METABOLISM AND CELL SIGNALLING JUNIOR GROUP

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OVERVIEW

In the Metabolism and Cell Signalling Lab we study the links between nutrients, cancer, and ageing. All cells integrate signals emanating from the abundance of intracellular nutrients and from the nutritional state of the entire organism. Integration of these signals is key for adjusting metabolic functions, energy storage and expenditure; and, importantly, the components of these signalling cascades are generally corrupted in cancer and are drivers of the metabolic complications of chronic nutrient overload. Conversely, dietary restriction regimes are extremely efficacious interventions against tumorigenesis and to delay the process of ageing, albeit we still ignore the fundamental molecular underpinnings of such protective effects. 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.

"Our studies support the targeting of nutrient signalling as a novel, efficacious and safe approach against the aberrant metabolism of cancer cells and to combat the process of ageing."

Graduate Students
Celia de la Calle, Lucía de Prado (since September), Nerea Deleyto, Ana Belén Plata

Technicians
Cristina Lebrero (TS)*, Ana Sagrera (TS)*, Alba Sanz

Titulado Superior (Advanced Degree)

Student in Practice
Lucía de Prado (January-June) (*Universidad Autónoma de Madrid*, Madrid, Spain)

Visiting Scientist
Sebastian Thompson (*IMDEA Nanociencia* Institute, Madrid, Spain)

RESEARCH HIGHLIGHTS

To understand the negative impact of chronic nutrient overload in systemic metabolism, and because the liver has a key role in metabolic homeostasis, we generated mice that have chronically high nutrient signalling only in hepatocytes (by liver-specific expression of an active RagA allele: $RagA^{GTP}$). $RagA^{GTP}$ livers exhibited high phosphorylation of mTOR targets (S6K1 and 4EBP1; FIGURE A) and, importantly, the sole activation of RagA in the liver, without altering nutrient intake, impaired glucose homeostasis, as revealed by loss of glucose tolerance (FIGURE B). This result highlights the relevance of a chronic nutrient surplus – liver Rag GTPase signalling axis in metabolic complications of the obesity state.

Studying the connections of nutrients and cancer, we previously found that activating mutations in the gene called RagC (key player, together with RagA, in the signal transduction of cellular nutrient levels) result in a subtype of B cell lymphoma, follicular lymphoma. Thus, a lot of interest to develop pharmacological inhibitors of this nutrient signalling pathway has recently spurred, but these drugs are still to be developed. Thus, to determine both the efficacy and safety of inhibition of nutrient signalling against follicular lymphomas, we undertook a genetic approach: we now generated mice expressing a hypomorphic allele of RagC, and asked whether 1) decreased nutrient signalling could suppress the development of follicular lymphoma; and 2) unanticipated side effects could preclude the use of such inhibitors. Hypomorphic RagC mutant mice ($RagC^{Q119L}$) showed a significant extension of survival when follicular lymphomas were induced (FIGURE C), and an exhaustive analysis of potential side effects revealed that B cells were selectively affected (FIGURE D), importantly, without detectable undesirable trade-offs in other organs (not shown). These results support both the efficacy and safety of nutrient signalling inhibitors in the treatment of B cell neoplasms. ■

FIGURE (**A**) Increased nutrient signalling - mTOR activity in $RagA^{GTP}$ liver samples. (**B**) Glucose intolerance in liver-specific Rag^{GTP} mice. (**C**) Endogenous expression of $RagC^{Q119L}$ protects against lymphomas induced by Bcl2. (**D**) Activation of B cells (Germinal Centre stain in brown) is impaired in $RagA^{Q119L/+}$ mice.

PUBLICATIONS

- Pae J, Ersching J, Castro TBR, Schips M, Mesin L, Allon SJ, Ordovas-Montanes J, Mlynarczyk C, Melnick A, Efeyan A, Shalek AK, Meyer-Hermann M, Victora GD (2020). Cyclin D3 drives inertial cell cycling in dark zone germinal center B cells. *J Exp Med*. PMID: 33332554.
- Ramón Y Cajal S, Sancho P, Soucek L, Peinado H, Abad M, Valiente M, Efeyan A, Pardo J, Quesada V, Jimeno J, Duque PM, Antón A, Varela I, Schuhmacher AJ (2020). A spotlight on cancer researchers in Spain: new paradigms and disruptive ideas. *Clin Transl Oncol* 22, 798-801.
- Spicer G, Gutierrez-Erlandsson S, Bernard H, Adam A, Efeyan A, Thompson S (2020). Harnessing DNA for nanothermometry. *J Biophotonics*. PMID: 33128802.

PUBLICATIONS AT OTHER INSTITUTIONS

- Do MH, Wang X, Zhang X, Chou C, Nixon BG, Capistrano KJ, Peng M, Efeyan A, Sabatini DM, Li MO (2020). Nutrient mTORC1 signaling underpins regulatory T cell control of immune tolerance. *J Exp Med* 217, e20190848.

AWARDS AND RECOGNITION

- Alejo Efeyan: EMBO Young Investigator Award, European Molecular Biology Organization.
- Ana Ortega was awarded a *Ramon y Cajal* Research Contract (*MCI*), Spain.
- Lucia De Prado received an *FPI* PhD Student Fellowship (*MCI*), Spain.