METABOLISM AND CELL SIGNALLING JUNIOR GROUP

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OVERVIEW

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 abundance of 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 disease states, such as cancer. Together with genetic mutations, environmental perturbations (such as those occurring in obesity) corrupt the cellular signalling cascades that control the responses to nutrients and hormones. In the lab, we combine mouse genetics and cell biological tools to gain insight into the genetic and environmental corruptions of nutrient signalling cascades, aiming to conceive therapeutic interventions in the context of cancer, obesity and the process of ageing.

"Mouse models with a very mild genetic activation of nutrient signalling foster cancer, autoimmunity, and ageing; this has profound implications when thinking about the consequences of human nutrient overload."

Post-Doctoral Fellow
Melania Zauri (since October)

Graduate Students
Celia de La Calle, Nerea Deleyto, Ana Belén Plata

Technicians
Camino Menéndez (until March) (TS)*, Ana Sagrera (TS)*, Alba Sanz (since April)

Titulado Superior (Advanced Degree)

Students in Practice
Tomislav Kostevc (until June) (*Universidad Pompeu Fabra*), Leyre Marin (since September) (*Universidad Politécnica*)

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 (FL), an incurable B lymphocyte tumour. By means of novel strains of mice that express mutant variants of the RagC GTPase, we found that subtle increases in nutrient signalling unleash activation and proliferation of B cells, suppress cell death and drive the development of FL (FIGURE). These results pave our way towards a novel therapeutic strategy against B cell lymphoma, aimed at targeting its corrupted nutrient signalling. In addition, and surprisingly, this mild increase in the signalling of nutrient abundance in B lymphocytes also drives an autoimmune disease.

Chronic signalling of elevated nutrients and premature ageing

The study of genetically engineered mice expressing a mildly activating form of RagC revealed that, in the absence of lymphoma, these mice suffer from symptoms and pathologies consistent with premature ageing, including a shortened lifespan (FIGURE). While caloric restriction (CR) and other fasting-like regimes are well-known to delay ageing, as is also the case with the pharmacological inhibition of mTOR with rapamycin in mammalian model organisms, this is the first time that a moderate increase in nutrient signalling in mice shows compromised longevity. We are currently investigating the cellular and molecular alterations responsible for this shortening of the life span. ■

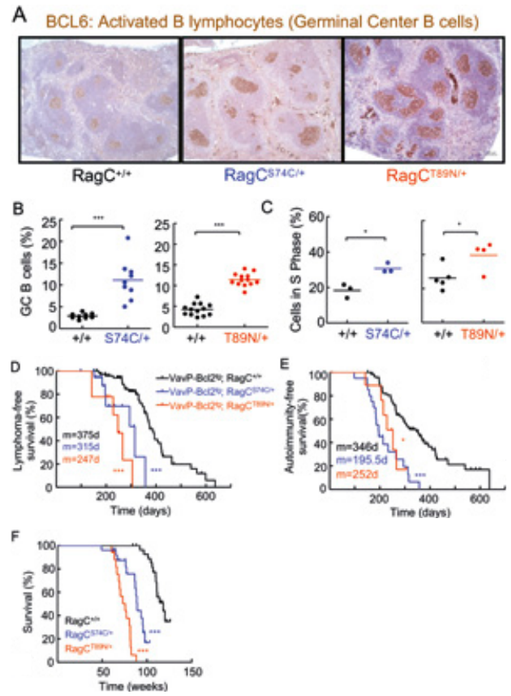

Figure (**A, B & C**) Readouts of enhanced B lymphocyte activation in RagC mutant mice. (**D & E**) Bred to the VavP-BCL2 strain (prone to lymphoma and autoimmunity), RagC mutant mice exhibit accelerated lymphomagenesis and autoimmune disease. (**F**) Lifespan consistent with accelerated ageing of RagC mutant mice.