Proteomic And Functional Impact Of Breast Cancer-Derived Cell-Free Dna On Benign Breast Epithelial Cells

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Abstract

Background: Tumor cells release cell-free DNA (cfDNA) into the adjacent tissue and blood circulation and it has been implicated to cancer progression and metastasis. CfDNA nucleoprotein content and its direct effects on non-cancerous cells remain largely unknown.

Objective: This in vitro study compares the proteome of cfDNA released by benign and cancer breast cancer cells and investigates how cfDNA from cancer cells alters the proteomic landscape of benign breast cells, potentially triggering oncogenic processes.

Methods: cfDNA was isolated from the breast cancer cell line MCF7 culture supernatant and was administered into the benign breast epithelial cell line MCF12A for 48 hours. A control group was treated with cfDNA from MCF12A to identify effects not exclusive to cancer. Proteomic analysis of nucleoprotein complexes precipitated from cell supernatants by chromatin immunoprecipitation (chIP) was performed using mass spectrometry (Nano LC-MS/MS), followed by differential expression analysis. Functional enrichment was conducted using Enrichr to identify Gene Ontology (GO) biological processes.

Results: MCF7 nucleoprotein profile is related to cytoskeletal remodelling, telomere maintenance, plasma membrane repair, and post-transcriptional regulation, suggesting enhanced survival and metastasis. In contrast, in MCF12A we detected proteins associated with apoptosis, mitochondrial autophagy, ion homeostasis indicating stable cellular maintenance and regulated cell death. 8.5% were common between MCF7 and MCF12A. Treatment with MCF7-derived cfDNA led to the identification of 35 unique proteins in MCF12A as compared to baseline levels. GO term enrichment analysis revealed significant activation of pathways related to leukocyte differentiation, lymphocyte regulation, cell motility, DNA damage repair (double-strand break repair, DNA ligation), and intracellular signalling (TORC2 signalling). Additionally, cfDNA from benign MCF12A induced distinct proteomic changes, mainly linked to stress responses and enhanced cell-type function.

Conclusion: These findings suggest that tumor-derived cfDNA may influence the immune microenvironment, DNA repair mechanisms, cell motility and intracellular signalling in recipient cells. This acquired phenotype might trigger progressively a cancer-like perturbation, highlighting the potential role of cfDNA in cancer progression and giving grounds to the hypothesis of “genometastasis” foreseeing that tumors release elements into the circulation able to transform healthy cells, via mechanisms such as horizontal oncogene transfer and activation of mitogenic signalling pathways.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.