INTEGRATED MULTI-OMICS APPROACH TO ACCELERATE ANTICANCER DRUG DISCOVERY BY TARGETING METABOLIC REPROGRAMMING IN HUMAN COLORECTAL ADENOCARCINOMA

DESCRIPTION FOR THE GENERAL PUBLIC

Otto Heinrich Warburg, the Nobel Prize winner from 1931, equated tumorigenesis with a change in the way cells obtain energy. During laboratory studies, he observed that rapid growth of cancer cells converted most of their glucose into lactate, even under oxygen-rich conditions. This phenomenon is now known as the Warburg effect or aerobic glycolysis. Further experiments indicated that **the metabolic reprogramming** observed by Warburg is due to the action of oncogenes and occurs to meet the challenges of increased macromolecular synthesis of proliferating cancer cells.

Some components of cancer cell metabolic reprogramming are relatively simple and involve a sustained reduction or increase in the intensity of some metabolic transformation; others are much more profound and lead to **the rewiring of entire metabolic circuits**. The profound changes in the way cells produce and use energy observed in tumorigenesis translate into the aggressiveness of cancer cells and their inability to evade immune responses.

Cell metabolism is subject to multistep regulation by, among others, G-protein-coupled receptors (GPCRs), which in response to the presence of ligands activate or suppress intracellular signalling pathways. For instance, activation of the GPR55 receptor activates YAP and TAZ proteins, which stimulate metabolic reprogramming by promoting glycolysis, lipogenesis, and glutaminolysis. It has been observed that activation of the GPR55 receptor promotes the development of colorectal cancer, which is the second most common malignancy in women and the third in men in terms of incidence worldwide. In its early stages, this cancer produces few or no symptoms, which translates into a high mortality rate. We have hypothesized that **pharmacological inhibition of GPR55 receptor will reverse pathological changes in colorectal cancer cell metabolism and will enhance the activity of traditional chemotherapeutics**, thus contributing to the reduction of their toxicity and side effects.

In this study, we will use analytical techniques to determine the effects of three chemically distinct GPR55 blockers on overall metabolism in eight different cancer cell lines and normal colon cells. We will examine accompanying changes in gene expression and production of key proteins. In parallel, we will examine how GPR55 receptor blockers affect tumour cell viability, both when administered alone and in combination with chemotherapeutic agents routinely used to treat colorectal cancer.

The study will significantly contribute to our understanding of the processes of normalization of reprogrammed metabolism under treatment with GPR55 blockers. In addition, the project will attempt to evaluate metabolic signatures that may reflect the efficacy of ongoing treatment. It opens the door to new cancer treatments and has a translational value that may lead to substantial improvement in the effective treatment of aggressive cancer types.