The role of MTARC2 protein-related metabolism changes in the intestinal tumorigenesis

1. Research Objectives

Tumor cells metabolize basic nutrients at much higher rates than non-tumor cells as a consequence of mitochondrial fatty acid oxidation (FAO) that provides energy and leads to dramatically increased glucose uptake and lactate production, even in the presence of oxygen. Therefore, metabolic alterations, which give the proliferative advantage to cancerous cells over normal cells, are considered a cancer hallmark. MTARC proteins (the mitochondrial amidoxime reducing component), MTARC1 and MTARC2, are molybdenum-containing enzymes located in the outer membrane of mitochondria. Both proteins are catalytic parts of an enzymatic complex, which perform reduction reactions of N-hydroxylated structures such as N-hydroxylamines, exemplified by the activation of pro-drugs containing an amidoxime functional group, such as Mesupron. The most extensively described physiological function of the MTARC complex is participation in cellular energy processes, related to lipid metabolism. Studies by our group have indicated that the activity of the complex is modulated in vivo under starvation and a high-fat diet (HFD) in mice. We were also the first to describe lowered MTARC2 expression in colon adenoma and adenocarcinoma. However, the bonafide endogenous MTARC substrates directly connected to lipid metabolism in healthy tissues and cancer have not been identified. In this regard, our preliminary studies have prompted us to prepare the current proposal.

2. Work plan

We hypothesize that inhibition of MTARC2 expression rewires the metabolic pathways towards the utilization of fatty acids for glucose production. To address this hypothesis we propose three separate tasks: **1).** Analysis of MTARC2 protein deletion consequences on molecular and metabolic pathways which characterize cancer metabolic alterations; **2).** Evaluation of *Mtarc2* deficiency effects on the colon cancer burden and lifespan of a mouse model on colon tumorigenesis in relation to the tumor and hepatic tissue molecular and metabolome alterations as well as to the stool microbiota and metabolome composition**; 3).** To analyze if DNA methylation of the MTARC2 promoter and/or first intron correlates with its expression in the colorectal cancer patient tissues.

3. Justification for tackling specific scientific problems by the proposed project

Currently, we do not understand how the MTARC enzymes are involved in energy metabolism and particularly in lipid metabolism and tumorigenesis.

4. Expected outcome

The experiments outlined in this proposal could provide crucial data on the link between *MTARC2* and cancer. In addition, we expect that these results could also explain the role of MTARC2-related metabolic disturbance in other comorbidities including obesity, where the role of the MTARC complex seems to be also relevant. Our preliminary data suggest that *MTARC2* deficiency conveys a more aggressive cancer phenotype which, in turn, further implicates this gene as a tumor suppressor gene. Such a role of MTARC2 has been suggested in hepatocellular carcinoma. We believe that the current proposal will provide further evidence on the *MTARC2* role in tumorigenesis that could be extended to other neoplasms with *MTARC2* deficiency. This knowledge could ultimately define the general role of MTARC2 and MTARC complex in health and disease.