Increased caveolin-1 expression following exposure to sub-cytotoxic doses of anti-neoplastic drugs increases migration and invasion of cancer cells

Díaz-Valdivia, N1,2,3., Calderón, C.1, Díaz, J1,2,4., Maldonado, H1,2,3., Ortíz R1,2,3., Leyton, L1,3., Torres, V4., Quest, AFG1,2.

1Laboratory of Cellular Communication, Center for Molecular Studies of the Cell (CEMC), 2Advanced Center for Chronic Diseases (ACCDiS), 3Biomedical Neuroscience Institute (BNI), Cell and Molecular Biology Program, Biomedical Sciences Institute (ICBM), Faculty of Medicine, University of Chile. 4Laboratory of Cellular and Molecular Biology, Department of Basic and communitarian Sciences, Faculty of Dentistry, University of Chile. nataliadiazvaldivia@gmail.com

Introduction: Chemotherapy remains an important approach to treat cancer, despite adverse secondary effects and the development of multi-drug resistance, which both significantly limit therapeutic success. Here we evaluated whether such treatments alter the expression of caveolin-1 (CAV1) and thereby favor migration and invasion of cancer cells. CAV1 plays a dual role in tumor progression and, although considered a tumor suppressor early on in tumor development, elevated CAV1 levels are associated with metastasis and multidrug resistance in later stages of cancer. However, the mechanisms that upregulate CAV1 levels in cancer cells and how such events may be triggered by chemotherapeutic drugs remain unclear.

Objective: Investigated whether the treatment of cancer cells expressing low endogenous CAV1 levels with different chemotherapeutic agents induced CAV1 upregulation, as well as increased migration and invasion of colon cancer cells and the signaling pathways involved in drug-induced CAV1 upregulation.

Materials and Methods: The colon cancer cell lines DLD1 and HT29(US) were treated with the anti-neoplastic drugs Methotrexate (MTX) or Etoposide (ET) and expression of CAV1 was analyzed by western blotting. To identify pathways involved in the induction of CAV1, cells were pre-treated with the MEK inhibitor (PD98059) or the anti-oxidant Trolox prior to MTX or ET exposure. Phosphorylation of MAPK and ROS levels were determined by western blotting and flow cytometry, respectively. Cell migration and invasion were evaluated in transwell and matrigel assays.

Results: In DLD1 and HT29(US) cells, CAV1 expression, migration and invasiveness increased upon treatment with anti-neoplastic drugs. CAV1 upregulation was mediated by a sequence of events including activation of the MEK/ERK pathway and ROS production by the treatment with MTX or ET.

Acknowledgements. CONICYT-FONDAP 15130011, Anillo ACT1111, FONDECYT 1130250 (AFGQ) and FONDECYT 1110149, BNI #P09-015-F (LL) and CONICYT PhD Student Fellowships (NDV, JD, HM).

Key words: Cancer, Caveolin-1, Invasion, Migration, Multi-drug resistance.