Mitochondrial network organization in cisplatin resistant cells

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Cisplatin is one of the most potent anticancer agents used in the treatment of various solid tumors[1]. Unfortunately the onset of resistance is the main limit of this therapy and severely compromises treatment effectiveness. Although several studies regarding cisplatin resistance has been performed, the molecular mechanisms are not completely understood. Recently it has been shown that only 5-10% of intracellular platinum is bound to nuclear DNA, while the great majority of the intracellular drug is available to interact with other nucleophilic sites including but not limited to phospholipids, cytosolic, cytoskeletal and membrane proteins, RNA and mitochondrial DNA[2].

The aim of this study was to investigate the mitochondrial influence on cisplatin-resistance in order to identify alternative pathways exploited by cancer cells to escape cisplatin cytotoxicity and to possibly prevent/overcome the onset of drug resistance.

Previously we have demonstrated that cisplatin-resistant ovarian cancer cells (C13) are characterized by a reduced respiratory chain activity and lower mitochondrial mass when compared to the cisplatin-sensitive counterpart (2008) as well as a different susceptibility to various metabolic stresses, in particular the exposure of glucose-free/galactose medium or rotenone, inhibitor of mitochondrial respiratory chain[3].

In this scenario we analyzed others cisplatin-resistant and sensitive cancer cells, in particular cervix squamous human carcinoma (A431 and A431-Pt), osteosarcoma (U2OS and U2OS-Pt) and ovarian carcinoma (SKOV3 sensitive and SKOV3 CDDP3) cell lines.

Previous results show no significant differences in mitochondrial membrane potential ($\Delta\Psi$) and mitochondrial mass between CDDP-resistant and sensitive cells; but we can see a different mitochondrial phenotype, in particular a fragmented mitochondrial network in all resistant clones. Mitochondria are highly dynamic organelles that are constantly dividing and elongating to form a network. Thus, our purpose will be to investigate the mitochondrial dynamics that may in part be involved in the pathophysiology of CDDP resistance.

The study of alterations in the processes that influence cancer mitochondrial dysfunction can be useful to develop more effective treatments to target specific cancer cells based on their mitochondrial profile to potentially enhance sensitivity of chemotherapeutic agents.

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