In the Metabolism and Cell Signalling Lab we study the interplay of nutrients, metabolism and cancer. Every cell in the organism integrates signals emanating from the intracellular nutrients and from the nutritional state of the organism as a whole. Integration of cellular and systemic nutrient abundance cues is key for adequate cellular and organismal functions, and importantly, the components of these signalling cascades are generally corrupted in cancer cells. Together with genetic mutations, environmental perturbations, such as those occurring in obesity, affect the cellular signalling cascades that control the fluctuations in nutrient levels to satiate the need for growth and proliferation, but these alterations also impose exploitable vulnerabilities.

A large fraction of tumours hijacks the normal responses to the fluctuations in nutrient levels to satiate the need for growth and proliferation, but these alterations also impose exploitable vulnerabilities.

**OVERVIEW**

**RESEARCH HIGHLIGHTS**

**Nutrient signalling in B cell lymphoma**

One of the most rapid proliferation bursts in mammalian cells is that of B lymphocytes upon encountering certain pathogens or antigens. This proliferation suddenly multiplies the energetic and metabolic demands of the activated B cell and, accordingly, precise nutrient sensing and signalling are key to successfully accomplish the energetically onerous rounds of growth and division. Recently, components of the Rag GTPase pathway, a key nutrient signalling pathway that enables the anabolic capacity of the cell for rapid proliferation, were found mutated in follicular lymphoma, an incurable B lymphocyte tumour. By means of novel strains of mice that express mutant variants of the RagC GTPase, we found that these mutations drive B cell activation and development of lymphomas, but underlie an exquisite sensitivity to pharmacological inhibition of the mTORC1 pathway (FIGURE A). Such treatment may be particularly efficacious for 1 out of 6 follicular lymphoma patients with RagC mutations, and also for patients without genetic mutations but with functional deregulation in the nutrient signalling pathway.

**Chronic signalling of elevated nutrients and premature ageing**

In the absence of lymphoma, mice with elevated nutrient signalling show multiple features of premature ageing (FIGURE B), including the thinning of dermal and subcutaneous fat layers of the skin (FIGURE C) and increased senescence-associated β-galactosidase activity in multiple organs (FIGURE D). These mice are the first genetic mammalian system to interrogate the mechanisms that link elevated nutrient signalling to premature ageing. They may contribute to the acceleration of ageing. We are currently investigating the cellular and molecular alterations responsible for this shortening of the life span, and the organ-to-organ crosstalk that may contribute to the acceleration of ageing.

**PUBLICATIONS**


**SPAINISH NATIONAL CANCER RESEARCH CENTRE, CNIO**

**ANNUAL REPORT 2019**

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