Parallel microevolution of metabolic plasticity and chemoresistance: a key to understand cancer relapse

Cancer remains one of the most challenging health issues, with rising numbers of cases putting immense pressure on healthcare systems worldwide. One of the primary reasons current treatments often fail is that cancer cells develop "phenotypic plasticity," which allows them to resist chemotherapy, leading to cancer relapse and metastases. Understanding how cancer cells adapt to the chemotherapeutic stress is essential to improving treatments and patient outcomes. One of the crucial aspects of this process is metabolic reprogramming of cancer cells. Normally, cancer cells in poorly oxygenated parts of a tumor switch to anaerobic (low-oxygen) metabolic pathways. However, when oxygen is present, long-term chemotherapy can cause cancer cells to reprogram their metabolism towards aerobic pathways. In this project, we aim to investigate how cancer cells adapt their metabolism when exposed to two critical types of stress: low oxygen conditions (hypoxia) and long-term exposure to chemotherapy.

Our study focuses on three key goals:

1. **Understanding Hypoxia's Role**: We will investigate how cancer cells respond to low oxygen levels during long-term chemotherapy. By studying this, we aim to uncover how oxygen deprivation contributes to cancer cells' ability to change their metabolism and resist treatment;
2. **Cyclic Hypoxia and Chemoresistance**: Tumors often experience cycles of oxygen deprivation and restoration (ischemia-reperfusion cycles). These cycles are believed to contribute to cancer microevolution. We will study how these fluctuations affect cancer cells' metabolic flexibility, drug resistance, and invasiveness. Importantly, we aim to identify the (epigenetic) mechanisms that account for the microevolution of metabolic plasticity, drug resistance and invasive potential. We are particularly interested in the epigenetic petrification of HIF1/2/3, Nrf2, and mitochondrial Cx43-dependent signalling axis and its interactions with cell invasiveness pathways regulated by Snail-1, Twist, and Slug activity;
3. **Impact on "Persister" Cells**: Some cancer cells, known as "persister" cells, can survive even the most aggressive treatments. These cells can stay dormant and later cause cancer recurrence. We will examine how ischemia/reperfusion cycles affect these "persister" cells in models of glioblastoma and prostate cancer. We will assess developmental potential of these cells and their progenies in vitro and in vivo.

To achieve these goals, we will use a combination of laboratory-based cancer cell models and animal studies, subjecting cancer cells to escalating doses of chemotherapy under varying oxygen conditions. By analyzing the cells at different stages of their evolution, we will use transcriptomics, proteomics, and metabolomics to map out how cancer cells change over time. We will also use single-cell analysis to pinpoint the specific metabolic and drug-resistance features of individual cancer cells, focusing on the "persister" cells that are most resistant to treatment. This research will establish new methods for studying how cancer cells evolve under combined metabolic and chemotherapy stress, setting a new standard for future research. By working with well-characterized models of glioblastoma and prostate cancer, the findings will be widely applicable and informative for researchers across multiple cancer types. By uncovering the cellular mechanisms that allow cancer cells to shift their metabolism and survive fluctuating oxygen levels, we aim to identify universal sensors/pathways that regulate this process. By understanding how oxygen fluctuations and metabolic changes contribute to dormant "persister" cells' phenotype, our research could help to understand the background of side-effects of current therapies. These findings will potentially pave the way for more effective treatments that reduce the risk of drug resistance and cancer relapse.