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Differentially Expressed miRNAs Linking Transportation Infrastructure to TNBC Stages at Diagnosis

Abstract

Background/Objectives. Breast Cancer (BC) is the most diagnosed cancer worldwide and the second leading cause of death in women. Triple negative breast cancer (TNBC) is a subtype of BC characterized by the absence of estrogen, progesterone, and HER2 receptors, and typically associated with greater aggressiveness and poorer clinical outcomes. According to the American Cancer Society, TNBC accounts for 10-15% of all BC cases. Recent studies suggest that, beyond biological causes, environmental factors, such as proximity to major transportation infrastructure, may play a role in BC development. However, the molecular mechanisms driving these associations remain unclear. MicroRNAs (miRNAs) regulate tumor growth and treatment response, acting as either tumor suppressors or oncogenes. Thus, we analyzed miRNA expression across varying environmental exposure groups in TNBC, aiming to examine how proximity to high volumes of transportation infrastructure may influence TNBC progression.

Materials/Methods. We analyzed 434 Formalin-Fixed Paraffin-Embedded (FFPE) TNBC tumor samples diagnosed between 2009 and 2019. Clinical and environmental data were integrated from the Louisiana Tumor Registry (LTR) and the 2022 Environmental Justice Index (EJI). RPL_EBM_DOM4 is the environmental variable representing the percentile rank of domain consisting of proximity to high volume roads, railways, and airports, categorized into 4 groups. TNBC stages were categorized as early or advanced. miRNA expression was profiled using high-throughput sequencing and normalized via the TMM method. Differentially expressed (DE) miRNAs were identified using *edgeR*, adjusting for plate effects. Shared DE miRNAs across TNBC stage and RPL_EBM_DOM4 were visualized using a *Venn Diagram*.

Results. A significant association was found between RPL_EBM_DOM4 and TNBC stages ($p = 0.0057$). A total of 196 DE miRNAs were identified as differentially expressed in relation to proximity to high-volume transportation infrastructure, and 69 DE miRNAs were associated with TNBC stage. Of these, 32 DE miRNAs were commonly differentially expressed across both RPL_EBM_DOM4 and TNBC stages.

Conclusions. There is a statistically significant relationship between proximity to transportation infrastructure and TNBC stages, suggesting that environmental exposure may increase the risk of advanced TNBC. This study identified DE miRNAs potentially mediating the influence of environmental exposures on TNBC progression. The discovery of shared DE miRNAs offers insights into the molecular mechanisms underlying TNBC disparities and suggests potential targets for intervention and prevention strategies tailored to environmentally influenced cancer outcomes.