Radiation therapy and asparaginase: building a new approach for a combined cancer therapy

Effective cancer treatment is nowadays one of the main challenges of the scientific community. Cancer is a difficult-to-treat disease, and it is a prevalent opinion that a more tumor/patient-tailored combined therapy is the main route to overcome cancer treatment resistance. The proposed project aims at studying the effect of combined chemotherapy and radiations for the treatment of cancers which are known to be difficult to treat. During the project the effect of a metabolic drug, L-Aparaginase, will be evaluated in combination with X-ray and protons. Targeting cancer metabolism is, indeed, an effective tool to block cancer spread and proliferation affecting not only tumor cells, but also the tumor microenvironment. L-Asparaginase is one of its kind enzyme drug used routinely for the treatment of Acute Lymphoblastic Leukemia (ALL) and, pharmacologically, it acts by removing the extracellular supply of two amino acids, L-asparagine and L-glutamine. Given the high metabolic demand of cancer cells, many cancers are unable to express sufficient amount of the human enzymes needed for L-ASN and L-GLN de novo synthesis and therefore become conditionally dependent on L-ASN and L-GLN extracellular supply. Radiation therapy is a common treatment used in the management of cancer. It involves the use of high-energy radiation to kill cancer cells or inhibit their growth. X-ray treatment causes direct and indirect DNA damages which can be fatal for cancer cells and effectively induce cancer cell death by apoptosis. Both Asparaginase and radiotherapy have some limitation and cancer cells can overcome treatment. In the proposed project, we are going to combine the Asparaginase-induced metabolic stress with radiotherapy with the aim to obtain a combined or, hopefully, synergic effect of the two treatments using *in vitro* cancer models in the form of cells lines, organoids and patient tissues. Once the mechanism is determined, we expect to be able to include further drugs with specific targets, able to enhance the effect even further (Guardamagna et al., 2023). Given the extensive use of X-ray in combination with Asparaginase, the project will be conducted in close collaboration with the laboratory of Radiations and Biophysics of the Physics Department lead by Prof. Giorgio Baiocco. This collaboration will give the opportunity to the PhD student to work in a stimulative and multidisciplinary research environment and to undertake an experience in a foreign lab.

Techniques: recombinant Asparaginase production, purification and characterization, cell culture, cell cycle analysis, flow cytometry, immunohistochemistry, immunofluorescence, confocal microscopy, western blot, real-time PCR, NGS. Mathematical models to determine the effect of combination therapy.

Reference

Guardamagna I, Iaria O, Lonati L, Mentana A, Previtali A, Uggè V, Ivaldi GB, Liotta M, Tabarelli de Fatis P, Scotti C, Pessino G, Maggi M, Baiocco G. Asparagine and Glutamine Deprivation Alters Ionizing Radiation Response, Migration and Adhesion of a p53null Colorectal Cancer Cell Line. Int J Mol Sci. 2023 Feb 3;24(3):2983. doi: 10.3390/ijms24032983. PMID: 36769302; PMCID: PMC9917910.