Metabolism in the microenvironment and the role of metabolic exchanges in tumor progression

To sustain the high proliferative rate, tumor cells have an increased demand for biosynthetic precursors used in the synthesis of macromolecules that will compose the daughter cells. For this, tumors consume a large amount of glucose and glutamine, mainly. The alteration in nutrient metabolism has been related to enzyme filamentation, a process conserved from yeast to mammalian cells, but still poorly understood from the point of view of tumor transformation. Furthermore, recent evidence suggests that dysregulation of tumor metabolism plays a crucial role in inhibiting the antitumor immune response and thus its progression and metastasis. It is known that in an immunosuppressive microenvironment, lymphocytes and macrophages operate with a metabolic disadvantage, since they are subjected to a shortage of crucial carbon sources (glucose and glutamine) and an increase in inhibitory signals. The subject of this proposal is the study of the molecular mechanisms behind the deregulation of nutrient metabolism and its role in the relationship of breast tumor cells with the immune system cells infiltrated in the microenvironment, and the tumor progression dependent on this interaction. Specifically, we stipulate two HYPOTHESES, associated with which we have two OBJECTIVES: HYPOTHESIS 1: GLS and GLS2, isoenzymes encoded by distinct genes, are related to the presence of distinct immune infiltrates in breast cancer; these profiles dictate different immune responses to the tumor. OBJECTIVE 1: To study whether there is synergy between GLS inhibition (or its gene manipulation) and immunotherapy with anti-Programmed cell death protein 1 (PD-1) antibody on triple negative breast tumors (no hormone receptor expression) and confirm whether high expression/activity of GLS corresponds to the HOT-like (inflamed) immune profile predicted in silico; To study whether high expression/activity of GLS2 in ER+ tumors is related to COLD-type (immunosuppressed) tumors and whether GLS2 expression is related to resistance to hormone therapies. 2. HYPOTHESIS 2: GLS and other metabolic enzymes filament into cells, in a process driven by nutritional stress and under the control of tumor genetic lesions. OBJECTIVE 2: To verify the impact of GLS filamentation on cellular mitophagy under glutamine deprivation and to search, in a group of 14 metabolic enzymes, for others that also filament under nutritional stress (glucose or glutamine); to verify the oncogenic signaling pathways that impact these phenomena and their importance in the tumor masses. Combining these two areas of activity, we will investigate the impact of GLS filamentation and other enzymes characterized by us on the profile of metabolites and immune cells infiltrated in tumor masses. Since the filament appears to obey nutritional stress processes and these phenomena affect the profile and activity of immune cells, we recommend that there may be a direct relationship between them. Thus, we will advance in two recent and innovative areas of research: 1. the study of enzymatic filamentation, with modern techniques of structural determination such as single particle Cryo-electron microscopy and Cryo-Focused ion bean electron tomography of cellular lamellae; 2. interface between glutamine metabolism in the tumor microenvironment and the phenotype and activity of infiltrated immune cells, a study that will benefit from the use of physiologically relevant tumor models such as patient tumors implanted in mice and tumor organoids. An in-depth understanding of metabolic challenges both at the molecular level and in the tumor microenvironment, and their impacts on the metabolic fitness of cancer cells and immune cells, may contribute to the discovery of new approaches combining metabolic fragilities and immunotherapy.