ROLE OF MITOCHONDRIA IN CISPLATIN-RESISTANCE PHENOMENA

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Cisplatin is one of the most potent anticancer agents used in the treatment of several solid tumors including lung, testicular and ovarian. The main problems of this treatment are the severity of the side effects and the onset of resistance. It is well established that cisplatin resistance is a multifactorial phenomenon correlated to reduced drug accumulation, inactivation by thiol-containing species and increased repair of platinum-DNA adducts, but the mechanism is not completely understood. It has been shown that approximately 5-10% of intracellular platinum is bound to nuclear DNA, leading to cell cycle arrest and apoptosis, while the majority is available to interact with other nucleophilic sites including phospholipids, proteins, RNA and mitochondrial DNA. The mtDNA, unlike the nDNA, does not possess effective repair systems, consequently it is more susceptible of mutations and oncogenic transformations.

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

Our studies focused on 2008 human ovarian carcinoma cells and C13 resistant clone; furthermore in order to investigate the impact of mitochondria on cisplatin-resistance, 2008 and C13 were depleted of their mitochondrial DNA (rho0 clones). Results showed that the IC50 of cisplatin was lower in 2008 cells than in 2008-rho0 but similar between C13-rho0 and C13 cells. Data also revealed that resistant cells were more dependent to glucose for survival, and presented a different susceptibility to rotenone exposure, inhibitor of the respiratory chain. C13 cells showed a lower oxygen consumption and a reduced mitochondrial membrane potential correlated to a lower mitochondrial mass. Once certain such differences between sensible and resistant cells, we also evaluated markers of mitochondrial biogenesis and mitophagy to better understand the role of mitochondria in the cisplatin-resistance phenomena.

Taken together our results show that profound metabolic changes underpin cisplatin resistance. The study of alterations in the processes that influence cancer mitochondrial dysfunction can be useful to develop more effective treatments and potentially improve the clinical impact of platinating drug, by counteracting resistance mechanisms.