Mammals, including humans, have evolved in an environment where the ability to efficiently use limiting nutrient sources has been a key survival adaptation that has shaped all our responses to nutrients. Unprecedented nutrient overabundance is in conflict with our cellular and organismal responses, which are best tuned to operate under scarcity. These aberrant responses not only lie at the core of the pathogenesis of the metabolic alterations observed in diabetes, but are also key in cancer and the process of ageing. We use genetically engineered strains of mice as a physiological framework to understand the molecular bridges from elevated nutrient levels to human disease. In particular, we have genetically modified the RagA and RagC GTPases, key players in the sensing of nutrients that activate a master regulator of metabolism, a kinase called mTOR.

Mice with gain-of-function mutations in RagA—therefore unable to sense a drop in nutrient levels—have an increased glycaemia in spite of a normal food intake and decreased adiposity. Furthermore, these mice show intolerance to glucose, which means that when glucose is administered it remains in the circulation, and peripheral organs (such as liver and skeletal muscle) are unable to uptake it. These perturbations are tightly associated with the development of type 2 diabetes. Indeed, when we examined the ability of peripheral tissues to respond to insulin we observed an impaired response to insulin, also known as insulin resistance, which leads to increased levels of glucose in circulation. We are currently characterising other metabolic imbalances observed in these mice and are performing a genetic dissection of these alterations by deregulating nutrient sensing in an organ-specific manner.

"By means of novel strains of mice with deregulated nutrient sensing we identified metabolic alterations that drive uncontrolled proliferation of B lymphocytes and nutrient imbalances associated with diabetes."

**OVERVIEW**

In the Metabolism and Cell Signalling Lab, we study the interplay between nutrients, metabolism and cancer. The alarming increase of overweight and obesity over the last decades and the epidemiological links between elevated nutrient levels and human disease calls for a better understanding of the molecular underpinnings of these connections. Conversely, limiting nutrient intake to an extent that does not cause malnutrition is not only protective against diabetes, but also prevents cancer development and delays ageing in most multicellular species by mechanisms that are poorly understood. In the lab, we combine mouse genetics and cell biological tools to gain insight into the cellular processes that become corrupted upon nutrient overabundance, aiming to conceive therapeutic interventions targeting these processes in the context of cancer and the process of ageing.