In vitro biological effects of breast cancer circulating cell free DNA on normal breast cells

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Background & objectives

The hypothesis of "genometastasis" proposes that tumors release elements into the circulation able to transform healthy cells, via mechanisms such as horizontal oncogene transfer and activation of mitogenic signaling pathways. In the present study, we investigate if circulating cell free DNA (ccfDNA) released by breast cancer cells can be a mediator of such effects, presenting a biologically active entity.

Methods

CcfDNA released by the human breast cancer cell line MCF7 (ccfDNAc) was added in the culture medium of the normal human breast cell line MCF12A in parallel to their own ccfDNA (ccfDNAh) and non-treated controls. Different growth/apoptosis parameters were monitored by MTT, scratch migration assay and FACS analysis, as well as changes in the methylation status of several cancer-related genes (*SOX17, BRMS1, KLK10, ENPP2, MRG, CLDN15, MSH2, GATA3, WNT5A, ZNF430*) by methylation specific qPCR. Also, the nucleoprotein content of the ccfDNA from the two breast cell lines was detected and compared by mass spectrometry following immunoprecipitation using specific anti-histone antibodies.

Results

CcfDNAc but not ccfDNAh enhanced the proliferation of MCF12A cells, as well as the cell migration potential. Neither ccfDNAc nor ccfDNAh affected the quantity of ccfDNA released by the cell line. Exposure to both ccfDNAc and ccfDNAh resulted in reduced MCF12A apoptosis as compared to non-treated cells. Moreover, ccfDNAc altered the methylation profile of some but not all studied cancer-related genes in the genomic DNA of the MCF12A cells. Finally, the nucleoprotein load of ccfDNAc and ccfDNAh showed marked differences which could account for distinct effects.

Conclusion

CcfDNA from a breast cancer cell line can cause specific effects on healthy breast cells related to their proliferation and apoptosis, which could contribute to their malignant transformation. Our results demonstrate biological activity of this biomolecule awaiting further investigation for its role in distant metastasis formation.