

Epigenetic mechanisms of the influence of aging on the development of breast cancer with the participation of retroelements

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Abstract

Breast cancer as a multifactorial disease is associated with aging and a variety of polymorphisms located mainly in intronic, regulatory and intergenic regions. Since retroelement genes are localized in these regions, it has been suggested that such polymorphisms lead to the development of breast cancer by altering the activity and functioning of retroelements. This assumption is also supported by the fact of pathological activation of retroelements during aging, which explains the increase in the incidence of breast cancer with age. This article describes the facts of activation and mechanisms of influence of LINE, SINE, LTR retroelements on breast cancer, which confirms the proposed assumption. In addition, the article describes the association of retroelement-derived oncogenic and tumor suppressor microRNAs involved in breast cancer carcinogenesis with aging, and reveals the mechanisms of interactions of retroelements with 86 microRNAs derived from them in these processes. The article describes promising ways of using the identified retroelement-derived microRNAs in targeted therapy of breast cancer using antisense oligonucleotides and the microRNAs themselves as tools. Using 17 of the retroelement-derived microRNAs described in the articles, the expression of which changes similarly in both breast cancer and aging, it is possible not only to target breast cancer therapy, but also to slow down aging.

Keywords: Long non-coding RNAs, carcinogenesis, microRNAs, breast cancer, retroelements, aging

Introduction

According to the latest data from the International Agency for Research on Cancer, the age-standardized incidence rate of breast cancer (BC) is 46.2 per 100,000 population, ranking first among all malignant neoplasms regardless of gender. The risk of developing BC is associated with aging [1, 2]. In addition, BC treatments accelerate aging. Women treated for BC suffer from higher rates of cognitive decline and physical development [3, 4]. Therefore, it is promising to develop methods of targeted therapy aimed at the mechanisms of breast cancer carcinogenesis

without increasing aging, which meets the principles of personalized medicine to ensure active longevity. About 10% of BC cases are monogenic due to heterozygous germline mutations in tumor suppressor genes. 1/5 of such monogenic forms of BC are caused by pathogenic mutations in the *BRCA1* and *BRCA2* genes, the remaining 4/5 are caused by mutations in the *ATM*, *BARD1*, *CHEK2*, *RAD51D*, *RAD51C*, *PALB2* genes. However, most cases of BC are multifactorial diseases influenced by environmental factors and hereditary predisposition under the influence of specific single nucleotide polymorphisms (SNPs) [5]. According to the conducted meta-analysis of the results of GWAS (genome-wide association study), 79 loci associated with BC were identified, among which 15 new SNPs were studied, which are located in the regulatory, intronic or intergenic regions of protein-coding genes. For example, rs72755295 is located in the intron of the *EXO1* gene (encodes a protein for the repair of mismatched nucleotides), rs6507583 is in the 18q12.3 region interacting with the *SETB1* promoter [6]. In 2020, a meta-analysis identified 32 new breast cancer susceptibility SNPs. Most of these SNPs are also located outside genes

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or in their introns, with a putative effect on the regulation of downstream genes or by an in trans mechanism as enhancers for genes such as *TBX3*, *SOX4*, *RNF115*, *POLR3C* [7]. In 2023, GWAS have identified over 300 SNPs associated with BC development [8]. A polygenic risk assessment including 313 SNVs has been developed and to predict BC risk [9]. In 2025, based on the GWAS results 191 SNP-related genes significantly associated with BC recurrence and metastasis [10]. In 2025, 332 independent association signals for breast cancer were identified, including 131 previously known signals. Using integrated functional genomics data analysis, 195 putative breast cancer susceptibility genes were identified, enriched in the Wnt/beta-catenin, p53, TNF/NF- κ B, PI3K/AKT pathways [11]. The location of SNPs in gene introns, in intergenic and regulatory regions, is characteristic of most multifactorial diseases [12] and is consistent with data indicating that these loci contain genes for retroelements (REs), long non-coding RNAs (lncRNAs) and microRNAs [13]. Accordingly, BC-associated SNPs may influence the activity of REs, lncRNAs, and microRNAs [14].

It should be noted that the genes of many non-coding RNAs (ncRNAs) originated from retroelements (REs) in evolution or are formed by processing their transcripts [15]. An example of the influence of SNP on epigenetic regulation of genes is the rs1972820 polymorphism in the 3'-UTR (untranslated region) of the *ERBB4* gene (encodes the tyrosine protein kinase receptor, a member of the epidermal growth factor receptor family). Polymorphism rs1972820 alters binding to the 3'-UTR of the gene with oncogenic microRNA miR-3144-3p (derived from LINE1 [15]), which reduces the risk of breast cancer [16]. Another example is the SNP within the EXO motif: GGAG and GCAG in the miR-1246 sequence (derived from ERVL-MaIR [15]), which affects its intracellular trafficking and stability [17]. This microRNA promotes metastasis and chemoresistance of breast cancer cells by inhibiting the expression of the *NFE2L3* gene (encodes a membrane-bound glycoprotein of the nuclear envelope and endoplasmic reticulum) [18]. Since aging, which is associated with breast cancer [1, 2], promotes progressive epigenetic derepression of REs [19], this factor may be a trigger for the induction of retroelements altered under the influence of breast cancer-associated SNPs for the development of BC carcinogenesis [6-11].

New directions in the study of epigenetic mechanisms of breast cancer development can become the basis for more effective and safe methods of targeted therapy. Of greatest interest in this regard is the study of the relationship between retroelements and epigenetic factors and aging in breast cancer carcinogenesis. REs are mobile elements that move within the genome using a copy-and-paste mechanism and occupy 46.67% of the human genome. The most common REs are autonomous non-LTR (long terminal repeat) LINEs (long interspersed nuclear elements), occupying 21% of the genome, while non-autonomous SINEs (short interspersed nuclear elements) account for 13%, and LTR-containing REs account for 9% of the human genome [13]. Since many breast cancer-associated

polymorphisms located in loci of the human genome where retroelements are located can lead to changes in REs activity, the aim of the study in this article is to describe experimental and clinical data on the involvement of pathologically activated LINE, SINE and LTR retroelements. Also for this purpose, the mechanisms of the influence of retroelements on the development of breast cancer are described. In order to determine additional facts in favor of the role of REs in breast cancer carcinogenesis, as well as to determine the significance of the study, an analysis of the involvement of retroelement-derived microRNAs in the development of breast cancer was carried out. The significance of identifying such microRNAs with oncogenic and tumor suppressor properties lies in the possibility of using them as targets and tools, respectively, for targeted therapy of breast cancer. Moreover, identifying specific microRNAs derived from REs and involved in both aging processes and breast cancer carcinogenesis will allow us to determine the mechanisms of the influence of aging on the development of breast cancer and to determine the ways of targeting these mechanisms.

The impact of LINE1 on breast cancer development

Epigenetic changes leading to LINE1 activation, characterized by hypomethylation of their loci, have been identified in breast cancer patients [20]. Worse prognosis of breast cancer was also associated with LINE1 hypomethylation [21]. In invasive breast cancer, LINE1 hypomethylation was correlated with negative ER status, and the degree of LINE1 hypomethylation varied significantly across breast cancer subtypes [22]. For LINE1 incapable of transposition (due to truncation of the 5'-end) in breast cancer cells, their ability to bind to transcription factors at their 3'-ends with a change in gene expression was determined [23]. Using reverse transcriptase PCR, it was shown that LINE1 expression suppresses breast cancer cell differentiation and promotes lymph node metastasis [24]. A study of 7769 samples of various malignant neoplasms showed an increase in the expression of retroelements in 3864 of them, which correlated with the activation of 106 oncogenes with onco-exaptation processes in half of the breast cancer samples [25]. Similar results were obtained in another study with a study of 2954 samples of various tumors, when RE insertions were detected in more than 50% of breast cancer tissues, mainly LINE1 [26]. Activated LINEs, in addition to activating oncogenes, can promote carcinogenesis by inactivating tumor suppressors. This property has been noted for LINE1 in relation to the *WT1* [27], *MCC* [28], *PTEN* [29], *APC* genes [30]. LINE activation in breast cancer stimulates carcinogenesis also by maintaining telomere length in cell divisions with hTERT induction [31]. In addition, abnormally expressed LINEs are sources of enzymes that retrotranspose non-autonomous retroelements such as Alu, which are also involved in breast cancer carcinogenesis [32]. Activated LINE1 in cancer promotes genomic instability and chro-

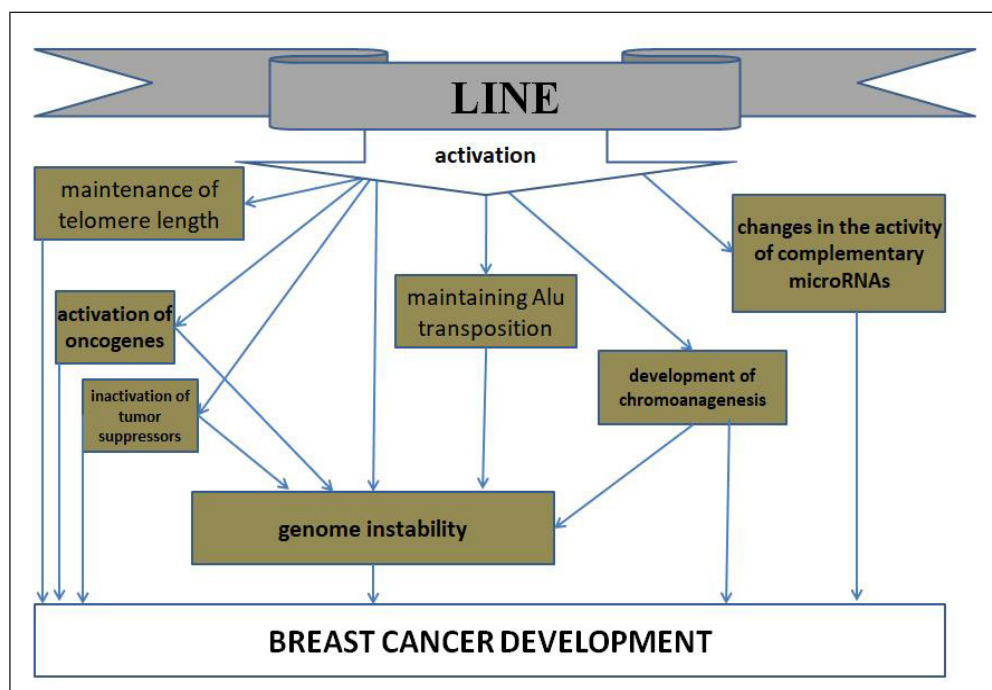


Figure 1. Pathways of LINE influence on breast cancer development.

moanagenesis [33], while this process is determined in more than 60% of cases of metastatic breast cancer [34] and in more than half of HER2-positive breast cancer [35]. Thus, LINES contribute to breast cancer development through various pathways, including through cross-regulation with their derived microRNAs (Figure 1).

The influence of SINE on the development of breast cancer

The most common SINEs in the human genome are Alu retroelements. Alu-PCR has revealed multiple events of genomic instability mediated by Alu elements, including deletions, insertions [36]. Under the influence of Alu, in breast cancer carcinogenesis, inactivation of *BRCA1*, *PIF*, *TSA*, *ELG*, *RRM3* tumor suppressor genes often occurs [37]. In normal cells, the CpG sites of Alu elements are methylated, which prevents their activation and transposition [38]. Accordingly, hypomethylation causes activation of these REs. In clinical studies, comparative analysis of Alu and LINE methylation in samples of normal breast tissue, cells with atypia, ductal carcinoma in situ and invasive breast cancer has determined a decrease in Alu methylation during the transition from carcinoma in situ to invasive breast cancer, correlating with the negative status of the estrogen receptor. In the HER2-enriched breast cancer subtype and with poor patient survival, the lowest level of Alu methylation was detected [22]. In metastatic breast cancer with early progression, hypomethylation of Alu was determined in immune system cells. Moreover, an increase in the number of unmethylated loci was associated with a worse prognosis [38]. A study of the epigenomic landscape of TNBC tissues deficient in homologous recombination identified a decrease in Alu methylation across the genome [39]. It should be noted

that elevated levels of SINE are also detected in the blood plasma of dogs with breast cancer, correlating with worse survival compared to healthy animals. Also, increased expression of SINE B1 was detected in breast cancer tissues at an early stage of tumor development in mice, with a marked increase during cancer progression [40]. The obtained data indicate the universality of SINE as a key player in breast cancer carcinogenesis in different species, including humans.

Promising biomarkers for breast cancer are circulating cell-free DNA, which is released into the blood by tumor cells [41]. In clinical studies, a recognized effective method for diagnosing and monitoring breast cancer is liquid biopsy, which can be used to detect molecules that play a role in carcinogenesis in extracellular material [32]. The role of actively expressed Alu in the development of breast cancer was also identified by determining cell-free DNA ALU-247 and ALU-115, which levels were statistically significantly higher in breast cancer patients compared to healthy controls. These indicators have been proposed as diagnostic markers for the early detection of breast cancer [42]. ALU-247 levels were significantly lower in the plasma of breast cancer patients after surgery compared with preoperative data, and significantly higher in patients with metastatic breast cancer [32]. Analysis of blood plasma samples before and after a course of neoadjuvant chemotherapy in breast cancer patients with determination of Alu-RNA levels by quantitative real-time PCR showed an increase in Alu expression, more pronounced in premenopausal women and in hormone-positive breast cancer [43, 44]. Analysis of circulating Alu also allows to assess their methylation status, which was found to be higher in breast cancer patients compared to healthy controls [41].

Alu play an important role in the formation of circular RNAs (circRNAs) that are involved in carcinogenesis,

including breast cancer. It has also been determined that the homologous splicing factor SLU7 regulates the formation of circCAPG circular RNA by binding to the flanking Alu sequences of circCAPG transcripts (which are used to form circCAPG). This circRNA promotes proliferation and metastasis of TNBC cells through the action of the CAPG-171aa polypeptide, which is formed during translation of circCAPG on ribosomes [45]. Inverted repeats of Alu (IRAlu) flank sequences of another circular RNA, circRNA-CREIT. The RNA-binding protein DHX9 interacts with these IRAlu, suppressing the expression of circRNA-CREIT, thus promoting the progression of doxorubicin-resistant TNBC [46]. SINE expression products can stimulate the body's antitumor response as inducers of the interferon response. This effect was determined using arginine methyltransferase type 1 inhibitor, which promotes the interferon antitumor response through antiviral defense pathways with a response to double-stranded RNA (formed from inverted repeats of Alu elements) [47]. This may explain the described phenomenon, when patients with low levels of circulating Alu and LINE were found to have a lower risk of breast cancer recurrence [48]. In addition to identifying the fact of SINE activation in breast cancer, the consequences of such events in the form of their integration into new loci of the genome with disruption of the functions of tumor suppressor genes and the transformation of proto-oncogenes into oncogenes were also determined. These events can be drivers in breast cancer carcinogenesis. Thus, when examining breast cancer samples in two independent studies, transpositions of retroelements, including Alu, were identified in half of them [25, 26]. A genome-wide analysis of the landscape of retroelement changes in breast cancer genomes conducted in 2024 using the ARTEMIS (Analysis of Repeat Elements in dISease) approach showed changes in 73% of Alu and 97% of MIR sequences [49]. It can be assumed

that such changes are recorded in the results of the analysis of SNP associations with breast cancer [6-11], since these SNPs are located mainly in introns and regulatory regions of genes where SINEs are located (Figure 2).

Effects of LTR retroelements on breast cancer development

Activation of LTR-REs is detected by direct identification of their expression in breast cancer tissues, indirectly by identifying a decrease in methylation of their loci in the genome, and also by analyzing cell-free DNA in the blood plasma of patients. In breast cancer cells, HERV-K expression was found to be stimulated by progesterone after exposure to estrogens [50], indicating a role for LTR-REs in hormone-mediated breast cancer growth. Analysis of HERV expression in breast cancer tissues using reverse transcriptase PCR showed the presence of HERV-K transcripts (and the absence of HERV3, HERV-E4-1) in most breast cancer samples and cell lines, indicating the influence of specific HERVs on the development of breast cancer. Full-length proviruses and mature HERV envelope (env) mRNA were detected. No such changes were found in normal breast tissue [51]. Further studies have shown that the level of HERV-K expression in a breast cancer cell line increases 5-10-fold when exposed to estradiol and progesterone [52], which may indicate a role for these retroelements in the progression of hormone-dependent breast cancer. Experiments on human T47D breast cancer cell lines revealed that the female sex hormones estradiol and progesterone synergistically activate HERV-K via nuclear receptors. The progesterone receptor isoform B binds to the progesterone response element (PRE) in the region of the specific LTR5HS of HERV-K. In addition, there is another transcription factor binding element

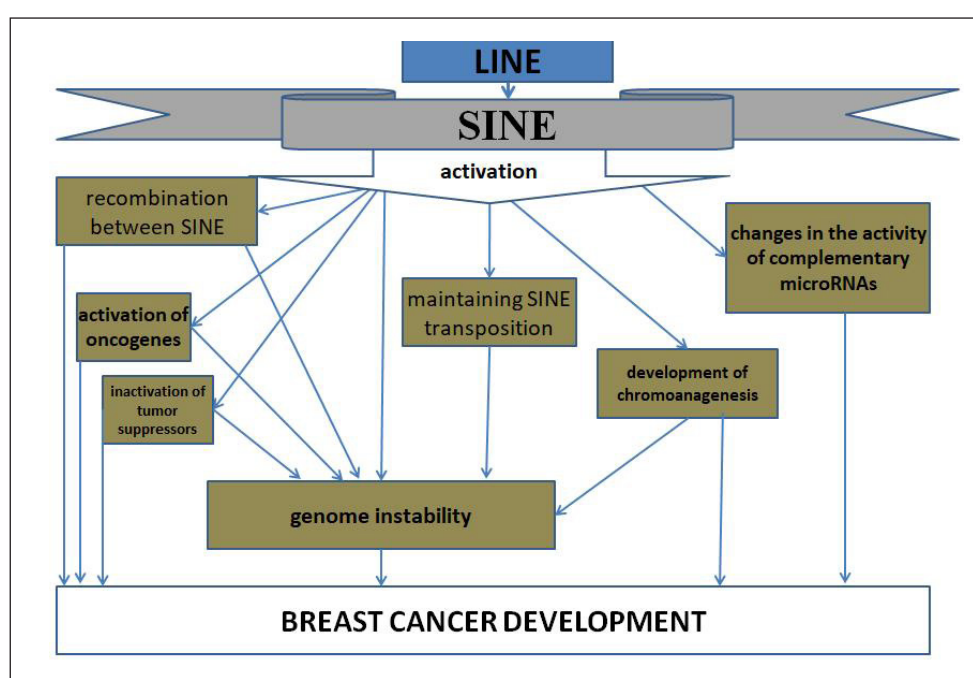


Figure 2. Mechanisms of influence of breast cancer-associated SNPs on the involvement of SINE in breast cancer carcinogenesis.

OCT4, an octameric motif required by hormones to activate HERV-K downstream of the LTR [53]. Suppression of HERV-K blocked the synthesis of Ras, p-RSK, p-ERK oncogenes that affect breast cancer, and HERV-K overexpression restored the Ras/Raf/MEK/ERK oncogenic pathways. HERV-K also activates CDK5, which suppresses the p53 tumor suppressor by disrupting p53 phosphorylation. In turn, CDK5 is a mediator of TGF- β 1-induced epithelial-mesenchymal transition and tumor cell migration [54]. It should also be noted that 1509 LTRs in the human genome contain a nearly ideal DNA binding site for the tumor suppressor protein p53, which exerts a regulatory effect on them [55]. At the same time, mutations in the *TP53* gene are found in 40-60% of breast cancer samples [56], which serves as one of the additional mechanisms of pathological activation of LTR-REs in breast cancer. Thus, breast cancer is characterized by an increase in the expression of LTR-REs, which may play an important role in the progression and clonal evolution of the tumor, especially given the influence of female sex hormones on this process. Indeed, a study of RE transcription in various types of breast cancer showed that the expression of LTR sequences is characteristic of luminal-B HER2-positive breast cancer [57]. Identification of cell-free DNA using whole-genome sequencing allowed us to identify breast cancer-specific LTRs, as well as their insertions near carcinogenesis driver genes. In breast cancer, changes were detected in 66% of LTR-ERV1, 68% of LTR-ERVK, 66% of LTR-ERVL, 78% of LTR-ERVL-MaLR, and 67% of LTR-Gypsy elements, indicating a global scale of genome transformations [49], since LTR-REs play an important role in regulating the expression of many genes during cell differentiation during development of the organism, since HERV transcripts function as lncRNAs to control human embryonic stem cells [58].

LTR-REs activated in breast cancer exert their influence on carcinogenesis in various ways. First of all, since they serve as regulators of cell differentiation during ontogenesis [58], pathological expression of the evolutionarily youngest of them, HERV-K, promotes dedifferentiation [59]. Since regulatory LTRs are globally distributed in the human genome, serving as binding sites for various transcription factors in the regulation of gene expression [60], their activation can cause increased expression of downstream oncogenes. Indeed, it has been found that activation of the oncogene *IRF5* (interferon regulatory factor 5) is due to the influence of the upstream LTR of this gene in Hodgkin's lymphoma [61]. Cases of insertion of LTR-REs into the intron of the *FABP7* proto-oncogene with its transformation into the *LTR2-FABP7* oncogene in B-cell lymphoma have been described [62], insertion of an LTR-containing REs into the *ERBB4* gene with the formation of the *LTR-ERBB4* oncogene [63], and transposition of LTR into the *ALK* gene with the formation of an alternative *LTR-ALK* transcript [64]. In addition, tumor suppressor genes, including *BRCA* [65], are characterized by the presence of hot spots for insertional carcinogenesis [66]. Therefore, activation of LTR-REs may cause decreased control of tumor suppressor genes. Activated LTR-containing REs are potential sources of chromoanagenesis in carcinogenesis [33]. Investigation of the causes of segmental duplications and large genomic transformations has identified 30 different LTR-Res on 12 separate chromosomes as the causes of these phenomena [67]. *In vitro* experiments on breast cancer cell lines (MCF-7, AU565, MDA-MB-231 and MB468) showed that HERV-K activation causes a regulatory effect on neighboring genes. Moreover, for different breast cancer cell lines, different changes in the expression of HERV-K_1q23.3, HERV-K_22q11.23, HERV-K_9q34.11, HERV-K_14q32.33

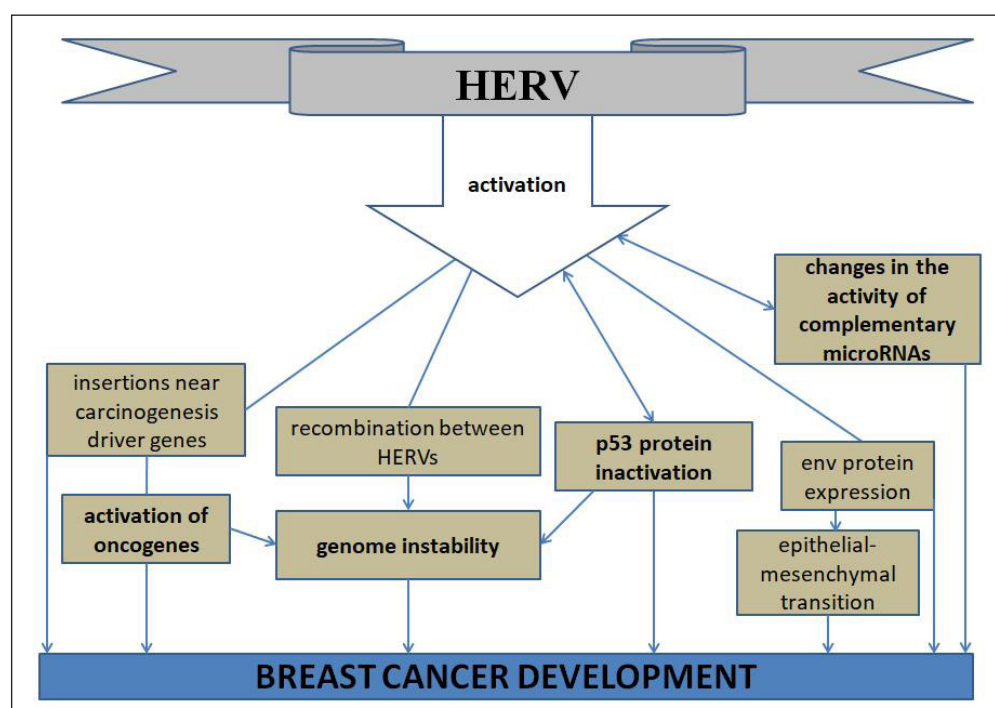


Figure 3. Mechanisms of carcinogenic action of HERV on breast cancer.

and adjacent genes were detected, including the *CD48*, *IGLL1*, *SLAMF1*, *SLAMF1* genes that positively correlate with immune infiltration of breast cancer [68]. The HERV-K envelope protein Env has oncogenic properties in breast cancer. Stimulation of its expression promotes epithelial-mesenchymal transition of normal breast cells [69]. In the blood of patients with breast cancer, elevated levels of the Env protein are detected not only of HERV-K, but also of endogenous retroviruses HERV-H, HERV-P, HERV-R, which are reduced under the influence of chemotherapy, to a greater extent than in patients receiving radiation therapy [70]. High levels of HERV-K expression are characteristic of the aggressive basal-like subtype of breast cancer, suggesting the potential use of HERV as prognostic biomarkers for breast cancer [71]. Antibodies to HERV-K are planned to be used for early diagnosis of breast cancer [72]. Thus, there are various mechanisms of influence of activated LTR-containing RE on the development of breast cancer, among which the relationship with epigenetic factors, which include DNA methylation, histone modifications and the influence of microRNA, is also important [66] (Figure 3).

Association of retroelement-derived oncogenic microRNAs involved in breast cancer carcinogenesis with aging

The human genome contains 7,565 small noncoding RNA genes, most of which are microRNA genes [13]. According to a recent publication of the MDTE (miRNA derived from transposable elements) database [15], 474 microRNAs were found in humans that completely or partially overlap with sequences of mobile genetic elements. After excluding multicopy miRNAs, 405 unique mature miRNAs were identified, among which 352 completely overlapped with mobile genetic elements, accounting for 15% of the total number of molecules analyzed (2652 miRNAs). The richest sources of such microRNAs were DNA transposons (144 microRNAs), despite their insignificant

share in the human genome. 116 microRNAs originated from LINE, 90 from SINE, and 50 microRNAs from LTR-RE [15]. It is possible that more microRNA genes derived from mobile genetic elements will be found in the future, since detailed genome analysis using specific oligonucleotides that recognize complementary mobile genetic elements (repeat sequences) has revealed that more than 2/3 of the human genome consists of such sequences [73]. The analysis of the microRNAs presented in the MDTE database with the data published in the scientific literature on the role of microRNAs in the development of breast cancer, as well as in the mechanisms of aging, allowed us to describe the microRNAs whose expression is increased (Table 1). Accordingly, microRNAs with increased expression exhibit oncogenic functions. Of the 43 microRNAs presented in the table, 17 microRNAs are characterized by changes in expression in specific tissues during human aging. The mechanism of the relationship between retroelements and oncogenic microRNAs in breast cancer may be due to the direct formation of microRNAs from transposable element genes [15]. Accordingly, increased expression of such microRNAs reflects the activation of such retroelements in breast cancer that inactivate tumor suppressor genes, promoting the inactivation of more tumor suppressor genes, thus enhancing carcinogenesis (Figure 4). In this regard, the use of such microRNAs as objects for targeted therapy of breast cancer (using anti-sense oligonucleotides) [74] in combination with reverse transcriptase inhibitors that suppress the transposition of activated retroelements is promising [75, 76].

Summarizing the general trends in Table 1, among the REs-derived miRNAs that are upregulated in BC, 9 miRNAs (miR-378d, miR-552-5p, miR-558, miR-576-5p, miR-1272-3p, miR-3135b, miR-4428, miR-4480, miR-5100) are also upregulated in aging. Of these, 4 miRNAs are derived from SINEs, 3 miRNAs from LINEs, and 3 from LTR-REs. That is, the uniform contribution of different REs of the human genome in such relationships is determined. This indicates that the activation of REs during aging can serve as a trigger for breast cancer carci-

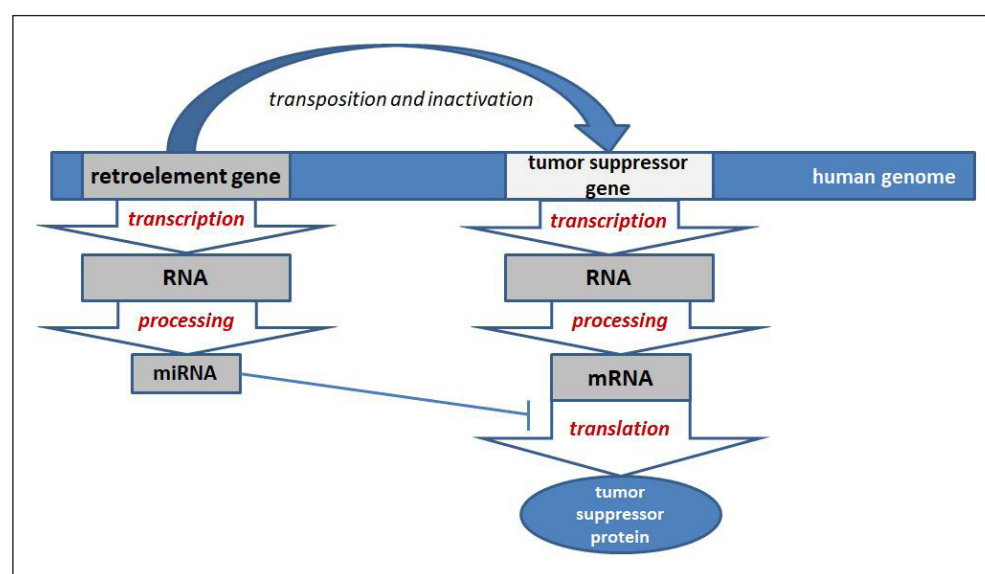


Figure 4. Scheme of the relationship between retroelements and oncogenic microRNAs in breast cancer carcinogenesis.

Table 1. Retroelement-derived microRNAs which expression is increased in breast cancer and altered with aging.

No	Re-source of microRNA	microRNA/ tissue	miRNA target genes/interaction with other ncRNAs	Changes in microRNA expression during aging (tissue)
1.	SINE-MIR	miR-378d/ exosomes [77]	<i>KLK4, NR2C2, NKX3-1, PHC3, ELAC1, ZNF124, RAB10, NCAPG, KCNIP2, VPS53, JADE3</i> (miRDB)	increased (colon tissue) [78]
2.	LINE1	miR-552-5p/ cancer [79]	<i>WIF1</i> / lncRNA SLC16A1-AS1 [79]	increased (human epidermal cells) [80]
3.	ERV1-MaLR	miR-558/ cancer [81]	<i>HOXA1, CGREF1, ZNF217, EDC3, ULK1, ITGBL1</i> (miRDB)	increased (mesenchymal stem cells) [82]
4.	LINE1	miR-576-5p/ cancer [83]	<i>MEIS2</i> / LINC-PINT [83]	increased (blood plasma) [84]
5.	LINE2	miR-1272-3p/ cancer [85]	<i>MEF24, DPYSL5, MTDH, USP3, WTAP, MAP3K20, ZCCHC10, STK35</i> (miRDB)	increased (human cerebral cortex) [86]
6.	SINE-Alu	miR-3135b/ cancer [87]	<i>LRRC27, FMNL3, TTC21B, CASTOR3, XPO7, PPM1A, DNMT1, RBP1</i> (miRDB)	increased (human hippocampus) [88]
7.	LTR-ERV1	miR-4428/ blood serum [89]	<i>EPHBI, MECP2, KAT6A, ADAR, RELN, CCT8, KLF9, NCBP1</i> (miRDB)	increased (human salivary exosomes) [90]
8.	SINE-MIR	miR-4480/ blood serum [89]	<i>IL-17A</i> [91]	increased (retina) [91]
9.	SINE-MIR	miR-5100/ cancer [92]	<i>AZIN1, MOXD1, SMARCA2, SPO11, MOSPD2, CSNK1G3, HTR2C</i> (miRDB)	increased (brain microglia) [93]
10.	LINE2	miR-151a-5p/ blood [94]	<i>UTY, FANCA, SEZ6L, AK2, RALGAP1A, APL1A, NDE1, RGS17</i> (miRDB)	decreased (serum) [95]
11.	LINE2	miR-325-3p/ cancer, breast cancer cell lines [96]	<i>S100A2</i> [96], <i>Trp53</i> [97]	decreased (human chondrocytes) [97]
12.	SINE-tRNA-RTE	miR-342-5p/ breast cancer cell lines [98]	<i>HER2</i> [98]	decreased (peripheral mononuclear cells) [99]
13.	SINE-MIR	miR-378a-3p/ exosomes [77]	<i>KLK4, NR2C2, NKX3-1, KIAA1522, PHC3, ELAC1, ZNF124, RAB10, NCAPG</i> (miRDB)	decreased (thymus epithelial cells) [100]
14.	SINE-MIR	miR-378a-5p/ cancer [101]	<i>SUFU</i> / lncRNA GAS5 [101]	decreased (human fibroblasts) [102]
15.	LINE-CR1	miR-582-5p/ cancer [103]	<i>CMTM8</i> [103], <i>FAM19A1</i> [104]	decreased (neural stem cells) [104]
16.	ERV1-MaLR	miR-1246/ cancer [18]	<i>NFE2L3</i> [18]	decreased (adipose tissue stem cells) [105]
17.	ERV1	miR-1269a/ cancer [106]	<i>CREBZF</i> / circPAPD4 [106]	decreased (ovaries) [107]
18.	LINE2	miR-95-3p/ cancer [108]	<i>AKAP12</i> / circ_0001777 [109]	data not found
19.	LINE2	miR-151a-3p/ cancer [110]	<i>FAM120AOS, AGO2, RPS6KA5, ME1, UPP2, YTHDF3, PITPN4</i> (miRDB)	data not found
20.	SINE-MIR	miR-378e/ cancer [111]	<i>KLK4, NR2C2, NKX3-1, PHC3, ELAC1, ZNF124, RAB10, NCAPG, KCNIP2, VPS53, JADE3</i> (miRDB)	data not found
21.	LTR-ERV1	miR-548ay-3p/ breast cancer cell lines [112]	<i>TMEM33, OGT, CCNA2, CDK17, SMC3, SNRPC, MIB1, CNOT7</i> (miRDB)	data not found

Table 1 continued.

No	RE-source of microRNA	microRNA/ tissue	miRNA target genes/interaction with other ncRNAs	Changes in microRNA expression during aging (tissue)
22.	LINE2	miR-616-3p/ cancer [113]	<i>TIIMP2</i> [113]	data not found
23.	LINE2	miR-887-3p/ cancer, extracellular vesicles [114]	<i>BTBD7</i> [114]	data not found
24.	LTR-ERV1	miR-1202/ serum [115]	<i>BICRAL</i> , <i>ZFH4</i> , <i>CTNND1</i> , <i>TOX</i> , <i>RRN3</i> , <i>DMTF1</i> , <i>CRISPLD1</i> (miRDB)	data not found
25.	Alu	miR-1268a/ cancer [116]	<i>STXBP1</i> , <i>EEPD</i> , <i>EGR4</i> , <i>CMIP</i> , <i>FCAR</i> , <i>HPD</i> , <i>USBI</i> , <i>SLC8A2</i> , <i>TARP</i> (miRDB)	data not found
26.	ERV1	miR-1269b/ cancer [117]	<i>URU1</i> , <i>DAAMI</i> , <i>AGAP1</i> , <i>CCL11</i> , <i>TRAF3</i> (miRDB) / lncRNA <i>BRCAT54</i> [117]	data not found
27.	Alu	miR-1285-3p/ cancer [118]	<i>TP53</i> , <i>BTRC</i> , <i>SMURF1</i> [118]	data not found
28.	Alu	miR-1304-3p/ cancer [119]	<i>NR3C1</i> , <i>NEATC4</i> , <i>SCP2</i> , <i>ZMYM3</i> , <i>CNN3</i> , <i>PAGR1</i> , <i>PGM1</i> (miRDB)	data not found
29.	ERV1-MaLR	miR-1587/ cancer [120]	<i>IRF7</i> [120]	data not found
30.	LINE2	miR-1825/ serum [121]	<i>CLCN3</i> , <i>NA440</i> , <i>FUT9</i> , <i>DHX58</i> , <i>ABCA1</i> , <i>SNN</i> , <i>TUBG1</i> (miRDB)	data not found
31.	ERV1-MaLR	miR-2909/ cancer [122]	<i>MRE11</i> , <i>RAD50</i> [122]	data not found
32.	LINE1	miR-3118/ cancer [123]	<i>ZMAT5</i> , <i>PPP1R7</i> , <i>RAB27A</i> , <i>MBNL1</i> , <i>KRAS</i> (miRDB) / lncRNA <i>HAND2-AS1</i> [123]	data not found
33.	LINE1	miR-3144/ cancer [16]	<i>ERBB4</i> [16]	data not found
34.	LTR-ERV1	miR-3200/ blood serum [124]	<i>ZRANB2</i> , <i>INSYN2</i> , <i>FBN1</i> , <i>ANKRD10</i> , <i>AFTPH</i> , <i>REM2</i> , <i>PURA</i> , <i>CARF</i> (miRDB)	data not found
35.	SINE-MIR	miR-3617-3p/ cancer [125]	<i>PPP2R2D</i> , <i>BMPR2</i> , <i>TET3</i> , <i>DAZI</i> , <i>LPGAT1</i> , <i>NEXMIF</i> (miRDB)	data not found
36.	Alu	miR-3908/ cancer [126]	<i>AdipoR1</i> [126]	data not found
37.	SINE-MIR	miR-4425/ cancer [41]	<i>PLEKHS1</i> , <i>PEG3</i> , <i>VW45A</i> , <i>PDZD2</i> , <i>SNX19</i> , <i>MEX3C</i> , <i>RRM2B</i> (miRDB) / <i>STXBP5-AS1</i> [41]	data not found
38.	LINE2	miR-4433b-5p/ extracellular vesicles [127]	<i>CAMKK2</i> , <i>ABHD13</i> , <i>SOX6</i> , <i>DDX20</i> , <i>STK32A</i> , <i>NAT8L</i> , <i>CNTN1</i> (miRDB)	data not found
39.	LTR-ERV1	miR-4448/ breast cancer cell lines [128]	<i>PAN3</i> , <i>ARID2</i> , <i>BPTF</i> , <i>CHD2</i> , <i>SOX7</i> , <i>ZNFY1</i> (miRDB)	data not found
40.	SINE-MIR	miR-5003-3p/ cancer [129]	<i>CDH11</i> [129]	data not found
41.	ERV1	miR-5694/ cancer [130]	<i>AF9</i> [130]	data not found
42.	LINE1	miR-5698/ blood plasma [131]	<i>MECP2</i> , <i>PPP1R9B</i> , <i>NFIX</i> , <i>WIZ</i> , <i>SLC6A17</i> , <i>CASTOR2</i> , <i>NR1D1</i> , <i>SRF</i> (miRDB)	data not found
43.	LINE1	miR-8084/ blood plasma, cancer [132]	<i>ING2</i> [132]	data not found

nogenesis not only by stimulating genomic instability, but also by forming microRNAs with oncogenic properties from the transcripts of these activated REs. 8 microRNAs (miR-151a-5p, miR-325-3p, miR-342-5p, miR-378a-3p, miR-378a-5p, miR-582-5p, miR-1246, miR-1269a) derived from REs (3 microRNAs derived from LINEs, 3 miRNAs from SINEs, 2 miRNAs from LTR-REs) are characterized by increased expression in breast cancer, but decreased expression in aging. This suggests that not only aging is an inducer of altered REs expression leading to breast cancer development, but also many other causes, including changes in epigenetic factors. This is also evidenced by the increase in the levels of 26 other REs-derived microRNAs for which changes in expression with aging have not been described in the scientific literature.

Increased miR-95-3p expression in TNBC tissues is associated with worse patient survival [108]. The target of miR-95-3p in these mechanisms is the mRNA of the *AKAP12* gene (the protein product of the gene enhances proliferation, migration and invasion of breast cancer cells). The levels of miR-95-3p-interacting circular RNA circ_0001777 are reduced in TNBC tissues. It is suggested that this circular RNA be used in targeted therapy of TNBC [109]. In breast cancer, the most pronounced increase in expression is determined for miR-151a-3p [110]. Among circulating microRNAs in patients with breast cancer, elevated levels of miR-151a-5p were identified, which decreased after surgical treatment of breast cancer [94]. Significantly Increased Levels of miR-325-3p Targeting S100A2 mRNA are detected in breast cancer tissues and cell lines [96]. MiR-342-5p is a potential regulator of *HER2* (human epidermal growth factor 2) in breast cancer [98]. Exosomal miR-378a-3p and miR-378d contribute to the development of breast cancer and chemoresistance by activating EZH2/STAT3 signaling [77]. MiR-378a-5p is the target of GAS5 lncRNA, which promotes breast cancer apoptosis. The target of miR-378a-5p is the mRNA of the *SUFU* gene [101]. MiR-378e expression is associated with worse survival in breast cancer patients treated with palbociclib. It is suggested that miR-378e contributes to resistance to this drug in breast cancer cells [111].

Rhythmic changes in miR-548ay-3p expression in breast cancer cell lines were identified [112]. Oncogenic miR-552-5p targeting WIF1 (Wnt inhibitory factor-1) is a target of lncRNA SLC16A1-AS1, the overexpression of which suppresses breast cancer growth and metastasis [79]. Increased expression of miR-558 was detected in TNBC tissues [81]. MiR-576-5p, which is a target of the tumor suppressor LINC-PINT, inhibits MEIS2 (Meis homeobox 2), which suppresses PPP3CC (protein phosphatase 3 catalytic subunit gamma) by inactivating nuclear factor κ B (NF- κ B) [83]. MiR-582-5p promotes TNBC metastasis and invasion by inhibiting CMTM8 (chemokine-like factor) [103]. MiR-616-3p promotes breast cancer metastasis by inhibiting the *TIMP2* gene (encodes a family of inhibitors of matrix metalloproteinases) with regulation of MMP (matrix metalloproteinase) signaling [113]. Increased levels of miR-887-3p targeting *BTBD7* were detected in breast cancer cells and extracellular vesicles. At the same

time, increased expression of *BTBD7* abolished chemoresistance of breast cancer cells [114].

MiR-1202 levels are elevated in the serum of breast cancer patients [115]. Tamoxifen-resistant LCC9 breast cancer cells express elevated levels of HNRNPA2/B1 (heterogeneous nuclear ribonucleoprotein A2/B1), which is a reader of the N(6)-methyladenosine tag in primary microRNAs (pri-miRNAs), promoting the processing of DROSHA into microRNA precursors (pre-miRNAs). In these mechanisms, HNRNPA2/B2 upregulates miR-1268a expression [116]. MiR-1269a, targeting CREBZF (negative-regulatory transcription factor) mRNA, is a target of tumor suppressor circPAPD4 in breast cancer [106]. Oncogenic miR-1269b is a target of lncRNA BRCAT54 (breast cancer-associated transcript 54), which suppresses breast cancer development [117]. A study of TNBC tissues showed increased expression of miR-1272-3p, involved in the regulation of thyroid hormone signaling pathways. Elevated miR-1272-3p levels are associated with TNBC recurrence [85]. MiR-1285-3p, a target of circ_0000376, promotes breast cancer carcinogenesis via inhibition of *TP53*, *BTRC*, *SMURF1* genes [118].

It was found that exosomal miR-1304-3p promotes the development of breast cancer by activating breast cancer-associated adipocytes [119]. MiR-1587, an inhibitor of *IRF7* gene mRNA (encoding interferon regulatory factor 7), promotes breast cancer development by regulating M2 macrophage activity [120]. Serum miR-1825 levels in breast cancer patients before surgery are significantly higher compared to healthy controls and patients after mastectomy [121]. MiR-2909 is involved in breast cancer development by inhibiting the *RAD50* (involved in the repair of double-strand DNA breaks) and *MRE11* (required for homologous recombination and DNA repair) genes [122]. MiR-3118, an inhibitor of *PHLPP2* (serine-threonine phosphatase), is a target of lncRNA HAND2-AS1, which suppresses breast cancer cell proliferation and migration [123]. Apocrine cell morphology of TNBC is characterized by increased expression of miR-3135b, which is involved in the regulation of Wnt signaling, MAPK, endocytosis, and ErbB signaling genes [87]. MiR-3200 levels elevated in breast cancer were found to be reduced by neoadjuvant chemotherapy [124].

Increased expression of miR-3617-3p was detected in breast cancer cells resistant to antitumor therapy [125]. MiR-3908 is a key mediator of breast cancer cell migration, enhancing their clonogenic process. The direct target of miR-3908 is AdipoR1, through the suppression of which SIRT-1, p-AMPK and AMPK are inhibited [126]. Oncogenic miR-4425 is a target of lncRNA STXBP5-AS1 in breast cancer carcinogenesis [41]. MiR-4428 expression is associated with breast cancer metastases in the brain [89]. The levels of miR-4433b-5p in extracellular vesicles of breast cancer samples are higher than in the normal control [127]. The association of increased miR-4448 expression with the development of breast cancer chemoresistance has been determined [128]. The association of elevated levels of miR-4480 with breast cancer metastases was revealed [89]. MiR-5003-3p has been identified to

promote epithelial-mesenchymal breast cancer transition by directly inhibiting the *CDH1* (E-cadherin) gene [129]. A significant increase in miR-5100 was detected in breast cancer tissues compared to normal samples [92]. MiR-5694, targeting the mRNA of the AF9 protein (metastasis suppressor), promotes the progression and metastasis of basal-like breast cancer [130]. Increased expression of miR-5698 in patients' serum is associated with worse survival in breast cancer [131]. In the blood plasma and tumor tissues of breast cancer patients, a significant increase in miR-8084 levels was determined, which promotes the proliferation of breast cancer cells by activating AKT and ERK1/2, and also inhibits apoptosis by suppressing p53-BAX-related signaling pathways. The target of miR-8084 is also the tumor suppressor gene *ING2* [132].

It should be noted that among the listed 43 oncogenic microRNAs derived from REs and involved in breast cancer carcinogenesis, for 17 microRNAs (Table 1), a decrease in expression was noted for 7 microRNAs (miR-151a-3p, miR-325-3p, miR-342-5p, miR-378a-3p, miR-378a-5p, miR-582-5p, miR-1246, miR-1269a), which is logical, since with age the proliferative potential of cells decreases with a decrease in the activity of oncogenic molecules. Accordingly, data for BC with aging are characterized by abnormal activation unrelated to aging mechanisms, but associated with the functioning of the REs from which they originated. In particular, miR-151a-5p levels are reduced in serum during physiological aging [95], while in breast cancer the levels of the same microRNA in the blood are increased [94]. Mechanical overload downregulates miR-325-3p expression in chondrocytes, promoting their aging and worsening lumbar facet joint degeneration via *Trp53* inhibition [97]. SIRT6 (Sirtuin 6) is a deacetylase that affects the structure of chromatin and slows down the aging of the human body. A study of young, middle-aged and old people did not show age-related differences in methylation of SIRT6 CpG islands. However, in long-lived people, a significant decrease in the expression of miR-342-5p in peripheral mononuclear cells was determined [99]. Experiments have shown that decreased expression of miR-378a-3p promotes thymus involution and aging [100]. MiR-378a-5p is a negative regulator of aging [102]. With aging, the ability of neural stem cells to proliferate decreases due to epigenetic mechanisms, including disruption of microRNA expression. It has been shown that miR-582-5p in these mechanisms helps maintain the proliferation of neural stem cells, preventing brain aging by inhibiting the secretory protein FAM19A1 [104]. Exosomes overexpressing miR-1246 from adipose-derived stem cells exhibit photoprotective effects against UV-induced photoaging. miR-1246 targets *GSK3β* gene mRNA. Accordingly, decreased expression of this microRNA contributes to aging [105]. MiR-1269a expression was found to be higher in the ovaries of young women compared to older women [107]. It can be speculated that during aging, increased expression of REs contributes to the decrease in the levels of these microRNAs due to complementary binding of their sequences as "sponges". However, oncogenes can induce senescence in response to

hyperactive oncogenic signals, since this develops protection against tumor development. Experiments on human diploid fibroblasts have shown that activated miR-378a-5p promotes the preservation of their proliferative capacity even in the presence of the Braf oncogene, delaying oncogene-induced senescence. This microRNA reduces the expression of senescence-associated β-galactosidase and p16^{INK4A} [102]. This example demonstrates the risks of using new methods to combat aging, since the side effects of using specific microRNAs that can slow down aging include mechanisms to stimulate the development of tumors, such as breast cancer. This demonstrates the subtle mechanisms of epigenetic regulation of carcinogenesis and aging, which are only partially related. And when using microRNAs as objects or tools for rejuvenation of the human body, it is first necessary to assess the risks of cancer development.

At the same time, with aging, an increase in the expression of 9 microRNAs (miR-378d, miR-552-5p, miR-558, miR-576-5p, miR-1272-3p, miR-3135b, miR-4428, miR-4480, miR-5100) was determined, the expression of which is increased in breast cancer, which indicates that epigenetic mechanisms of aging can contribute to carcinogenesis, in particular the development of breast cancer. A possible reason is the hyperactivation of REs, since microRNAs can be transcribed not only from their own genes, but also directly from REs transcripts [15]. For example, in colon tissues, increased expression of miR-378d has been identified with aging [78]. In skin aging, elevated calcium concentration in the basal layer reduces cell proliferation with increased expression of miR-552-5p. Under the influence of lncRNA SPRR2C, which binds complementarily to this microRNA, this aging effect is suppressed [80]. Increased expression of miR-558 is detected in aging mesenchymal stem cells [82]. Elevated plasma miR-576-5p levels detected in frail elderly compared to young adults [84]. Increased miR-1272-3p levels in the cerebral cortex have been identified during physiological aging in humans [86]. About 80% of differentially expressed genes in the hippocampus are regulated by miR-192-5p and miR-3135b, which are elevated in older adults. However, miR-3135b expression in the hippocampus was reduced in centenarians, suggesting that miR-3135b contributes to accelerated aging [88]. In saliva exosomes of elderly people, significantly more pronounced (2-fold) expression of miR-4428 was determined compared to young people [90]. An example of the influence of SNP on the characteristics of human aging is rs7747909 in the 3'-UTR of the *IL-17A* gene, which affects the binding of miR-4480 to it, predisposing to the development of retinal degeneration with aging [91]. Increased expression of miR-5100-3p detected in brain microglia during aging [93].

Association of retroelement-derived tumor suppressor microRNAs involved in breast cancer carcinogenesis with aging

In the development of breast cancer, a decrease in the

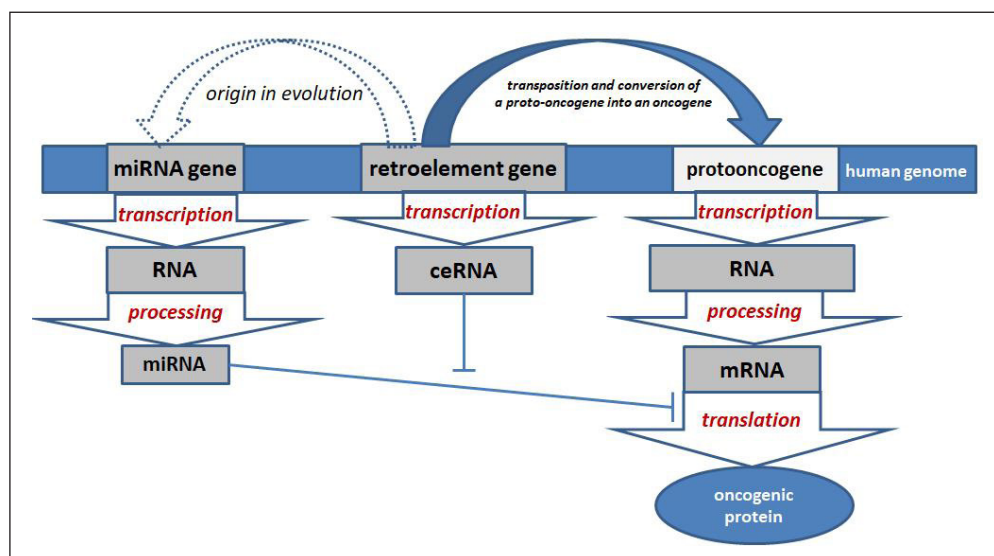


Figure 5. Scheme of interaction of retroelements with tumor suppressor microRNAs in breast cancer carcinogenesis.

expression of a number of microRNAs has been noted, which have tumor suppressor properties, since they inhibit oncogene miRNA. Accordingly, such microRNAs can serve as tools for targeted therapy of breast cancer. Analysis of the MDTE database [15] revealed 43 REs-derived miRNAs that are downregulated in breast cancer. This indicates unique epigenetic mechanisms of carcinogenesis, when REs activation promotes breast cancer development, while REs-derived microRNAs have tumor suppressor properties. It can be assumed that one of the mechanisms of antitumor action of such microRNAs, in addition to inhibition of oncogenes, is competitive binding to REs transcripts, leveling their initiating effect on carcinogenesis (due to promoting genomic instability, inactivation of tumor suppressors and activation of oncogenes). Since REs were the sources of miRNAs in evolution, this suggests that they interact complementarily. Accordingly, REs transcripts may act as competing endogenous RNAs (ceRNAs) [133], negating the tumor suppressor effect of miRNAs. Accordingly, this is another mechanism of the activating effect of REs on oncogenes in breast cancer carcinogenesis. Thus, REs-derived microRNAs that function as tumor suppressors can be used as tools whose effect will consist not only in post-transcriptional inactivation of oncogenes, but also due to complementary interaction with REs transcripts. As a result of the introduction of high concentrations of such microRNAs, it is possible not only to eliminate the activating effect of REs transcripts on oncogenes (functioning as ceRNAs), but also to inhibit REs themselves post-transcriptionally. Accordingly, knowledge of specific REs-derived microRNAs that have an oncosuppressive effect affects the development of breast cancer in several ways (Figure 5).

Changes in microRNA levels in breast cancer are determined both in peripheral blood and in tumor tissues. In this case, interactions of microRNA with other ncRNAs, such as lncRNAs and circRNAs, are determined. For example, miR-28-3p levels in the blood plasma of breast cancer patients are reduced compared to healthy women [134]. Breast cancer tumor suppressor miR-1249-3p

targeting *HOXB8* gene mRNA is a target of MIF-AS1 lncRNA that promotes breast cancer proliferation, migration, and epithelial-mesenchymal transition [135]. MiR-28-5p, which inhibits breast cancer cell migration by regulating *WSB2* (WD repeat and SOCS box containing 2) [136], *CENPF* (centromere-kinetochore complex-associated protein) [137], and *LDHA* (lactate dehydrogenase A) [138] genes, is a target of lncRNA MCM3AP-AS1, which promotes breast cancer progression [137] and circ-CSNK1G (involved in TNBC migration, invasion, and proliferation) [138].

MiR-130a-3p exhibits tumor suppressor properties by blocking the Wnt signaling cascade in TNBC by inhibiting *ID4* gene mRNA [139]. In TNBC, low levels of miR-181c-5p are detected, which inhibits the mRNA of *MAP4K4* protein (oncogenic serine-threonine protein kinase) [140]. MiR-330-5p, which targets mRNA of *ELK1* gene, is a target of circRNA_000166, which promotes breast cancer progression [141]. MiR-342-3p functions as a tumor suppressor, inhibiting metastasis of chemoresistant breast cancer cells by targeting *ID4* mRNA (inhibits DNA-binding protein family) [142]. MiR-345-5p is a target of lncRNA *RacGAP1P* (a pseudogene of *RacGAP1* (Ras GTPase-activating protein 1)), which promotes metastasis and invasion of breast cancer. Interestingly, miR-345-5p is a target of mRNA of the *RacGAP1* gene, the pseudogene of which is lncRNA that inhibits this microRNA [143].

MiR-374c-5p inhibits BC development by binding to the TATA box of the *TAF7* gene [144]. MiR-422a exhibits tumor suppressor properties by inhibiting mRNA of *PLP2* gene (encodes an integral membrane protein of the endoplasmic reticulum), preventing the formation of breast cancer microspheres and tumor cell proliferation [145]. MiR-493-5p functions as a suppressor of breast cancer cell growth and invasiveness by targeting *FUT4* gene by binding to the 3'UTR of its mRNA [146]. MiR-576-3p, a target of oncogenic circ0012673, inhibits *SOX4* (SRF-box transcription factor 4), thereby suppressing breast cancer cell proliferation, migration, and invasion [147]. MiR-

578, a target of oncogenic circ_0008673, inhibits GINS4 (a protein that plays a role in the initiation of DNA replication) [148]. MiR-582-3p is a negative regulator of *SFXN1* gene mRNA (encodes sideroflexin, a mitochondrial membrane protein), the expression of which is associated with poor prognosis in patients with breast cancer [149]. Expression of tumor suppressor miR-588 is reduced in breast cancer tissues, so the use of miR-588 loaded into exosomes by electroporation, which has shown its effectiveness, can be used in targeted therapy of breast cancer [150].

MiR-606 suppresses the development and metastasis of TNBC by affecting the *STC1* gene (encodes the glycoprotein Stanniocalcin 1, which has autocrine and paracrine functions). Transfection of miR-606 TNBC suppresses the proliferation, migration and invasion of tumor cells, inducing their apoptosis. Therefore, this method is promising for targeted therapy of TNBC [151]. MiR-607 suppresses the development of breast cancer by interacting with the mRNA of *EGFR* gene [152]. MiR-612 inhibits myosin-2 phosphorylation and breast cancer cell invasion [153]. MiR-625, which is the target of oncogenic breast cancer circSEPT9, is expressed at low levels in breast cancer tissues and in breast cancer cells. The target of miR-625 in the mechanisms of oncosuppressive action is PTBP3 (Polypyrimidine Tract Binding Protein 3), a regulator of cell differentiation [154]. MiR-634 expression is significantly reduced in breast cancer tissue and cells compared to normal tissues. At the same time, ectopic expression of miR-634 inhibits the proliferation and metastasis of breast cancer. The direct target of miR-634 is the mRNA of *FOXA1* gene (encodes a DNA-binding protein) [155]. MiR-640 is a breast cancer suppressor by regulating Wnt7b/beta catenin signaling pathways [156]. MiR-646 prevents the proliferation and progression of breast cancer by inhibiting *HDAC2* (histone deacetylase) [157]. MiR-708-3p suppresses breast cancer metastases and chemoresistance by inhibiting the epithelial-mesenchymal transition [158]. MiR-708-5p is a target of lncRNA LOXL1-AS1, which is a driver of breast cancer cell metastasis and invasion [159]. MiR-885-3p inhibits the PIK3/AKT pathways and NTRK2 expression, being a target of circ_0006014, which stimulates the progression of breast cancer [160]. MiR-921, which expression is reduced in breast cancer, inhibits the *ADAM9* gene mRNA, and is a target for circNINL [161].

MiR-1183 is the target of circ_0000851, which promotes proliferation and migration of breast cancer cells. MiR-1183 inhibits *PDK1* gene mRNA (encodes pyruvate dehydrogenase kinase) [162]. MiR-1267 exhibits suppressive properties in relation to the initiation and progression of breast cancer [163]. MiR-1268b expression is reduced in the tissues of chemoresistant breast cancer compared to chemosensitive tissues [164]. MiR-1271-5p suppresses the proliferation and progression of breast cancer by inhibiting *SPIN1* gene (encodes spindylin-1, involved in the activation of Wnt pathways) [165]. MiR-1271-5p targets the chromatin of *DDIT3* gene (DNA damage-inducible transcript 3). Due to this, repeated administration of miR-

1271 effectively restores the expression levels of alpha exogenous receptors, thereby enhancing the sensitivity of breast cancer cells to letrozole. This is an example of the possibility of effectively using microRNAs to eliminate breast cancer resistance to chemotherapy [166].

The worst prognosis of breast cancer in women is associated with low expression of miR-1285-5p, which is significantly lower in all women in breast cancer samples compared with healthy tissues. At the same time, oncosuppressive miR-1285-5p inhibits the proliferation of breast cancer cells regardless of the tumor subtype. *TMEM194* (encodes the transmembrane protein 194A) plays an important role among the target genes of this microRNA [167]. MiR-1294 suppresses the development of breast cancer by regulating ERK signaling [168]. MiR-1303 inhibits the *PTBP3* gene, a protein product of which stimulates the development of breast cancer. Accordingly, lncRNA BCRT1, which binds complementarily to miR-1303, is oncogenic for breast cancer [169]. Oncosuppressive miR-1972 can be used for effective targeted breast cancer therapy, since the introduction of miR-1972 mimics inhibits genes involved in angiogenesis and metastasis (*SHC1*, *NEK1*, *MMP9*, *MAP2K1*), suppressing the proliferation of breast cancer cells [170]. MiR-2355-5p is a target of lncRNA SNHG11, which promotes proliferation and migration of breast cancer cells. MiR-2355-5p targets the mRNA of the *CBX5* gene (encodes a non-histone protein, a member of the heterochromatin protein complex) [171].

Reduced levels of miR-3139, which is a target for LINC00514, were detected in breast cancer tissues (this lncRNA promotes proliferation, migration, and invasion of breast cancer by suppressing apoptosis) [172]. MiR-3163 expression, which functions as a tumor suppressor, is reduced in breast cancer tissues compared to normal tissue [173]. MiR-3194-3p inhibits the progression of breast cancer by interacting with the mRNA of the *AQP1* gene (encodes aquaporin 1) [174]. Significant increase in the expression of miR-3674, which targets mRNA of *ATF3* (encodes transcription factor) gene, was detected in breast cancer cells [175]. The association of low miR-3923 expression with lymph node metastases in patients with breast cancer has been determined [176]. Oncogenic miR-4472, whose expression is significantly increased in breast cancer metastatic tissues, promotes breast cancer proliferation and aggressiveness by targeting *RGMA* (encodes Repulsive guidance molecule A, cancer metastasis suppressor) and inducing the epithelial-mesenchymal transition by suppressing E-cadherin with the initiation of vimentin, Slug and beta-catenin [177]. Breast cancer is characterized by decreased expression of oncosuppressive miR-5586-5p, which inhibits angiogenesis by suppressing *VEGFA* (encodes vascular endothelial growth factor A), *ANGPTL4* (encodes angiopoietin-like protein 4), *HBEGF* (encodes heparin-binding EGF-like factor) genes [178]. MiR-7978, which is the target of oncogenic BC circHS-DL2, inhibits *ZNF704*, thus regulating Hippo pathways [179].

Among the 43 microRNAs that originated from REs,

Table 2. Retroelement-derived microRNAs which expression is decreased in breast cancer and altered with aging.

RE-source of microRNA	microRNA/ tissue	miRNA target genes/interaction with other ncRNAs	changes with aging (tissue)
1. LINE2	miR-28-5p/ blood plasma [136-138]	<i>WSB2</i> [136], <i>CENPF</i> [137], <i>LDHA</i> / lncRNA MCM3AP-AS1 [137], circ-CSNK1G [138]	decreased (human blood plasma) [186]
2. LINE-RTE-BovB	miR-181c-5p/ cancer [140]	<i>MAP4K4</i> [140]	decreased (human blood plasma) [187]
3. LINE1	miR-588/ cancer [150]	<i>SPTLC2</i> , <i>RHBDP1</i> , <i>MGAT1</i> , <i>PRKARIA</i> , <i>COL4A4</i> , <i>TUSC1</i> , <i>RIMS1</i> (miRDB)	decreased (skin tissue) [189]
4. SINE-MIR	miR-612/ cancer [153]	<i>AHL</i> , <i>BTRC</i> , <i>DAB2IP</i> , <i>FMO5</i> , <i>SIKE1</i> , <i>SAR1A</i> , <i>SEC63</i> (miRDB)	decreased (human skin) [189]
5. LINE2	miR-708-5p/ cancer [159]	<i>TNS3</i> , <i>FOXJ3</i> , <i>IKBKB</i> , <i>ASPA</i> , <i>BCAM</i> , <i>NPY2R</i> , <i>ARL17A</i> , <i>CNTFR</i> (miRDB) / lncRNA LOXL1-AS1 [159]	decreased (human skin) [190]
6. LINE2	miR-1249-3p/ cancer [135]	<i>HOXB8</i> [135]	decreased (ovaries) [188]
7. LINE2	miR-1271-5p/ cancer [165, 166]	<i>DDIT3</i> [166], <i>SPIN1</i> [165]	decreased (human mesenchymal stromal cells) [191]
8. SINE-Alu	miR-1972/ cancer [170]	<i>SHC1</i> , <i>NEK1</i> , <i>MMP9</i> , <i>MAP2K1</i> [170], <i>BAIAP3</i> [192]	decreased (brain) [192]
9. LINE2	miR-28-3p/ blood plasma [134]	<i>FRMD7</i> , <i>VIM</i> , <i>RSBNIL</i> , <i>C5</i> , <i>MBL2</i> , <i>RAD51B</i> , <i>UNKL</i> , <i>IKZF5</i> (miRDB)	increased (human endothelial cell culture) [180]
10. SINE-MIR	miR-330-5p/ cancer [141]	<i>ELK1</i> / circRNA_000166 [141]	increased (bone marrow mesenchymal stem cells) [181]
11. LINE2	miR-493-5p/ cancer [146]	<i>FUT4</i> [146], <i>WNT5A</i> , <i>SOX1</i> [182]	increased (human bone marrow stromal cells) [182]
12. LINE-CRI	miR-582-3p/ cancer [149]	<i>SFXN1</i> [149]	increased (liver tissue) [184]
13. LINE-RTE-BovB	miR-2355-5p/ cancer [171]	<i>ERRF1</i> [185], <i>CBX5</i> / lncRNA SNHG11 [171]	increased (cartilage tissue) [185]
14. LINE-RTE-BovB	miR-130a-3p/ cancer [139]	<i>ID4</i> [139]	data not found
15. SINE-rRNA-RTE	miR-342-3p/ cancer [142]	<i>ID4</i> [142]	data not found
16. SINE-MIR	miR-345-5p/ cancer, breast cancer cell line [143]	<i>RacGAP1</i> / lncRNA RacGAP1P [143]	data not found
17. LINE2	miR-374c-5p/ cancer [144]	<i>TAF7</i> [144]	data not found
18. SINE-MIR	miR-422a/ cancer, breast cancer cell line [145]	<i>PLP2</i> [145]	data not found
19. LINE1	miR-576-3p/ cancer [147]	<i>SOX4</i> / circ0012673 [147]	data not found
20. LINE2	miR-578/ cancer [148]	<i>GINS4</i> / circ_0008673 [148]	data not found
21. LINE1	miR-606/ cancer [151]	<i>STC1</i> [151]	data not found

Table 2 continued.

RE-source of microRNA	microRNA/ tissue	miRNA target genes/interaction with other ncRNAs	changes with aging (tissue)
22. SINE-MIR	miR-607/ cancer [152]	<i>EGFR</i> [152]	data not found
23. LINE1	miR-625-5p/ cancer [154]	<i>PTBP3/ circSEPT9</i> [154]	data not found
24. LINE1	miR-634/ cancer [155]	<i>FOXAI</i> [155]	data not found
25. SINE-MIR	miR-640/ cancer [156]	<i>Wnt7b</i> [156]	data not found
26. ERVL	miR-646/ cancer [157]	<i>HDAC2</i> [157]	data not found
27. LINE2	miR-708-3p/ cancer, breast cancer cell line [158]	<i>SCAMPI, JARID2, TRAF3, VIM, BAZ1B, SPRED1, HSPA4L</i> (miRDB)	data not found
28. SINE-MIR	miR-885-3p/ cancer [160]	<i>NTRK2/ circ_0006014</i> [160]	data not found
29. SINE-MIR	miR-921/ cancer [161]	<i>ADAM9/ circNINL</i> [161]	data not found
30. LINE2	miR-1183/ cancer [162]	<i>PDK1/ circ_0000851</i> [162]	data not found
31. ERVL-MaLR	miR-1267/ cancer [163]	<i>SALL1, SMIM8, MAN2A1, RUFY2, SHROOM2, BBS10, DDI2</i> (miRDB)	data not found
32. Alu	miR-1268b/ cancer [164]	<i>STXBP1, EEPDI, EGR4, CMIP FCAR, HPD, USB1, SLC8A2</i> (miRDB)	data not found
33. Alu	miR-1285-5p/ cancer [167]	<i>TMEM194</i> [167]	data not found
34. SINE-MIR	miR-1294/ cancer [168]	<i>PAPP4, INPP5A, CD164, MYCL, SKIL, CDC34, THRSF, HAS2</i> (miRDB)	data not found
35. Alu	miR-1303/ cancer [169]	<i>PTBP3/ lncRNA BCRT1</i> [169]	data not found
36. LINE2	miR-3139/ cancer [172]	<i>TNS3, IKBKB, FOXJ3, ARL17A, RPTN</i> (miRDB) LINC00514 [172]	data not found
37. SINE	miR-3163/ cancer [173]	<i>SMC3, AHCTF1, HCN1, ME14, PDK3, ZC3H6, TMX3, HIPK3, SAMD8</i> (miRDB)	data not found
38. SINE-MIR	miR-3193-3p/ cancer [175]	<i>AQP1</i> [174]	data not found
39. LTR-ERV1	miR-3674/ cancer, breast cancer cells [175]	<i>ATF3</i> [175]	data not found
40. ERVL-MaLR	miR-3923/ cancer [176]	<i>MSR1, HDX, ST8SIA1, CPED1</i> (miRDB)	data not found
41. Alu	miR-4472/ cancer [177]	<i>RGMA, CDH1</i> [177]	data not found
42. LINE1	miR-5586-5p/ breast cancer cells [178]	<i>ANGPTL4, VEGFA, HBEGF</i> [178]	data not found
43. LINE1	miR-7978/ cancer [179]	<i>ZNF704/ circHSDL2</i> [179]	data not found

the expression of which is reduced during breast cancer, 13 microRNAs have a change in expression with aging. At the same time, 5 microRNAs (miR-28-3p, miR-330-5p, miR-493-5p, miR-582-3p, miR-2355-5p) showed increased levels in various tissues during aging. This indicates that not all epigenetic mechanisms of aging involving oncosuppressive microRNAs derived from REs play a role in the initiation and development of breast cancer. This circumstance is logical, since not all women develop breast cancer with age. Changes in the expression of such microRNAs have been detected in various organs and tissues. For example, during early replicative senescence of endothelial cells, a significant increase in miR-28-3p expression was detected [180]. An increase in the expression of miR-330-5p was detected during aging of bone marrow mesenchymal stem cells [181]. Accumulation of kynurenine, a metabolite of tryptophan, plays a role in age-related pathophysiological changes, including bone loss. As a result of this accumulation, proliferation and differentiation of bone marrow stromal cells decrease. In experiments on human bone marrow stromal cells treated with kynurenine, miR-493-5p expression increased [182]. A decrease in miR-493-5p expression was also detected in senescent pig skeletal muscle cells [183]. Increased levels of miR-582-3p in liver tissue during aging have been determined [184]. Increased levels of miR-2355-5p have been determined by inhibiting *ERRFII* during aging and intervertebral disc degeneration [185].

For 8 microRNAs derived from REs, the expression of which is reduced during breast cancer, a decrease in levels during aging is also determined: miR-28-5p, miR-181c-5p, miR-588, miR-612, miR-708-5p, miR-1249-3p, miR-1271-5p, miR-1972. This indicates that the epigenetic mechanisms of aging are important in the development of breast cancer. A decrease in the expression of miR-28-5p in human blood plasma during physiological aging was revealed [186]. In blood plasma, a decrease in miR-181c-5p expression with age correlates with the accumulation of amyloid beta [187]. An increase in the expression of miR-1249-3p in the ovaries during aging has been determined [188]. Increased expression of circRNAs was detected in aging skin samples: circRNA-0088179, -0132428, -0094423, -0008166, -0138184, -0135743, -0114119, -0131421, the targets of which are miR-588 and miR-612. Accordingly, the levels of these microRNAs decrease with skin aging [189]. During aging, a decrease in miR-708-5p expression is detected in various tissues and cells. MiR-708-5p directly inhibits the mRNA of the *Dab2* gene, as a result of which the activation of mTORC1 is suppressed. In addition, activation of AMP-activating protein kinase stimulates miR-708-5p by increasing DICER expression [190]. In human mesenchymal stromal cells, a decrease in miR-1271-5p levels was detected during their aging [191]. In elderly people with physiological aging, leukoarrhoea of the brain is observed in the form of hyperintensity, in which there is a decrease in the expression of miR-1972, the target of which is the mRNA of *BALIP3* gene [192]. Table 2 shows oncosuppressive microRNAs derived from retroelements and changes in their activity during aging.

The use of the above-mentioned oncosuppressive microRNAs as tools will not only suppress the functions of oncogenes, but also competitively inhibit REs transcripts, which is associated with the complementarity of the sequences of such microRNAs with the REs from which they originated. Taking into account the role of such microRNAs in aging, a differentiated approach to the methods of administration is possible, since it is most advisable for microRNAs that promote aging to be injected directly into the tumor tissue.

Summarizing the overall trends in Table 2, it can be seen that among the 43 REs-derived miRNAs whose levels are reduced in BC, 8 miRNAs (of which 6 miRNAs are LINE-derived and 2 miRNAs are SINE-derived) also show a decrease in expression with aging. This may indicate that the downregulation of retroelement-derived tumor suppressor miRNAs during aging is a trigger for the development and progression of breast cancer. REs (from which such tumor suppressor miRNAs originate) activated in such pathways contribute to the downregulation of these miRNAs by complementary binding of their transcripts, acting as ceRNAs [133]. This may explain the decrease in expression of tumor suppressor microRNAs derived from REs due to activation of such REs. In addition, Table 2 presents 5 microRNAs derived from REs, the expression of which is decreased in breast cancer but increased in aging. This circumstance may be explained by the fact that not all molecular epigenetic mechanisms of aging contribute to breast cancer carcinogenesis, but many of them do (8 microRNAs are more than 5 microRNAs). In addition, for 30 microRNAs presented in Table 2, no evidence of involvement of these microRNAs in aging mechanisms was found in the scientific literature. All this suggests that breast cancer carcinogenesis is a complex multicomponent process in which aging and REs activation are some of the links in the development of pathology, but are not the only factors in breast cancer carcinogenesis. However, research in this area can become the basis for more effective therapy of the disease and for explaining individual components of breast cancer pathogenesis. The RE-derived tumor suppressor miRNAs described in Table 2 can be used as tools for specific inhibition of retroelements and oncogenes that are pathologically activated in breast cancer. Thus, the use of such miRNAs can have a dual-targeted antitumor effect in the treatment of breast cancer. An additional mechanism of action on activated REs in these processes may be the use of reverse transcriptase inhibitors [75, 76].

Conclusions

Analysis of scientific literature indicates the role of epigenetic mechanisms of aging in the development of breast cancer as a multifactorial disease. In these mechanisms, during aging, epigenetic derepression of retroelements occurs, the activation of which is a factor in carcinogenesis due to the inactivation of tumor suppressor genes, the induction of genomic instability and the activation of

oncogenes. Breast cancer-associated SNPs may influence changes in the functioning and activation of retroelements, potentiating age-associated breast cancer development. This may explain why not all women develop breast cancer with aging. In addition, breast cancer-associated SNPs may alter the nucleotide sequences of retroelements, disrupting their complementary interaction with microRNAs, since retroelement transcripts function as ceRNAs. Accordingly, changes in retroelement activity in breast cancer are reflected in the levels of microRNAs derived from them. Indeed, analysis of the MDTE database with scientific literature data on the effect of specific microRNAs on breast cancer development revealed a decrease in the expression of 43 microRNAs derived from retroelements and an increase in the levels of 43 microRNAs derived from retroelements in breast cancer. Moreover, 30 of these miRNAs are characterized by impaired expression with aging, which indicates epigenetic relationships at the level of complementary interactions of retroelements with miRNAs between aging and breast cancer development. The use of the obtained data in modern medicine for targeted therapy of breast cancer using the described microRNAs to modulate the activity of retroelements is promising. The use of retroelement-derived microRNAs described in the article is promising for targeted therapy of breast cancer in personalized medicine, since they can be used to influence specific molecular links in breast cancer carcinogenesis. Namely, onosuppressive microRNAs can be used as tools for suppressing the expression of REs (due to complementary interaction with their transcripts) and oncogenes. In these pathways, the use of such microRNAs as miR-28-5p, miR-181c-5p, miR-588, miR-612, miR-708-5p, miR-1249-3p, miR-1271-5p, miR-1972 can also slow down the aging process, since the levels of these microRNAs are reduced during aging. Oncogenic microRNAs derived from REs can be used as targets for their inhibition using antisense oligonucleotides. This method can also inhibit pathologically activated REs in the treatment of breast cancer through complementary nucleotide binding. Moreover, the use of antisense nucleotides against miR-378d, miR-552-5p, miR-558, miR-576-5p, miR-1272-3p, miR-3135b, miR-4428, miR-4480, miR-5100 can also have an anti-aging effect, since the expression of these microRNAs decreases with age.

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