GLUCOSE-6-PHOSPHATE DEHYDROGENASE AS PHARMACOLOGICAL TARGET TO OVERCOME CISPLATIN RESISTANCE

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Despite the advances of the last decades, cisplatin still remains one of the more effective chemotherapeutic agents for a wide variety of solid tumour. However, although a consistent rate of initial responses, the treatment often results in a cisplatin-resistant state leading to cancer relapse, failure of subsequent treatments and eventual death of patients. The therapeutic effectiveness of the drug is therefore limited by the onset of drug resistance, whose molecular mechanisms are today poorly understood. In the last years, emerging evidences support the idea that, among others, cisplatin resistance can be achieved by a rewiring of key metabolic pathways, leading to increase cell defense and counteract the drug cytotoxic effects. Our previous investigation revealed that cisplatin-resistant ovarian cancer cells (C13), as compared to the sensitive counterpart (2008), exhibit altered mitochondrial bioenergetics with reduced mitochondrial potential and oxygen consumption associated with a lower mitochondrial mass. Moreover, C13 cells were also extremely more dependent from glucose and glutamine, which were in part used to maintain cell's antioxidant defenses. Here, we further investigate the hypothesis of a metabolic rewiring towards antioxidant pathways, extending the study to one more cancer cell line (A431 cervix adenocarcinoma). In line with our previous observations, we found that both resistant lines (C13-A431pt) exhibit increased glucose uptake and are more sensitive to glucose deprivation. Interestingly we also observed that, between the glycolysis enzymes, only GLUT1 is over-expressed in cisplatin-resistant cells suggesting a metabolic switch towards the Pentose Phosphate Pathway (PPP). In line with this hypothesis, we found that the expression and enzymatic activity of G6PDH are higher in C13 and A431pt cells, that result more sensitive to G6PDH inhibition as compared with their sensitive counterparts. Moreover, the association of 6-AN and CDDP results in an addictive effect selectively in resistant cells, making G6PDH a good target to overcome cisplatin resistance. In this scenario, the PPP pathway becomes an interesting focus to further investigate with the aim of designing novel molecules able to prevent or overcome cisplatin resistance.