Phosphoproteome Reveals Critical PKC and JAK-Stat Signalling Involvement on Breast Cancer Cells Chemical Resistance

Nascimento, A.S.[1], Ferreira, M.R.[1], Fernandes, C.J.C.[1], Carandina, R.F.[1], Zambuzzi, W.F.[1]

[1]Bioassays and Cell Dynamics Lab, Dept. of Chemistry and Biochemistry, Bioscience Institute, UNESP, Botucatu-SP, 18618-693. Email: wzambuzzi@ibb.unesp.br

INTRODUCTION: Breast cancer is the second most common type in the world being responsible for 25% of cancer cases and 15% of deaths from cancer among women. The treatment is usually long, and the tumor cells acquire resistance against the chemotherapy treatment. In this sense, to understand the intracellular molecular fingerprint of this process is necessary to propose more effective treatment.
OBJECTIVE: Our main objective was to conduct phosphoproteome of resistant cells in order to identify potential biomarkers of this phenotype.
MATERIAL AND METHODS: Routinely MCF7$^{ADR-res}$ were maintained with presence of Daunorubicin^{TM} in order to keep the resistant phenotype. MCF-7 and MCF7$^{ADR-res}$ cells were conducted to phosphoproteome analysis by performing Pepchip array (microarray peptide). Thereafter, the results were validated by conducting western blotting approach. As the phosphoproteome reveled JAK as a potential biomarker of this event, we decided to validate this result by treating the cells with JAK inhibitor (5 and 10mM) previous to treat with Daunorubicin^{TM}.
RESULTS AND DISCUSSION: The results indicated the involvement of signaling pathway JAK-STAT and the difference in the activity of PKC isoforms in the process of resistance in breast cancer cells. Furthermore, we showed activation of ERK, Ras and an increased expression of MMP-9. These results demonstrate the malignant potential of these resistant cells. From these, we decided to evaluate the response of resistant cells to chemotherapy associated with JAK-2 inhibitor and our results clearly showed that inhibiting JAK-2, MCF7$^{ADR-res}$ cells became more sensitive to Daunorubicin^{TM}, increasing the rate cell death in front of chemotherapeutic response.
CONCLUSION: Based on these results, we concluded that activation of the JAK-STAT is one of the events responsible for the acquisition of the resistant phenotype of breast cancer cells. Thus, these data indicate the potential development of inhibitors of JAK-2 as a strategy for the treatment of patients unresponsible to conventional therapies.

Key Words: Breast Cancer; JAK-STAT; Resistance; PepChip; PKC.
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