METABOLIC CROSSTALK IN CANCER

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Cancer is a multifactorial disease with widespread effects on patients' health. Cancer cells undergo metabolic rewiring to sustain continued proliferation and to survive in hostile environments. This includes alterations in the uptake and utilization of nutrients and metabolites. As such, the tumour microenvironment is important for metabolite supply to cancer cells and the presence of a tumour affects the normal function of its host organ. In addition, cancer is associated with systemic metabolic changes that can dramatically impact quality of life for patients and their fitness to undergo treatments. Research in our laboratory focuses on metabolic crosstalk between the host and tumours, ultimately aiming to develop new, more efficient therapies.

Implications of the gut microbiome in cancer

Gut microbiome dysbiosis is associated with various malignancies and this has implications for cancer onset, progression and therapy sensitivity. We previously showed that enzymes of tumour-associated bacteria metabolize commonly used anticancer drugs. Depending on drug-specific pharmacology, this results in decreased (e.g. gemcitabine) or increased (e.g. fludarabine) anticancer activity. This argues for careful consideration of the microbiome as a therapy-modulator. In addition, microbial metabolites are emerging as key players in cancer. Using untargeted metabolomics, we recently demonstrated that gut microbiota affect not only the local intestinal metabolic environment but also profoundly affect the blood metabolome (Figure 1).

We study metabolic interactions between microbiota and host cells using preclinical cancer models and patient samples, focusing on how microbial metabolites impact disease onset, progression and sensitivity to therapies. Because of its unique association with the gut microbiome, we have a particular interest in colorectal cancer (CRC). Dietary patterns with reduced fibre intake and high intake of processed food, sugar, fat and red meat affect gut microbial metabolism, and increase an individual's CRC risk. CRC is the second most common cause of cancer-related death worldwide, and there is an urgent need for better prevention strategies and therapies.

Certain gut microbiota produce genotoxic metabolites which affect the host intestine and may therefore contribute to CRC. Colibactin is a well-studied toxin produced by pks$^+$ *Escherichia coli* which induces a characteristic mutational signature. We recently contributed to a collaborative study, reporting how specific bacterial adhesion of pks$^+$ *E. coli* to the host epithelium is critical to exert its genotoxic effects. This highlights the potential value of anti-adhesive therapies to reduce the risk of CRC or to impair disease progression (Jans *et al.*, 2024, *Nature*).

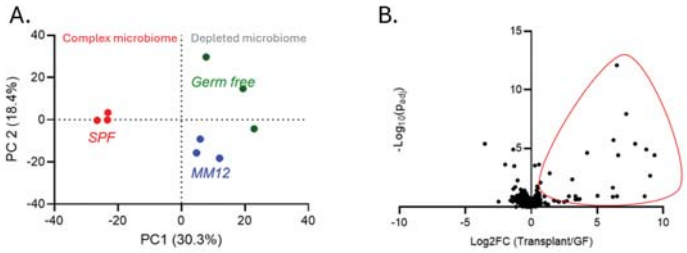

Figure 1. Untargeted metabolomics shows microbiome dependent alterations in blood metabolites
(A) PCA of serum metabolomics of germ-free mice and mice with a minimal (MM12; defined community of 12 bacterial strains) or complex microbiome (SPF).
(B) Volcano plot showing alterations in circulating metabolites in germ-free mice after introduction of a complex microbiome by faecal microbiota transplantation (FMT) with stool of SPF mice. Red shape indicates metabolites that are increased in animals that received an FMT.

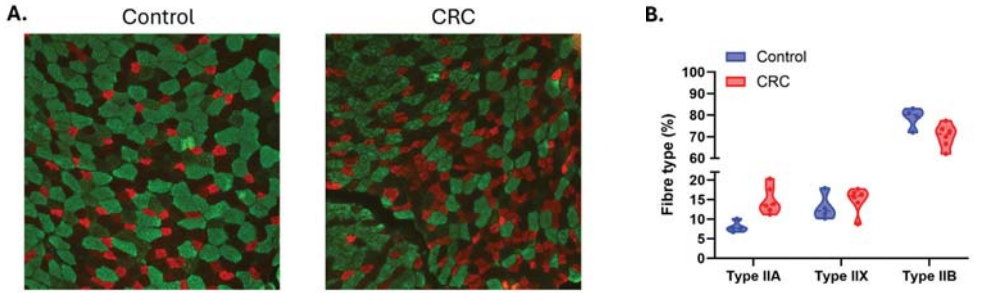

Figure 2. CRC affects muscle myofiber distribution
(A) Immunofluorescence images and (B) myofiber distribution of tibialis anterior muscle sections of control and tumour-bearing mice. Type IIA, 2X and 2B fibres are shown in red, no staining and green, respectively.

Metabolic determinants of cancer-associated cachexia

Cancer cachexia is a wasting syndrome defined by ongoing loss of skeletal muscle mass, with or without loss of fat mass, which cannot be restored by conventional nutritional support. This involves hypercatabolism, systemic inflammation, and ultimately leads to functional impairment. As such, cancer cachexia reduces quality of life, fitness for treatment and associates with increased mortality. Cachexia is part of the common functional decline affecting 80% of advanced cancer patients and is responsible for 30% of cancer deaths. At present, there is no cure and the underlying mechanisms of this debilitating condition are poorly understood.

Studies report that up to fifty percent of CRC patients experience cachexia during their disease. There is a lack of representative preclinical models of CRC-associated cachexia, and this impedes the development of novel, efficacious treatments. We use genetically engineered and orthotopic transplantation mouse models of CRC and study how these recapitulate important features of cachexia. Tumour-bearing animals of selected models show inability to thrive, loss of lean muscle and fat mass and pronounced alterations in tissue composition (Figures 2&3). Our ambition is to harness these models to identify targetable metabolic determinants of cachexia.

Publications listed on page 129

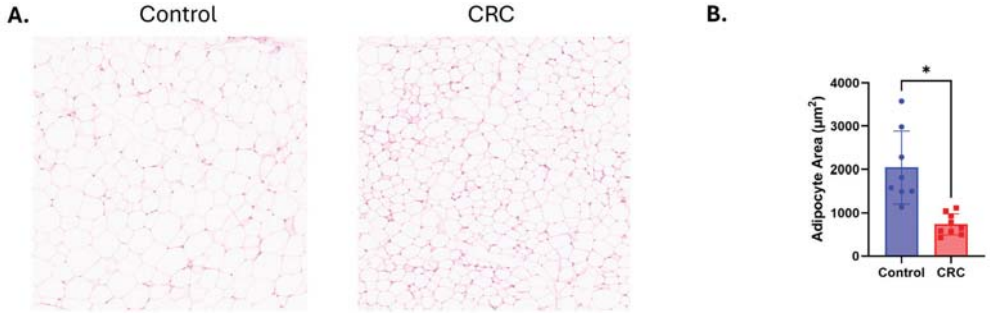

Figure 3. CRC affects adipose tissue architecture
(A) H&E images and (B) adipocyte area of inguinal white adipose tissue of control and tumour-bearing mice.