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The Cancer Control Challenge:
Better Understanding It to Better Face It

TUMOR-EDUCATED PLATELETS AS A MINIMALLY INVASIVE SOURCE OF BIOMARKERS OF BREAST CANCER DIAGNOSIS

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Introduction: Breast cancer (BC) remains the most prevalent malignancy and the leading cause of cancer-related death among women worldwide. Currently, diagnosis and therapeutic decisions rely primarily on tissue biopsies, which are invasive and time-consuming. Emerging evidence suggests that cancer cells can alter the molecular profile of circulating platelets, transforming them into tumor-educated platelets (TEPs). Recent studies have demonstrated that TEPs represent a promising, minimally invasive source of complementary biomarkers in several solid tumors, including BC. **Objectives**: We aimed to identify differentially expressed genes in TEPs from BC patients, which could be potential diagnostic biomarkers. **Results**: RNA-seq data derived from platelets were downloaded from the Gene Expression Omnibus (GEO) under the accession numbers GSE68086 and GSE183635, comprising 104 breast cancer (BC) patients and 191 healthy donors. Low-quality reads were filtered using FastP, and the remaining high-quality reads were aligned to the human genome (GRCh38.p13 v43) using Salmon. The aligned reads were then imported into RStudio via the Tximport package for further analysis. Differential gene expression analysis was performed using the DESeq2 package, considering genes with |log2FoldChange| > 1 and an adjusted p-value < 0.05 as significantly differentially expressed. Gene Ontology (GO) enrichment analysis was carried out with the clusterProfiler package. Additionally, expression data from tumor tissue (n = 704) and normal tissue (n = 91) from BC patients were obtained from TCGA using the TCGAbiolinks package. Expression data from 18 microvesicle samples derived from BC cell lines were also downloaded from GEO (GSE188385 and GSE211556). Receiver Operating Characteristic (ROC) curves were generated using the pROC package for genes shared across TEPs, tissue, and microvesicles. In the differential analysis, 5,583 genes were differentially expressed, of which 131 were upregulated, and 5,452 were downregulated. GO enrichment analysis of upregulated genes highlights biological

processes such as blood coagulation, hemostasis, and reactive oxygen species metabolism. On the other hand, downregulated genes are mainly associated with RNA processing, methylation, and mitochondrial gene expression. Five genes were shared between TEPs, tumor tissue, and vesicles. These genes – *H2AC11*, *H2BC4*, and *IFI27* – had moderate performance to distinguish BC patients from healthy donors using platelets (AUC: 0.80, 0.79, and 0.77 respectively). **Conclusions**: Our results revealed that *H2AC11*, *H2BC4*, and *IFI27* expressed in TEPs could be a potential less invasive biomarker for BC diagnosis. These findings reinforce the role of platelets as a minimally invasive source of biomarkers for the diagnosis and management of cancer.

Keywords: Tumor-educated platelets; biomarkers; diagnosis; liquid biopsy.