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The Development of the Regulatory Net of microRNA–mRNA Interactions in General Biological Processes and Signaling Pathways in Breast Cancer

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INTRODUCTION & AIM

The biological heterogeneity of breast cancer (BC) complicates the choice of an effective treatment approach. Data on the participation of microRNAs in the regulation of mRNA targets and, through them, biological processes occurring during carcinogenesis and signaling cascades carried out in the tumor allow us to understand the molecular architecture of BC and identify key regulatory elements suitable as diagnostic and prognostic markers or targets for targeted therapy.

The aim of the study was to analyze the differential expression of microRNAs in paired samples of tumor and adjacent normal breast tissue and to assess their potential cooperative participation in common biological processes and signaling pathways.

METHOD

The clinical and morphological characteristics of the BC samples used in the work are presented in Table 1. MicroRNA expression was analyzed using the TaqMan MicroRNA Reverse Transcription Kit, TaqMan Fast Universal PCR MasterMix, and Taq Man MicroRNA Assays Kit (ThermoFisher Scientific). Differences between groups were assessed using the nonparametric Mann–Whitney U test. Spearman's correlation coefficient was calculated to identify co-expression. Functional annotation and enrichment analysis for Gene Ontology (GO) terms and KEGG signaling pathways were performed in the R environment (clusterProfiler, org.Hs.eg.db, enrichplot), (adj. p-value)<0.05 (according to Benjamini–Hochberg).

Table 1. Clinical and morphological characteristics of breast cancer samples.

Clinicopathological data		Number of samples N = 40
Histological type	Infiltrative ductal carcinoma	30
	Infiltrative lobular carcinoma	10
Stage	I	6
	II	23
	III	10
	IV	1
Primary tumor size, parameter T	T1	6
	T2	24
	T3	7
	T4	3
Metastasis to lymph nodes	N0	17
	N1-N3	23
Grade	G1	4
	G2	32
	G3	4

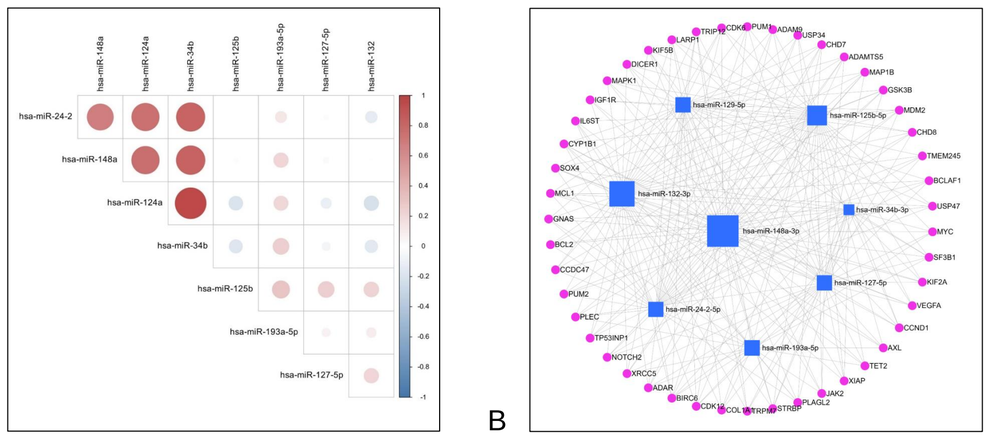

Fig. 1. **A**. Correlation matrix reflecting the degree of co-expression among microRNAs miR-125b-5p, miR-127-5p, miR-129-5p, miR-132-3p, miR-148a-3p, miR-193a-5p, miR-24-2-5p, miR-34b-3p in paired BC samples. **B**. Complete network of microRNA interactions of miR-125b-5p, miR-127-5p, miR-129-5p, miR-132-3p, miR-148a-3p, miR-193a-5p, miR-24-2-5p, miR-34b-3p with genes significant in oncogenesis.

RESULTS & DISCUSSION

A significant decrease in the expression level of microRNA miR-125b-5p, miR-127-5p, miR-129-5p, miR-132-3p, miR-148a-3p, miR-193a-5p, miR-24-2-5p, miR-34b-3p in tumor tissue compared to normal tissue was shown. Positive correlations in expression were found for 7 pairs of microRNAs: miR-127-5p/miR-125b-5p (Rs=0.47), miR-148a-3p/miR-125b-5p (Rs=0.44), miR-148a-3p/miR-132-3p (Rs=0.46), miR-193a-5p/miR-127-5p (Rs=0.51), miR-24-2-5p/miR-127-5p (Rs=0.43), miR-34b-3p/miR-193a-5p (Rs=0.54) and miR-34b-3p/miR-24-2-5p (Rs=0.58) (**Fig. 1A**). A network of interactions between the studied microRNAs and onco-significant genes was constructed (**Fig. 1B**). Enrichment analysis revealed coinciding processes for four pairs of microRNAs: miR-127-5p/miR-125b-5p (28 common processes), miR-148a-3p/miR-125b-5p (355 common processes), miR-148a-3p/miR-132-3p (195 common processes), and miR-34b-3p/miR-193a-5p (3 common processes). The most significant common biological processes are presented in **Fig. 2**.

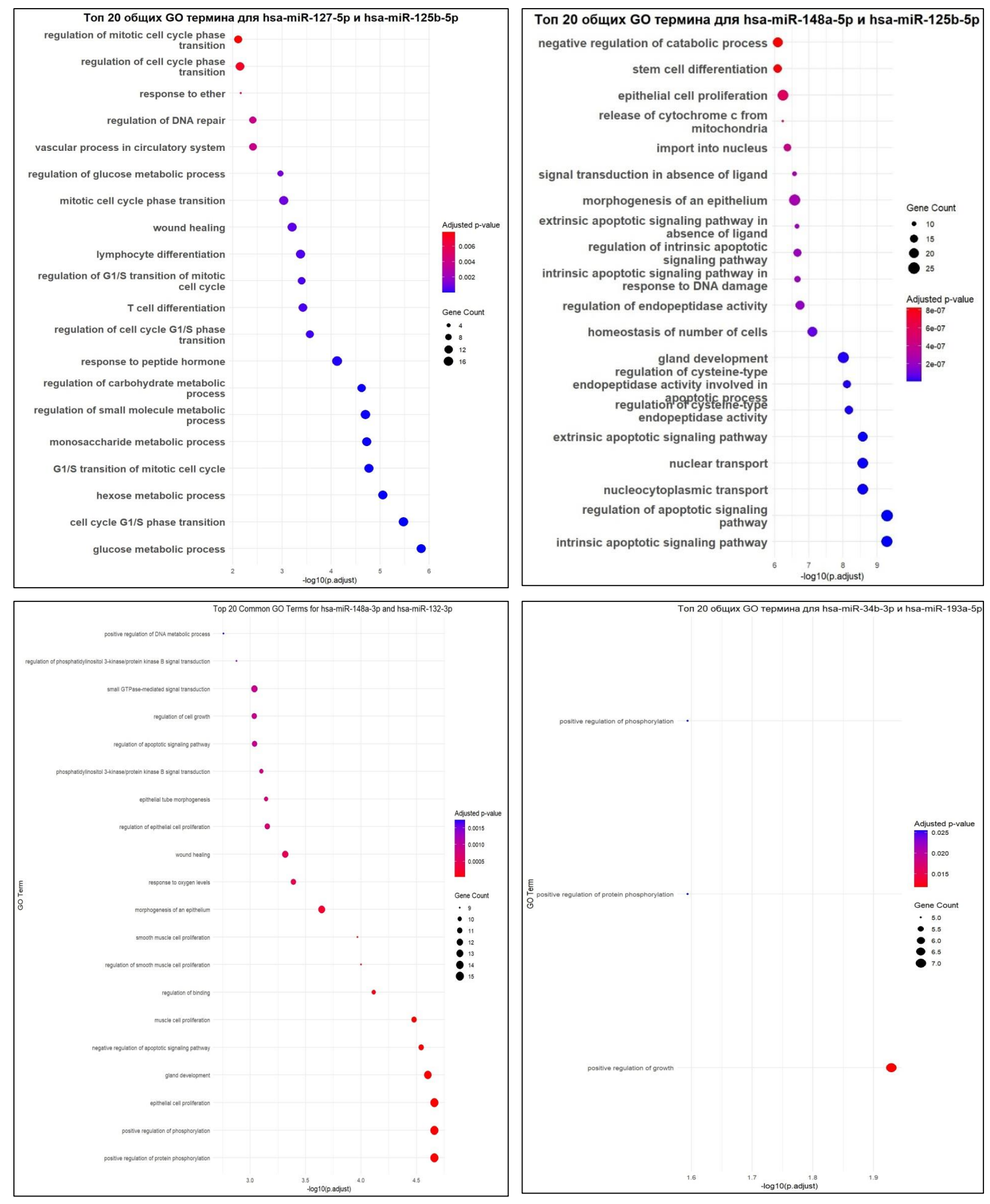

Fig. 2. Top 20 common signaling pathways in GO terms for the pairs miR-127/ miR-125b, miR-148a-3p/miR-125b-5p, miR-148a/miR-132, miR-34b/miR-193a.

CONCLUSION

To provide a comprehensive view of the obtained data, we constructed a regulatory network of miRNA–mRNA interactions with the inclusion of epigenetic regulators. The central node of the network is miR-125b-5p, which binds to multiple oncogenic and tumor suppressor genes, including APC, BCL2, STAT3, and LDLR, and is also potentially regulated by EZH2, which is responsible for histone methylation, and DNA demethylases DNMTs, indicating the possibility of epigenetic control of its activity (**Fig. 3**). Coincident targets, such as APC and CDKN1A, bound by several miRNAs, indicate coordinated post-transcriptional regulation. The presented network demonstrates potentially significant regulatory axes combining miRNAs, their targets, and epigenetic mechanisms, which emphasizes their possible role in the pathogenesis of breast cancer.

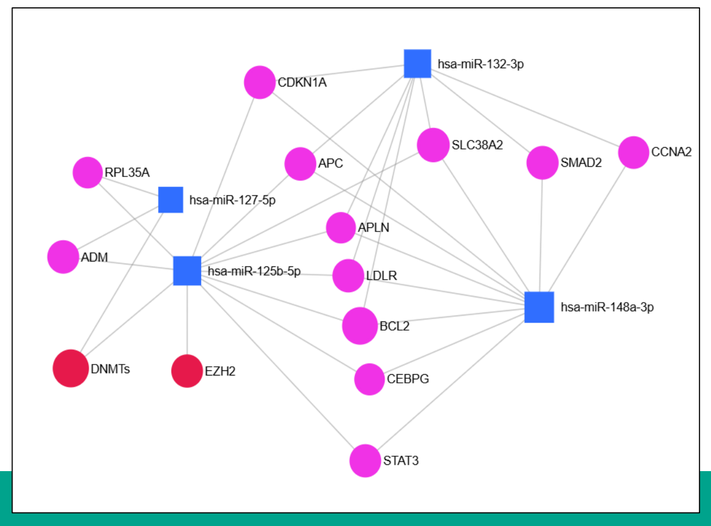

Fig. 3. Regulatory network of interactions of co-expressed microRNAs (miR-125b-5p, miR-127-5p, miR-132-3p, miR-148a-3p), their potential mRNA targets and epigenetic factors.

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