METABOLISM AND CELL SIGNALLING JUNIOR GROUP

Alejo Efeyan
Junior Group Leader

Staff Scientists
Bárbara Martínez, Ana Ortega (until August)

Graduate Students
Celia de la Calle (until March), Lucía De Prado, Nerea Deleyto, Ana Belén Plata, Elena Sánchez (since March)

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

Titulado Superior (Advanced Degree)

Student in Practice
Elena Fernández (since November) (*Universidad Complutense de Madrid*, Madrid, Spain)

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

OVERVIEW

In the Metabolism & Cell Signalling Lab we study the links between nutrients, cancer and aging. All our 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, as well as for 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. 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.

"We are beginning to understand why and how excessive nutrient levels deregulate cellular metabolism, pinpointing actionable links between nutrients, cancer and the process of ageing."

RESEARCH HIGHLIGHTS

Cellular nutrients, such as amino acids and glucose, and systemic metabolic hormones, such as insulin, are key mediators of cellular metabolism by control of the mTORC1 kinase, a master switch for most anabolic processes in the cell. We and others have previously dissected the impact of deregulated nutrient signalling (N-ON mice, mimicking a chronic increase in intracellular nutrient levels) and deregulated hormonal signalling (H-ON mice, mimicking chronically high levels of insulin signalling) in the mouse liver. While suppression of either input resulted important to unleash the metabolism of the fasted state, chronic nutrient surplus in humans typically causes synchronous activation of both nutrient and hormonal signalling. Thus, we generated a mouse strain harbouring deregulated nutrient and hormonal signalling to mTORC1 in hepatocytes. Genetic activation of either nutrient or hormonal signalling on their own resulted in high mTORC1 activity, regardless of the fed/fasted state of the mice. To our surprise, simultaneous activation of both nutrient and hormonal signalling (N+H-ON) minimally increased mTORC1 signalling (FIGURE 1A). In contrast to this mild increase, the livers of the N+H-ON mice showed multiple evidence of a synergic interaction between nutrient and hormonal signalling. These include a large increase in liver size, accumulation of several markers of liver damage, and aberrant bile acid and bilirubin metabolism (FIGURE 1B, C and D). In addition, N+H-ON mice experience rapid development of liver carcinomas, starting at 15 weeks of age (Figure 1E). We are currently determining whether such synergism, which failed to be explained exclusively by the modest increase in the activation of mTORC1, is caused by a) nutrients and hormonal signalling differentially activating downstream targets of mTORC1, or b) mTORC1-dependent and -independent functions of nutrient and/or hormonal signalling. ■

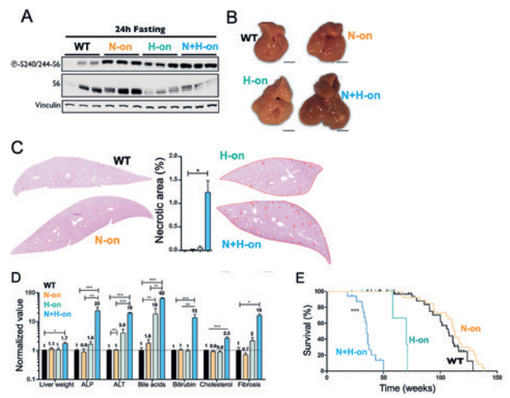

FIGURE 1 (**A**) Modest increase in mTORC1 activity (compared with N-on and H-on, seen by phospho-S6) in livers from fasted N+H-ON mice. (**B**) Micrographs of enlarged N+H-ON livers. (**C & D**) Multiple readouts of liver damage in livers from N+H-ON mice. (**E**) Premature death of N+H-ON mice due to liver carcinomas.

PUBLICATIONS

- de la Calle Arregui C, Plata-Gómez AB, Deleyto-Seldas N, García F, Ortega-Molina A, Abril-Garrido J, Rodriguez E, Nemazanyy I, Tribouillard L, de Martino A, Caleiras E, Campos-Olivas R, Mulero F, Laplante M, Muñoz J, Pende M, Sabio G, Sabatini DM, Efeyan A (2021). Limited survival and impaired hepatic fasting metabolism in mice with constitutive Rag GTPase signalling. *Nat Commun* 12, 3660.
- 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 (2021). Cyclin D3 drives inertial cell cycling in dark zone germinal center B cells. *J Exp Med* 218, e20201699.
- Ortega-Molina A, Lebrero-Fernández C, Sanz A, Deleyto-Seldas N, Plata-Gómez AB, Menéndez C, Graña-Castro O, Caleiras E, Efeyan A (2021). Inhibition of Rag GTPase signaling in mice suppresses B cell responses and lymphomagenesis with minimal detrimental trade-offs. *Cell Rep* 36, 109372.
- Martinez-Pastor B, Silveira GG, Clarke TL, Chung D, Gu Y, Cosentino C, Davidow LS, Mata G, Hassanieh S, Salsman J, Ciccia A, Bae N, Bedford MT, Megias D, Rubin LL, Efeyan A, Dellaire G, Mostoslavsky R (2021). Assessing kinetics and recruitment of DNA repair factors using high content screens. *Cell Rep* 37, 110176.
- Deleyto-Seldas N, Efeyan A (2021). The mTOR-autophagy axis and the control of metabolism. *Front Cell Dev Biol* 9, 655731.
- Spicer G, Gutierrez-Erlandsson S, Matesanz R, Bernard H, Adam AP, Efeyan A, Thompson S (2021). Harnessing DNA for nanothermometry. *J Biothonics* 14, e202000341.
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- Ortega-Molina A, Efeyan A (2021). From mouse genetics to targeting the Rag GTPase pathway. *Mol Cell Oncol* 8, 1979370.

AWARDS AND RECOGNITION

- Alejo Efeyan:
  - EMBO Young Investigator, European Molecular Biology Organization.
  - *Leonardo* Grant for Researchers and Cultural Creators, *BBVA* Foundation, Spain.
  - Keynote Speaker, Keynote Lecture, 2nd "TOR de France" 2021 meeting, France.
- Elena Sanchez Garcia was selected for an *FPI* PhD Student Fellowship (*MCI*), Spain.