 8; Linc, long intergenic non-coding RNA; MAML, mastermind-like transcriptional coactivator; NICD, Notch intracellular domain; NTM, Notch transmembrane subunit; NUMB, NUMB endocytic adaptor protein; OIP5, Opa interacting protein 5; STAT3, Signal Transducer and Activator of Transcription 3; SKA1, Spindle And Kinetochore Associated Complex Subunit 1.

cells treated with an miR-150 inhibitor had decreased Notch1 and Notch3 expression as well as reduced cell invasion and migration.⁵⁵ According to research by Yang *et al.*, BC patients undergoing chemotherapy have higher levels of miR-378d and miR-378a-3p in their serum exosomes, which was linked to chemoresistance. This indicates that exosomal miR-378d and miR-378a-3p can be released by BC cells after treatment. As shown in Figure 1, chemotherapy-induced exosomal miR-378d and miR-378a-3p modulate Notch and WNT/ β -catenin stemness pathways through targeting DKK3 and NUMB.⁵⁶ Wang *et al.* proposed that miR-449a targets Notch1 and showed that cell proliferation and migration were facilitated by the upregulation of miR-449a.⁵⁷ Using direct suppression of the E3 ubiquitin ligase, NEDD4L, Guarnieri *et al.* demonstrated that Notch1 was upregulated by an miR-106b-25 cluster in

various BC cell lines. They further showed that in both ESR+ and TNBC breast tumor cells, overexpression of Notch1 was required for tumor-initiating cell induction downstream of miR-106b-25.⁵⁸ EMT is known to be inhibited by Notch3, which is overexpressed in luminal BC cells. Liang *et al.* provided evidence that MDA-MB-231, SKBR3, and BT549 cells (basal-like subtypes) had significantly high levels of miR-221/222, which reduced Notch3 levels and promoted migration, invasion, metastasis, and EMT.⁵⁹ As described in Figure 1, Wang *et al.* showed that miR-146a can specifically target the 3'-untranslated regions of NUMB to prevent translation in BC. Furthermore, KLF8 (Kruppel-like Factor 8) can upregulate miR-146a expression resulting in the induction of pro-tumorigenic mammary stem cells and the activation of Notch signaling.⁶⁰ As Peng *et al.* described, miR-21 is upregulated in BC. Ad-

ditionally, when miR-34a was silenced, or miR-21 was increased, the impacts of 3,6-Dihydroxyflavone on PTEN and Notch1 were significantly reduced, and inhibition of the PI3K/Akt/mTOR axis was further suppressed.⁶¹

miRNAs negatively regulate BC through the Notch signaling

On the other hand, numerous studies have indicated that miRNAs are downregulated and function as tumor suppressors in BC via the Notch signaling pathway. Chaudhari *et al.* stated that synthesized gold nanoparticles, in addition to transfecting miR-206, also led to apoptosis of MCF-7 cells by inducing cell cycle arrest in the G0-G1 phase via downregulating Notch3.⁶² Furthermore, Samaeekia *et al.* reported that breast tumor stemness and metastasis are suppressed by hsa-miR-206. They showed that Notch2 mRNA levels were significantly reduced by forced expression of miR-206.⁶³ These interactions are shown in Figure 1. Xiao *et al.* provided evidence that the inhibitory effects of miR-129 were eliminated when siRNAs inhibited NUMB. They established that miR-129 inhibited ESR1 and stopped cyclin D1/DICER1 from maintaining let-7, allowing let-7 to degrade NUMB.⁶⁴ According to Liu *et al.*, miR-526b-3p suppressed HIF-2 α , Nanog, ALDH1, Notch1, and HEY2 in BC cells treated with paclitaxel, causing colony formation and paclitaxel resistance. Conversely, HIF-2 α , which is a target of miR-526b-3p,⁶⁵ can mitigate the impacts of miR-526b-3p. Chiang *et al.* indicated that miRNA sponge suppression of miR-182 dramatically increased FBXW7 protein expression and decreased cyclin E and Notch. According to these findings, H184B5F5/M10-miR-182 cells were highly sensitive to hypoxia.⁶⁶ Mugisha *et al.* explained that MFNG increased expression of the Notch target genes HEY1 and HES1 in TNBC cells. These results indicate that GATA3 binds directly to the promoter of MFNG and inhibits transcription. These findings support the hypothesis that miR-205-5p reduces the malignancy of TNBC cells by suppressing MFNG transcription. Furthermore, GATA3, miR-205-5p, and MFNG constitute a unique feed-forward loop in the control of TNBC development, as GATA3 was found to directly modulate miR-205-5p transcription.⁶⁷ In addition, Chao *et al.* provided evidence that reduction of miR-205 was positively associated with increased Notch2 and ZEB1 expression levels in invasive BC. HES1 binds directly to the specific promoter site of miR-205 binds, and JAG1 stimulates HES1 to downregulate miR-205 gene expression.⁶⁸ Zhao *et al.* revealed that miR-27-3p overexpression prevents activation of the Notch pathway via preventing Notch protein cleavage by γ -secretase (Fig. 1). Thus, in turn, miR-27-3p sensitizes TNBC cells to Olaparib, an anticancer drug.⁶⁹ Shi *et al.* demonstrated that targeting MAML1 through silencing miR-133a-3p might enhance BC cell invasion, EMT, migration, proliferation, and activation of Notch signaling. By regulating DNMT3A and MAML1, there is positive feedback that regulates promoter methylation of miR-133a-3p.⁷⁰ Li *et al.* showed that low levels of miR-1179 corresponded to a lower overall survival rate. Increasing miR-1179 could thus downregulate Notch1, Notch4, and HES1, ultimately stopping BC cells from proliferating and metastasizing.⁷¹ Kong *et al.* demonstrated that miR-3178 inhibits cell proliferation, metastasis, and EMT by reducing Notch1 expression in TNBC.⁷² As illustrated in Figure 1, Shui *et al.* showed that miR-130b-3p targets Dll-1, arresting Notch signaling directly. BC invasion and migration were reduced by high levels of miR-130b-3p.⁷³ Chen *et al.* concluded that miR-139-5p strongly decreased the protein expression of Notch1 and HES1, as well as OIP5, which are overexpressed in BC.⁷⁴ Zhang *et al.* illustrated that miR-139-5p, a tumor suppressor

miRNA, could prevent breast tumor migration by downregulating the expression of Notch1, which prevented MMP2, MMP7, and MMP9 expression.⁷⁵ Zhang *et al.* discovered that miR-30a inhibits BC cell invasion and migration, induces apoptosis, and retards the development of BC by targeting Notch1.⁷⁶ Guan *et al.* reported that an miR-101 mimic could considerably decrease the expression of HES1, HEY1, and JAG1, and miR-101 decreased BC cell proliferation and assisted in apoptosis by inhibiting the Notch pathway, which may be mediated by EYA1 (Fig. 1).⁷⁷ Kang *et al.* showed that miR-34a, as a tumor suppressor, impacted proliferation, invasion, and migration by Notch1 functionally targeting and blocking the Notch pathway.⁷⁸ Further, De Carolis *et al.* indicated that both Notch3 and JAG1, which are targets of miR-34a, were enhanced by overexpression of Carbonic Anhydrase Isoenzyme 9, which acts as an endogenous miRNA sponge.⁷⁹ Deng *et al.* also illustrated that miR-34a functions as an endogenous tumor suppressor in TNBC. Restoring intracellular miR-34a levels has been shown to directly target Notch1 to reduce BC cell migration.⁸⁰ Mohammadi-Yeganeh *et al.* concluded that Notch1 expression was increased while miR-9 expression was reduced in TNBC. As such, by directly targeting Notch1, miR-9 can decrease metastatic characteristics in TNBC.⁸¹ Sun *et al.* proposed that protein expression of Notch1, VEGF, MMP-2, and MMP-9 is blocked by high levels of miR-34a and miR-224, which prevents BC cell survival, migration, and angiogenesis.⁸² Brabletz and Burk *et al.* indicated that the miR-200 family interacts not just with ZEB1 but also with some components of the Notch pathway, notably JAG1, MAML2, and MAML3, in BC. In a mutual feedback loop, members of the ZEB1 and miR-200 families suppress one another's expression; ZEB1 can inhibit the expression of miR-200, which in turn indirectly stimulates Notch signaling. Overexpressing miR-141 and miR-200c or knocking down expression of ZEB1 can reduce JAG1 expression.^{83,84}

To develop effective treatment strategies, a thorough understanding of the mechanisms of drug resistance, EMT, invasion, migration, and proliferation in BC is necessary. The studies described above highlight the importance of miRNAs in breast carcinogenesis, and thus clearly demonstrate a role for miRNAs in reducing drug resistance. Due to their adaptability, miRNA mimics and inhibitors could prove to be beneficial therapeutic approaches for BC. However, effective miRNA delivery methods remain a significant challenge.⁹⁴

lncRNAs impact BC through Notch signaling

lncRNAs are transcribed RNAs consisting of more than 200 nucleotides that are not translated to proteins. lncRNAs are functional units, and subcellular localization is essential for their function.⁹⁵ Initial lncRNA annotations provided the framework for microarray concepts, allowing researchers to carry out basic functional genomics studies and identify lncRNAs in various processes, notably cardiac differentiation,⁹⁶ interfering with differentiation of neurons,⁹⁷ tumor suppression,^{98,99} reprogramming,¹⁰⁰ and pluripotency of embryonic stem cells.¹⁰¹ lncRNAs also support the establishment of robust, quick, and precise transcriptional and post-transcriptional control.¹⁰² There are many reports on the deregulation of lncRNAs in BC. For instance, the lncRNA DSCAM-AS1 is increased in BC, and its elevated expression is related to BC development.¹⁰³ Studies have demonstrated that lncRNAs are vital in the modulation of several signaling pathways, notably Notch in BC, where each subtype has a unique set of abnormalities in various signaling pathways.¹⁰⁴ lncRNAs interact with miRNAs and

Table 2. Outline of lncRNA mechanisms of action through the Notch signaling pathway in BC

lncRNAs	Target(s)	Function(s)	Expression	Model (<i>in vitro</i> , <i>in vivo</i>)	Mechanism of action	Reference(s)
KCNQ1OT1	Notch3	Induced proliferation, migration, and invasion	Upregulated	<i>in vitro/in vivo</i>	Increases Notch3 by inhibiting miR-34a	85
NDR1	Notch1	Caused BC stemness, metastasis, and drug resistance	Upregulated	<i>in vitro</i>	Upregulates NICD1	107
SNHG3	Notch2	Promoted metastasis and proliferation	Upregulated	<i>in vitro/in vivo</i>	Upregulates Notch2 by acting as a competing endogenous RNA of miR-154-3p and	86
linc-00052	Notch2	Induced metastasis, invasion, proliferation, and migration	Upregulated	<i>in vitro/in vivo</i>	Targets miR-548p (which targets Notch2)/ Increases phosphorylation of Pyk2 (downstream factor of Notch2)	87
CCAT2	Notch2	Promoted proliferation and metastasis	Upregulated	<i>in vitro/in vivo</i>	Upregulates Notch2 by sponging miR-205	88
SNHG7	Notch1	Promoted cell growth and EMT	Upregulated	<i>in vitro/in vivo</i>	Sponges miR-34a (which inhibits Notch1)	89
linc-OIP5	JAG1, YAP1 (HIPPO)	Increased proliferation, metastasis, and angiogenesis	Upregulated	<i>in vitro</i>	Controls YAP1/Notch/NRP1 and Dll-4/Notch/NRP1 signaling circuits by upregulating JAG1 and YAP1	108,109
BREA2	NICD1	Activated the Notch signaling pathway and induced metastasis	Upregulated	<i>in vitro/in vivo</i>	Stabilizes NICD1 by diminishing the WWP2-NICD1 complex	110
linc-00514	JAG1 and STAT3	Induced metastasis	Upregulated	<i>in vitro/in vivo</i>	Upregulates STAT3 (which increases JAG1)	111
MALAT1	JAG1, VEGFA	Induced angiogenesis	Upregulated	<i>in vitro/in vivo</i>	Upregulates JAG1 and VEGFA/Sponges miR-140-5p (which targets JAG1)	90
MEG3	Notch1	Promoted proliferation and EMT	Downregulated	<i>in vitro/in vivo</i>	Inhibits Notch1	112

Dll, Delta-like; EMT, epithelial-to-mesenchymal transition; JAG, jagged; KCNQ1OT1, Potassium Voltage-Gated Channel Subfamily Q Member 1 Opposite Strand/Overlap Transcript 1; NDR1: N-Myc Downstream-Regulated 1; lncRNA, long non-coding RNA; NICD1, Notch1 intracellular domain; Pyk2, Proline-Rich Tyrosine Kinase 2.

mRNAs, and lncRNA-miRNA-mRNA interaction networks function as substantial mediators in various pathogenic pathways.^{105,106} As summarized in Table 2,^{85-90,107-112} lncRNAs can induce metastasis, invasion, proliferation, migration, and drug resistance in BC through positive or negative regulation of the Notch pathway, as discussed below.

lncRNAs positively regulate BC through Notch signaling

Ren *et al.* inhibited KCNQ1OT1 expression using shRNA in BC cell lines, which reduced tumor growth and invasion, migration, and proliferation both *in vivo* and *in vitro*. As depicted in Figure 1, upregulation of KCNQ1OT1 can inhibit miR-34a, preventing the suppressive impact of miR-34a on BC invasion, migration, and proliferation. Thus, KCNQ1OT1 significantly increases expression of Notch3 in BC.⁸⁵ According to research by Wang *et al.*, NDR1 controls drug resistance (to Epirubicin and Taxol) and apoptosis in BC cells. NICD1 was further expressed by NDR1 and

promoted its target genes c-MYC and HES-1. In addition, Wang *et al.* discovered that increased NDR1 expression was associated with poor survival in BC.¹⁰⁷ Jiang *et al.* indicated that SNHG3 expression is increased in BC tissues. To promote the growth, migration, and invasion of BC cells, SNHG3 may act as an endogenous RNA with miR-154-3p and regulate the Notch signaling pathway.⁸⁶ Huang *et al.* indicated that overexpression of long intergenic non-coding RNA (linc)-00052 in BC cell lines induced metastasis, invasion, proliferation, and migration through the linc-00052/miR-548p/Notch2 axis (Fig. 1). Additionally, linc-00052 stimulated migration and invasion by increasing Proline-Rich Tyrosine Kinase 2 phosphorylation (downstream factor of Notch2).⁸⁷ The first miRNA sponge interaction between miR-205 and CCAT2 was identified by Xu *et al.*, who showed that Notch2, a crucial miR-205 target gene, was upregulated in TNBC; miR-205 downregulated the Notch2 target gene, whereas CCAT2 increased its expression.⁸⁸ Sun *et al.* revealed that SNHG7 stimulates miR-34a through EMT induction and the Notch1 pathway, which promotes BC growth and progression.⁸⁹ Moreover, several studies provided

Table 3. Outline of circRNA mechanisms of action through the Notch signaling pathway in BC

circRNAs	Target(s)	Function(s)	Expression	Model (<i>in vitro</i> , <i>in vivo</i>)	Mechanism of action	Reference(s)
circ-FAT1	Notch2	Promoted metastasis, proliferation, and drug resistance	Upregulated	<i>in vitro</i>	Targets miR-525-5p (which targets SKA1)	91
circ-UBR5	Notch1, Notch4, HES1, and UBR5	Induced growth and metastasis	Upregulated	<i>in vitro/in vivo</i>	Sponges miR-1179 and upregulates UBR5 (oncogene)	92
circ-000911	Notch1	Suppresses cell proliferation	Downregulated	<i>in vitro</i>	Upregulates Notch1 by sponging miR-449a	93

circRNA, circular RNA; FAT1, FAT Atypical Cadherin 1; HES1, Hairy and Enhancer of Split-1; UBR5, Ubiquitin Protein Ligase E3 Component N-Recognin 5.

evidence that lncRNAs precisely target Notch signaling components (Table 2). In MDA-MB-231 cells treated with linc-OIP5 siRNA, Zhu *et al.* demonstrated that cell invasion, migration, and proliferation were downregulated, whereas apoptosis induction was upregulated. Mechanistic studies showed that downregulation of linc-OIP5 decreased the expression of JAG1 and YAP1 (Fig. 1).¹⁰⁸ The findings of Zhu *et al.* described, at least in part, a novel angiogenic signaling circuit (YAP1/Notch/NRP1) in breast malignancies, raising the possibility of linc-OIP5 as a target for therapy in breast tumor angiogenesis.¹⁰⁹ Zhang *et al.* indicated that by maintaining NICD1 stability, BREA2 promotes BC metastasis. Mechanistically, WWP2 is an E3 ubiquitin ligase for NICD1, in which BREA2 disrupts the WWP2-NICD1 complex.¹¹⁰ Based on the report by Tao *et al.*, linc-00514 overexpression promoted BC cell proliferation and invasion, which also increased the volumes of xenograft tumors and pulmonary metastatic nodules. As indicated in Figure 1, linc-00514 promoted the transcription of JAG1 by increasing STAT3 (Signal Transducer and Activator of Transcription 3) phosphorylation.¹¹¹ Liu *et al.* stated that JAG1 and VEGFA expression decreased in TNBC following siRNA inhibition of MALAT1. Thus, exosomal MALAT1 may enhance angiogenesis via the MALAT1-miR-140-5p-JAG1/VEGFA axis, and MALAT1 could mechanistically inhibit miR-140-5p and miR-140-5p via targeting JAG1.⁹⁰

LncRNAs negatively regulate BC through Notch signaling

As shown by Pan *et al.*, MEG3 knockdown in association with 5-AzaC or sh-DNMT1 therapy recovered Notch1 receptor expression, activated the Notch1 pathway, and accelerated EMT in BC.¹¹² Large-scale -omics research has provided a wealth of information on lncRNA transcription in BC, suggesting that lncRNAs may be indicators for early recognition, assessment, and prognosis of BC.¹¹³ As stated in prior studies, lncRNAs interact with miRNAs, Notch components, and other genes to regulate the cascade and may be exploited as possible targets and prognostic markers. Interestingly, lncRNAs both directly and indirectly target the ligands and receptors of the Notch signaling pathway, leading us to hypothesize that these axes could be targeted to establish a useful treatment for BC patients.

CircRNAs impact BC through Notch signaling

The transcriptome of eukaryotes contains a large number of circRNAs, a unique and distinct family of endogenous ncRNAs that construct a continuous covalently bound cycle.¹¹⁴ Most circRNAs are expressed only in specific tissues or during particular phases

of development. It has been demonstrated that circRNAs carry out essential tasks such as translating proteins and peptides, sponging RNA binding proteins, regulating gene splicing and transcription, and sponging miRNAs.¹¹⁵ Additionally, recent studies have demonstrated that circRNAs play a critical role in the modulation of numerous transduction pathways and various cancer types, notably Notch signaling and BC (Table 3).^{91-93,116}

CircRNAs positively regulate BC through Notch signaling

Reports of how circRNAs function within the Notch signaling pathway in BC are scarce, but those that have been published are discussed here. Yao *et al.* showed that tolerance of BC cells to oxaliplatin (OX) decreases with circ-FAT1 knockdown. Circ-FAT1 directly targets miR-525-5p, which is upregulated in OX-resistant BC cells.⁹¹ SKA1, a target of miR-525-5p, is elevated in BC cells (Fig. 1). SKA1 may stimulate Wnt and Notch signaling pathways, as evidenced by suppression of β -catenin, Glycogen synthase kinase-3, and Notch2 expression in BC cells after SKA1 knockdown.⁹¹ Gong *et al.* found that the TNBC oncogenic characteristics of circ-UBR5 are mediated by miR-1179 sponging and upregulation of UBR5.⁹² As illustrated in Figure 1, we can conclude that overexpression of circ-UBR5, which sponges miR-1179, activates the Notch signaling pathway in different types of BC.^{71,92}

CircRNAs negatively regulate BC through Notch signaling

As Wang *et al.* indicated, Notch1 is downregulated in BC cells. CircRNA-000911 is also overexpressed, and this significantly inhibits the capability of BC cells to proliferate, promote wound healing, and trigger apoptosis. The incremental expression of circRNA-000911 can significantly reduce miR-449a expression in BC cells. Hence, circRNA-000911 positively regulates Notch1 expression by sponging miR-449a.⁹³

Lu *et al.* conducted a human circRNA array and found that 715 and 440 circRNAs were increased and decreased, respectively, in BC tissues, indicating their value as diagnostic biomarkers.¹¹⁷ Notably, circRNAs can be used as biomarkers in various diseases due to their high abundance and excellent stability. Furthermore, due to their diverse functions, circRNAs play a crucial role in the modulation of tumor progression.¹¹⁸ These findings suggest that circ-FAT1, circRNA-000911, and circ-UBR5 may be regarded as diagnostic and prognostic markers for BC.

Therapeutic applications of ncRNAs in BC

MiRNA therapies are designed as oligonucleotides that adjust the

aberrant expression of miRNAs and related pathways.¹¹⁹ This is accomplished by substituting defective tumor-suppressive miRNAs and inhibiting oncogenic miRNAs. A wide range of prior preclinical research on migraine therapeutic modification has suggested that this could be an effective method of enhancing cancer therapy.¹²⁰ For example, Zhao *et al.* demonstrated that miR-21 suppression significantly decreased the development of breast tumors and angiogenesis *in vivo* by inhibiting the HIF-1 α /VEGF/VEGFR2 axis.¹²¹ Therapeutic modulation of lncRNAs can be achieved by either upregulating or downregulating their expression. Small molecule inhibitors, CRISPR-Cas9 system, antisense oligonucleotides, and RNA interference (RNAi) are a few methods that could be used to suppress lncRNA expression.¹²² For instance, Liu *et al.* utilized RNAi-mediated knockdown of MALAT1 in TNBC to hinder angiogenesis by downregulating VEGFA and JAG1.⁹⁰ Since circRNAs are miRNA sponges and could play a role in drug resistance and the development of BC, they could be upregulated or silenced to serve as potential therapeutic targets.¹²³ In this case, Yao *et al.* indicated that RNAi-mediated knockdown of circ-FAT1 decreased OX-resistance and cell viability. Specifically, circ-FAT1 was shown to sponge miR-525-5p, leading to SKA1 upregulation and triggering Wnt and Notch pathways.¹²⁴

Future remarks

Due to the advancement of novel therapies, precision medicine may be used to effectively treat cancers. However, for different reasons, various treatments should be offered at each stage. Despite the discovery of more and more anti-cancer medications, tumor drug resistance remains a problem. Due to the intricacy of human physiology, it is challenging for standard drugs to be effective, and cancer cells can develop resistance to treatment and have a significant self-renewal capacity.⁴⁶ Over the past 20 years, it has been well established that Notch signaling is essential for mammary gland development and the etiology of BC. High Notch signaling is present in all cancers, however, it is particularly linked to cancers that show therapy resistance (e.g., TNBC) and have a poor prognosis.¹²⁴ Mis-regulation of Notch signaling elements, such as Notch ligands and receptors, and their interactions in BC provide a launching pad for tumor initiation, development, and survival by triggering abnormal tumorigenesis (tumor regeneration, stemness induction) while establishing vascular integrity, migration, invasion (EMT), and drug resistance.

Conclusions

According to the literature, ncRNAs that interact with Notch components and downstream factors are deregulated in BC. Some ncRNAs show antitumor activities, but others act as tumor promoters in BC. This highlights the complexity of ncRNA function and possible implications in BC progression, which should be considered more seriously in diagnosis, development of new therapeutic strategies, and prognosis. As promising therapeutic approaches, targeting linc-00514 (an oncogene) and employing miR-206 mimic nanoparticles, may have good outcomes. Furthermore, circUBR5 (an oncogene), found in a panel of human malignancies, serves as a prognostic biomarker. Developing targeted therapeutic strategies based on the utilization of lncRNAs, miRNAs, and circRNAs requires knowledge of the precise process of BC carcinogenesis. Although, the described processes of ncRNA functioning through the Notch pathway in BC tumorigenesis could be beneficial in precision therapy, further research is still needed.

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Conflict of interest

The authors declare that there is no conflict of interests.

Author contributions

AA and AM had the idea for the article. AA, AM, MKK, and SG performed the literature search and provided the first draft of the manuscript. AA and AM made the first draft of the manuscript. MKK and SG scientifically updated the literature search and critically revised the work. All authors read and commented on the final draft of the manuscript.

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