Molecular Oncology Programme

Growth Factors, Nutrients and Cancer Group

Overview

Over the last 2 decades, research has primarily focused on understanding the functions of mutated genes in cancer, neglecting the roles of environmental factors that can induce the expression of harmful proteins and tissue damage. These factors pose ongoing challenges, and their mechanisms in causing cancer-related pathologies are largely unknown. Identifying links between environmental stress and cancer progression is crucial for uncovering disease mechanisms and therapeutic targets.

Our laboratory employs genetically engineered mouse models and advanced technologies to investigate mechanisms of diseases associated with environmental stressors. We specifically study conditions related to toxic diets, nutrient imbalances, and sedentary lifestyles, which can lead to obesity and associated disorders, such as diseases from the digestive tract.

Our particular focus lies in diseases affecting the liver (non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma), intestine (colitis and colorectal cancer), and pancreas (diabetes, pancreaticitis and pancreatic cancer). These organs are primarily affected by environmental stressors, including nutrient overload and lack of physical activity, that can cause severe inflammatory conditions. In addition, their functions are interconnected and potentially regulated by the nervous system, through unknown mechanisms. Accordingly, we recently started to explore the intricate relationship between diet and the nervous and immune systems in aggressive cancers, including metastasis, a perspective we plan to emphasise further in the future, within the emerging field of cancer neuroscience and neuroimmunomodulation.

Furthermore, our research encompasses tissue regeneration (intestine and liver), the dysregulation of metabolic pathways in cancer initiation, inflammatory processes, and the initial stages of embryonic development, shedding light on fundamental mechanisms applicable to various diseases. Our goal is to guide the development of novel medicines, with a special focus on potential immunomodulatory therapies for these disorders.

“We continuously strive to generate new and unique preclinical mouse models to elucidate the mechanisms of diseases and capture the complexity of human disorders, with a particular focus on diseases associated with obesity and the digestive tract.”
Using genetically engineered mouse models, along with other model systems and cutting-edge technologies (including cell biology with organoid culture and quantitative imaging, biochemistry, and functional genomics), and human data, our laboratory has dedicated significant effort over the past years to comprehend the molecular, cellular, and pathophysiological mechanisms that connect environmental stresses to disease pathogenesis. In particular, we have studied the mechanisms of diseases associated with obesity and the digestive system, with a focus on liver and intestinal disorders. These conditions often stem from unhealthy diets, nutrient imbalances, and sedentary lifestyles, all of which can contribute to severe inflammatory conditions (see Figure 1). Organs of the digestive system are indeed primarily impacted by environmental stressors but are also physiologically interconnected and influenced through their endocrine and/or paracrine functions. Significant discoveries have been made, and several future research projects are planned as follows:

Mechanisms of obesity

Our groundbreaking work has uncovered the mechanisms behind the inflammatory properties of nutrients and their connection to various disorders. Our recent research has linked inflammation, particularly IL-17A, to obesity and autoimmune disorders, connecting them to hepatitis and liver disease-induced hepatocellular carcinoma. Our findings have gained significant attention from pharmaceutical companies exploring IL-17A blockers as potential treatments for these disorders. Our ongoing research aims to further understand how nutrients can be inflammatory by themselves leading to obesity. Additionally, we will dedicate special efforts to identify the specific inflammatory cells responsible for obesity and its associated metabolic disorders.

Diet, nutrients and cancer

We discussed in an extensive review how various diets could impact cancer development. This suggests that nutritional interventions could be beneficial for both the prevention and treatment of cancer.

Mechanisms of liver cancer progression

Environmental stress, nutrient overload and toxic diet can lead to chronic liver diseases, including cirrhosis, which may progress to hepatocellular carcinoma (HCC). To comprehend the influence of cirrhosis on HCC development, our work focuses on studying the mechanobiology of liver tissue at the molecular, cellular, and tissue levels. This involves investigating and genetically manipulating mice to apprehend the mechanical forces within and between various liver cells, as well as their interactions with microenvironments. Mathematical models and bioinformatics analyses will be used to complement our studies, with the ultimate goal of understanding the progression from an injured and diseased liver to a cancerous tissue.

Cell dormancy in HCC relapse

Despite numerous therapeutic strategies, cancer relapse is common, occurring months to years after treatment. Tumour relapse is thought to be driven by dormant, non- or slow-cycling resistant cells, yet conclusive proof-of-concept studies are lacking. Our laboratory aims to address this gap by utilising a genetically modified mouse model. We plan to label and track dormant cells to understand their role in HCC recurrence.

Mechanisms of intestinal diseases and colorectal cancer

Colorectal cancer (CRC) is a multi-hit neoplasia originating from APC mutation-induced adenomatous polyps, which progress to malignancy through the acquisition of p53 loss. Our research is focused on comprehending the mechanisms underlying CRC initiation and the transitional mutations leading to the transformation of polyps into malignant carcinomas. Additionally, we are prioritising the investigation of why the majority of colorectal cancers exhibit resistance to immune checkpoint inhibitors, which have proven ineffective in patient treatment.

Mechanisms of totipotency-to pluripotency transition

We are currently elucidating the mechanisms that govern the smooth and precise transition from totipotency to pluripotency, which is a crucial process in embryonic development. This transition generates pluripotent stem cells with the capability to form all cell types.

Structure of the URI prefoldin-like complex

One of our future goals is to determine the functions of the URI prefoldin-like complex by unravelling its structural organisation through advanced techniques such as electron microscopy.