AUTOCRINE SIGNALING OF ANNEXIN A1 PROTEIN IN BASAL-LIKE BREAST CANCER CELL LINE MDA-MB-231

Vecchi, L\textsuperscript{1}; Zóia, MAP\textsuperscript{1}; Ramos, CMC\textsuperscript{1} and Goulart, LR\textsuperscript{1}

\textsuperscript{1}Laboratório de Nanobiotecnologia, Universidade Federal de Uberlândia, UFU (MG) Brasil

laravecchi7@gmail.com
lrgoulart@ufu.br

Introduction:
Annexin A1 (AnxA1) is a calcium and lipid binding protein that contains an N-terminal domain displaying a biological activity. Although AnxA1 has been extensively studied for its anti-inflammatory properties, recently its involvement in cancer progression has been described. An increase in AnxA1 expression correlates with gastro-intestinal cancers aggressiveness.

Objectives:
Since AnxA1 role in breast cancer is still controversial probably because of the heterogeneity of this type of cancer, we investigated AnxA1 expression and signaling by using two breast cancer cell lines: MCF7 (luminal A subtype, estrogen dependent) and MDA-MB-231 (basal-like subtype, estrogen independent and highly aggressive) and a cell line derived from normal breast tissue (MCF 10A).

Material and methods:
AnxA1 expression and localization was analyzed by Western blotting and immunofluorescence analysis. EGFR signaling was analyzed by flow cytometry.

Results:
AnxA1 is expressed only in MDA-MB-231 and MCF 10A cells, displaying a higher expression in both nuclear and cytoplasmic compartments of MDA-MB-231 cells. AnxA1 is massively secreted by MDA-MB-231 cells and only slightly secreted by MCF 10A. Since secreted AnxA1 can activate the “formyl peptide receptors” (FPRs), we analyzed the expression of FPRs in these cell lines. Accordingly to AnxA1 expression, MDA-MB-231 cells express exclusively FPR1 whereas MCF 10A express both FPR1 and FPR2. Therefore, we used a FPR1 specific inhibitor (Boc-fMLF) to study AnxA1 signaling in MDA-MB-231 cells. We found that AnxA1 autocrine signaling through FPR1 leads to a trans-activation of EGFR and its downstream signaling pathways. We found that Boc-fMLF treatment reduces the level of transactivation of EGFR by reducing EGFR Y992 phosphorylation levels, subsequently reducing ERK1/2 activation and PI3K/Akt phosphorylation. All these effects were accompanied by reduced migration and invasion potential of MDA-MB-231 cells.

Conclusions:
In conclusion, these results suggests that AnxA1 autocrine signaling though FPR1 could be a good target for future therapies of breast cancer.
Keywords: AnxA1, FPR1 and EGFR

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