PROJECT

Tutor's Name	Monica Montopoli
Cotutor's Name	

1) Project title

Study of metabolic reprogramming and identification of innovative pharmacological targets in chemotherapy resistance

2)Abstract (max 500 words)

Resistance to chemotherapeutic treatment is one of the major causes that hamper the therapeutic efficacy, inducing cancer relapse, failure of subsequent treatments, and eventual patients' death. Some tumors may be refractory to treatment with certain drugs due to some genetic characteristic or, in many cases tumors may develop resistance following exposure to the drug. A huge effort in research has been made to identify factors that can predict the onset of resistance in order to adapt the therapeutic strategy.

Recent studies show that the metabolic state of cells influences the response to chemotherapy and that cancer cells reprogram their metabolism in response to chemotherapeutic drugs. These observations indicate that the metabolic rewiring is an important mechanism of acquired resistance and can be exploited for improving the efficacy of the treatment. Cancer cells, in fact, are able to rewire their metabolism in order to survive in a harsh and challenging environment, provided also by drug treatment. Reprogramming could involve different pathways including glycolysis, shift toward pentose phosphate pathway, lipid and glutamine synthesis and alterations in mitochondrial functions.

We found that ovarian cells resistant to cisplatin present an increased glucose-uptake and consumption and exhibit increased expression and enzymatic activity of the Pentose Phosphate pathway (PPP) enzyme Glucose-6-Phosphate Dehydrogenase (G6PDH). the combined treatment with the G6PDH inhibitors and cisplatin, showed a selective additive effect on cisplatin-resistant cells. Furthermore, to reduce the toxicity of cisplatin and prolong its action, a lyophilized stealth liposomal formulation was developed and the combination treatment of G6PDH inhibitor and liposomal cisplatin showed promising cytotoxic activities in drug-resistant cells and a prolonged pharmacokinetics in rats.

Recently we have also demonstrated that cisplatin resistant ovarian and osteosarcoma cells present a mitochondrial dysfunction that results in increased mitophagy (selective mitochondria autophagy), allowing cells to elude chemotherapy toxicity. The inhibition of autophagy trough selected molecules can sensitize resistant cells to platinum. Analogous mitochondrial alterations are emerging in osteosarcoma cells resistant to doxorubicin, further supporting the implication of mitochondria in chemotherapy resistance.

Therefore, the major objective of our research line is to point out altered metabolic pathways in resistant cells furnishing novel prognostic and predictive biomarkers for chemoresistance. Moreover, the identification of altered metabolic targets can open up new possibilities for innovative pharmacological strategies and approaches able to sensitize resistant cells to chemotherapy.