Shaped by Signals: Leveraging Breast Cancer Nuclear Morphology to Elucidate Regulatory Pathways as Therapeutic Targets

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Breast cancer (BC) is the most expensive cancer to treat in the United States and a leading cause of cancer-related mortality worldwide. Nuclear enlargement is a well-established histopathologic hallmark of aggressive BC and poor prognosis, however the pathways driving this phenotype and their therapeutic relevance remain incompletely defined. This study leverages BC nuclear morphology to elucidate regulatory pathways driving tumor aggressiveness. Using scRNA-seq data from the Human Tumor Atlas Network (n=10) and non-BC breast tissue from the Genotype-Tissue Expression project (n=9), paired with histology-based nuclear size quantification, a fourfold increase in nuclear size in BC relative to non-BC tissue was observed. High-dimensional weighted gene correlation network analysis revealed dysregulated co-expressed gene sets in BC, reflecting increased transcriptional variability. Linear regression across all genes identified EPDR1 ($p<.001$, $R^2=0.94$) as one of the strongest and most reproducible nuclear-size-associated BC genes. Cross-dataset gene set comparison and pathway enrichment analyses implicated PI3K/AKT signaling, alongside metabolic pathways, as nuclei-size-associated mechanisms. EPDR1 loss increases intracellular mechanical stress, promoting PI3K/AKT hyperactivation, rapid cell cycling, chromatin decondensation, and nucleomegaly. Additionally, miRNA motif analysis identified miR-615-3p activity ($p = 3.57 \times 10$) as significantly upregulated in BC, targeting the CCGAGCC motif within the EPDR1 3'UTR and likely contributing to its reduced expression. Together, these findings reveal a mechanistic framework linking miR-615-3p-mediated EPDR1 loss to PI3K/AKT-driven nucleomegaly and highlight upstream modulators as promising therapeutic opportunities.

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