INHIBITION OF STAT3 INCREASES DOXORUBICIN SENSITIVITY IN A HUMAN METASTATIC BREAST CANCER CELL LINE

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Metastatic breast cancer is an incurable disease, often characterized by poor response to standard chemotherapy, which is mainly based on anthracyclines and taxanes; increasing tumor cell sensitivity to these agents is an attractive goal towards improving the clinical management of this disease. The present study investigates the effects of signal transducer and activator of transcription 3 (Stat3) inhibition on the response of the highly metastatic MDA-MB-231 human breast adenocarcinoma cell line to doxorubicin (DOX). Stat3 is a transcription factor that is often constitutively activated in breast tumors and cell lines, due to overexpression of growth factor receptors and/or unrestrained activation of oncogenic and antiapoptotic pathways; accumulating experimental evidence indicates that Stat3 significantly contributes to malignant transformation and progression by transactivation of a host of target genes involved in cell proliferation and survival, angiogenesis and invasiveness. Intracellular levels of activated Stat3 were determined in MDA-MB-231 cells by immunoprecipitation and Western blot, both under baseline conditions and following DOX treatment, and were found to be higher than in the non metastatic breast cancer cell line MCF-7; this finding was associated to a significant difference in DOX cytotoxicity in the two cell lines, with IC_{50} values of 0.36 ± 0.018 μM for MCF-7 cells vs 0.5 ± 0.052 μM for MDA-MB-231 (Mean ± SE of 5 experiments; \( p < 0.05 \)). Stat-3 activation was subsequently inhibited in MDA-MB-231 cells by a) exposure to the tyrphostin derivative AG490 (an inhibitor of the upstream activating Janus kinases); b) transfection with a dominant negative form of Stat3; or c) treatment with JM216 (also known as satraplatin), a tetravalent platinum derivative that directly interferes with Stat3 activation. All three approaches yielded significant increases in the response of MDA-MB-231 cells to the pro-apoptotic effect of DOX, as assessed by flow cytometry. Overall, these observations suggest that suppression of Stat3 signaling might provide a novel therapeutic approach to overcoming DOX resistance in metastatic breast cancer cells.