GRUPPO: Biochimica- Cancer Metabolism
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ABSTRACT:

Metabolic reprogramming is an active process occurring in cancer cells, responsible for the rewiring of aerobic glycolysis and oxidative phosphorylation to increase production of antioxidant molecules and biosynthetic intermediates needed for cell growth and proliferation.
An essential process in cancer pathogenesis is the aberrant activation of the serine/glycine one-carbon (SGOC) metabolism, a complex network based on the chemical reactions of folate compounds. We are interested in elucidating the role of one-carbon metabolism in different cancer models, with particular attention to the conversion of serine to glycine, catalysed by the enzyme serine hydroxymethyltransferase (SHMT). In the SGOC network, the enzyme serine hydroxymethyltransferase (SHMT), expressed both in the cytoplasm (SHMT1) and in mitochondria (SHMT2), acts as a metabolic checkpoint, channelling one-carbon units deriving from a common serine pool to nucleotides synthesis and/or production of antioxidants. Our working hypothesis is that selective targeting of SHMT in different tumor types will allow to interfere with cell proliferation not only by regulating nucleotide synthesis, but also by controlling oxidative stress in different cellular compartments.
We have recently shown that cytosolic SHMT knockdown induces apoptosis in lung cancer cells by causing uracil misincorporation. Determination of the crystal structure of human mitochondrial SHMT and solution studies comparing the PLP-dependence of the aggregation state of both cytosolic and mitochondrial SHMTs have suggested important differences between the two isoforms. Recently, we have begun to study also the changes occurring in one-carbon metabolism under hypoxic conditions, to unveil the contribution of SGOC metabolism to the redox balance of cancer cells .In parallel, we are exploiting the potential of SHMT inhibition to reverse the cancer cell anabolism of serine, by working both on antifolates and exploring novel compounds.
More recently we have also begun to investigate the relationships between immunity and metabolic reprogramming in prostate cancer.

Expertise: cell biology, crystallography, binding and kinetic studies, bioinformatics.

5 Selected references:
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