**Comparative profiling of whole-cell and exosome samples reveals protein signatures that stratify breast cancer subtypes**

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The identification of novel breast cancer biomarkers will improve patient stratification, enhance therapeutic outcomes, and help to develop non-invasive diagnostics. Herein, we present the proteomic and functional characterization of breast cancer cells (BCCs) and breast cancer cell-derived exosomes (BCDEs) representative of four clinically recognized subtypes, demonstrating intrinsic differences, correlations with clinical scenarios, and applicability as non-invasive biomarkers to improve breast cancer patient stratification and disease monitoring.. We validated our proteomic signature using The Cancer Genome Atlas (TCGA) and The Cancer Proteome Atlas (TCPA) databases, verified that differentially-activated pathways in BCDEs cause a corresponding response in receptor cells, and confirmed that the BCDE proteomic signature reflects their cell-of-origin and identifies candidate disease biomarkers in liquid biopsies. The BCDE signature offers a promising starting point for further analysis of the role of exosomes as biomarkers of the Triple Negative (TN) subtype in liquid biopsies and could contribute to the identification of biomarkers that will support breast cancer patient stratification and the development of novel therapeutic strategies.