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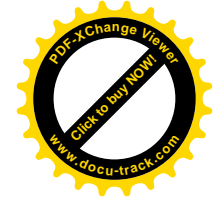
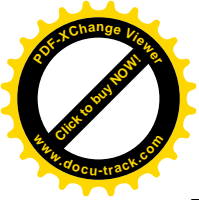
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PO49

Title: IMPACT OF LEPTIN ON ROS PRODUCTION IN HUMAN MAMMARY EPITHELIAL CELLS IS DEPENDENT OF NEOPLASIC STATUS

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Abstract: Nutritional status and hormonal factors, such as leptin, an adipokine highly regulated in obesity, induce cellular signaling pathways, some of which involving reactive oxygen species (ROS) as intracellular messenger. High levels of ROS contribute to oxidative stress, cellular damages and pathogenesis. That's why ROS production associated to obesity could be a major risk factor of mammary carcinogenesis.

This study aimed to determine leptin effects on ROS production in 3 human epithelial mammary cell models which present different neoplastic status (healthy primary (HP) cells, MCF-7 and MDAMB-231). ROS production is measured by fluorescence in presence of two leptin concentrations (10 ng/ml close to physiological values, 100 ng/ml as obesity level) with several probes at 2 μ M (Dichlorofluorescein (DCF) for total cellular ROS, Diaminofluorescein (DAF) for NO, Dihydrorhodamine (DHR) for mitochondrial ROS and Dihydroethidine (DHE) for cytosolic superoxyde anion (O₂^{•-}). Gene expression and catalytic activities of ROS production systems (NADPH oxidases, NO synthases, Dual oxidases) and of anti-oxidant enzymes (glutathione reductase, heme oxygenase, glutathione S-transferase) are performed.

Whatever the cell model and the leptin concentration, a slight increase of total cellular ROS production is observed. This increase is independent of mitochondrial activity as DHR signal remained stable for HP cells (5.51 ± 0.40 RFU) and decreased for MCF7 and MDAMB-231 cells. Inversely, this ROS increase is dependent of cytosolic O₂^{•-} production as shown by DHE signal enhanced for HP cells (0.66 ± 0.01 to 0.81 ± 0.01 RFU), for MCF7 (0.79 ± 0.02 to 0.89 ± 0.03 RFU) and for MDAMB-231 (0.82 ± 0.01 to 0.89 ± 0.02 RFU). Interestingly, this ROS production is dependent of the NADPH oxidase 5 (Nox5) expression and contributes to a different antioxidative response in regard to the neoplastic cell status. Leptin activates, only in HP cells, the antioxidative enzymes expression and activities such as heme oxygenase or glutathione reductase.

These data suggest that leptin could modulate the oxidative status of epithelial mammary cells in different ways according to the neoplastic cell status. Therefore leptin induces a similar ROS production for the 3 cell models whereas the anti oxidant cell response is not modified in MCF-7 and MA-MB-231 cells. This study highlights lower capacities of neoplastic cells to fight against oxidative stress.