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.

“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.”