METABOLISM AND CELL SIGNALLING JUNIOR GROUP

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OVERVIEW

In the Metabolism & Cell Signalling Lab we study the links between nutrients, cancer and ageing. 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 how excessive nutrient levels deregulate cellular metabolism as well as cell-to-cell and interorgan communication, contributing to tumour development and the process of ageing."

Technicians
Alba Sanz

Titulado Superior (Advanced Degree)

Students in Practice
Elena Fernández (until June)

(Master's Thesis, *UCM*, Madrid, Spain), Paula Seghers (since Oct.) (Undergraduate Student, *Universidad Politécnica de Madrid*, Spain), Andrea Pinilla (since Nov.) (Undergraduate Student *Universidad Industrial de Santander*, Spain),

Camila Silva (until Aug.) (Master's Thesis, *UAM*, Madrid, Spain)

Visiting Scientists
Cristina Lebrero and Ana Ortega (*Centro de Biología Molecular Severo Ochoa*, *CBMSO*, Madrid, Spain),

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

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 genetic activation of either input resulted important to unleash the metabolism of the fasted state, chronic nutrient surplus in humans typically causes synchronous, concomitant activation of nutrient and hormonal signalling. Thus, we generated a mouse strain harbouring deregulated nutrient and hormonal signalling to mTORC1 in hepatocytes (N+H-ON). 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) resulted in a minimal additional increase in mTORC1 signalling, as compared to either H-ON or N-ON livers (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). Pharmacological suppression of mTORC1 by rapamycin (FIGURE 1F) dramatically delays tumorigenesis and corrects metabolic defects, while chronic restriction in caloric intake (diminishing circulating nutrients and circulating growth factors) fails to correct the phenotype (FIGURE 1G). These findings support a critical role for nutrient and hormonal signalling through mTORC1 in the beneficial effects of dietary restriction. ■

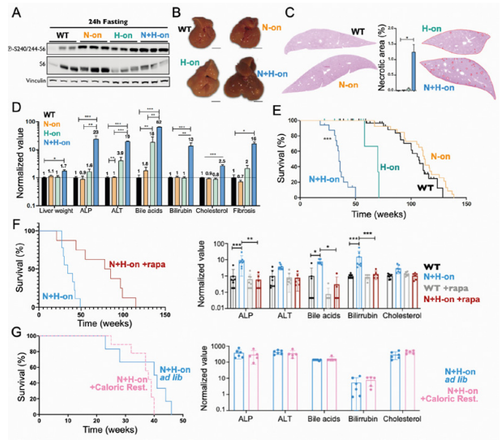

FIGURE 1 (**A**) Increase in mTORC1 activity (seen by phospho-S6) in livers from fasted N+H-ON mice. (**B**) Enlarged N+H-ON livers. (**C & D**) Readouts of liver damage in livers from N+H-ON mice. (**E**) Premature death of N+H-ON mice due to liver carcinomas. Rapamycin (**F**) corrects survival and readouts of liver damage in N+HON mice, but caloric restriction (**G**) does not.

PUBLICATIONS

- Fernández LP*, Deleyto-Seldas N*, Colmenarejo G, Sanz A, Wagner S, Plata-Gómez AB, Gómez-Patiño M, Molina S, Espinosa-Salinas I, Aguilar-Aguilar E, Ortega S, Graña-Castro O, Loria-Kohen V, Fernández-Marcos PJ, Alejo Efeyan A# and Ana Ramírez de Molina# (2022). Folliculin-interacting protein FNIP2 impacts on overweight and obesity through a polymorphism in a conserved 3' untranslated region. (*) Co-first authors. (#) Co-last and Co-corresponding authors. *Genome Biology* 23, 230.
- Vivas-García Y, Efeyan A (2022). The metabolic plasticity of B cells. *Front Mol Biosci* 9, 991188.
- Ong YT, Andrade J, Armbruster M, Shi C, Castro M, Costa ASH, Sugino T, Eelen G, Zimmermann B, Wilhelm K, Lim J, Watanabe S, Guenther S, Schneider A, Zanconato F, Kaulich M, Pan D, Braun T, Gerhardt H, Efeyan A, Carmeliet P, Piccolo S, Grosso AR, Potente M (2022). A YAP/TAZ-TEAD signalling module links endothelial nutrient acquisition to angiogenic growth. *Nat Metab* 4, 672-682.
- Barradas M, Plaza A, Colmenarejo G, Lázaro I, Costa-Machado LF, Martín-Hernández R, Micó V, López-Aceituno JL, Herranz J, Pantoja C, Tejero H, Diaz-Ruiz A, Al-Shahrour F, Daimiel L, Loria-Kohen V, Ramirez de Molina A, Efeyan A, Serrano M, Pozo OJ, Sala-Vila A, Fernandez-Marcos PJ (2022). Fatty acids homeostasis during fasting predicts protection from chemotherapy toxicity. *Nat Commun* 13, 5677.
- Di Lorenzo G, Iavarone F, Maddaluno M, Plata-Gómez AB, Aureli S, Quezada Meza CP, Cinque L, Palma A, Reggio A, Cirillo C, Sacco F, Stolz A, Napolitano G, Marin O, Pinna LA, Ruzzene M, Limongelli V, Efeyan A, Grumati P, Settembre C (2022). Phosphorylation of FAM134C by CK2 controls starvation-induced ER-phagy. *Sci Adv* 8, eabo1215.

AWARDS AND RECOGNITION

- Yurena Vivas was recipient of a *Fundación Domingo Martínez* CNIO Friends Fellowship.
- Ana Belen Plata received an Award for best Selected Short Talk in the EMBO Meeting on Energy Balance in Metabolic Disorders, October 2022, Torremolinos, Spain.
- Nerea Deleyto, excellent *Cum Laude* thesis defence and 'Outstanding PhD Thesis' award in the field of molecular biosciences, Autonomous University of Madrid, Spain.