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APPLICATIONS OF TRANSCRIPTOMICS METHODS IN BREAST CANCER

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ABSTRACT

Gene expression studies using cDNA microarrays have revolutionized the breast cancer subclassification. The application of RNA sequencing technologies has revealed additional complexity of breast cancer. The integrated genomic/transcriptomic analysis of breast tumors (METABRIC) and the Cancer Genome Atlas (TCGA) with clinical follow-up data shaped the molecular landscape of breast cancer the last decade. High-throughput RNA sequencing technologies have shown that large proportions of mammalian transcriptome include regulatory non-protein-coding RNAs (ncRNAs) besides protein-coding RNAs. Role of ncRNAs have been well documented in breast cancer. Using RNA sequencing and probe-based transcriptome analyses, several studies, including ours, have emphasized the role alternative splicing events in breast cancer progression. We have demonstrated that Epithelial Splicing Regulatory Protein 1 (ESRP1), a splicing factor, is associated with poor prognosis and endocrine resistance in human ER-positive (ER+) breast tumors. These studies have further implicated that aberrant regulation of alternative splicing plays an important role in all hallmarks of cancer and provide novel strategies for the therapeutics in breast cancer. In addition to bulk sequencing, deconvolution methods such as CIBERSORT was useful to understand the role of individual cells in cancer progression. Using TCGA and METABRIC cohorts, we identified immune-subtypes with better outcomes in triple negative breast cancer (TNBCs). Recently, single cell RNA-seq (sc-RNAseq) and spatial RNA-seq technologies have enabled analysis of single tumor cell phenotypes and intratumor heterogeneity. The application of these technologies to formalin-fixed paraffin-embedded (FFPE) tumor samples with clinical outcomes will present a valuable resource for understanding the inter and intra-tumor heterogeneity in breast cancer.

Keywords: Breast Cancer, RNA Sequencing, ncRNAs, Alternative Splicing, CIBERSORT, Spatial Transcriptomics