Research Project Proposal
Academic year 2021-2022

Project Nº 20 ASIGNADO
Title: Metabolic alterations in cancer cells and their implication in immunotherapy
Department/ Laboratory Laboratory where the project will be carried out indicating Department, Area, Faculty, CUN, CIMA etc: **CIMA/ISTUN**
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Summary: Malignant growth and proliferation of cancer cells consume large quantities of bioenergy and biomaterials, which enhance the carbon flux through glycolysis and glutaminolysis to fulfill energetic and biosynthetic demands of cancer cells. Research on cancer metabolism currently shows that cancer cells have three clearly defined objectives: to avoid cell death, to survive in acidic, hypoxic and low-nutrient environments, and to grow indefinitely. Cancer cells are thus capable of modifying specific metabolic pathways in order to obtain energy highly efficiently by enhanced uptake of glutamine and glucose, the latter through what is known as the Warburg effect. In addition to glucose, glutamine plays an important role in providing both carbon and nitrogen necessary for anabolic metabolism. As glucose is metabolized through glycolytic pathways to lactic acid, glutamine can fuel the tricarboxylic acid (TCA) cycle, generating metabolic intermediates to serve as building blocks for lipids, proteins, and nucleic acids that are crucial to anabolic growth and proliferation. It is described that blocking glutamine metabolism would not only inhibit tumor growth but also restore of antitumor immunity. It is also known that abnormal amino acid metabolism affects the T cell function in tumors limiting the efficacy of cancer immunotherapy. Tumor cells disrupt methionine metabolism in CD8+ T cells, thereby lowering intracellular levels of methionine and impaired T cell immunity. Mechanistically, tumor cells avidly consume methionine and outcompete T cells for methionine by expressing high levels of the SLC43 family of methionine transporters. Since infiltrating effector T cells compete with the tumor cells for metabolites, in this work, we want to explore whether targeting tumor glutamine and methionine metabolism would enhance the antitumor immune response. For the development of this project, different techniques of cell and molecular biology will be used, such as cell cultures, real-time PCR, western blot, design and construction of siRNA, shRNA and lentivirus, as well as subcutaneous implantation of tumors in mice and their subsequent monitoring, mainly.

yes	x	Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?
no		