GROWTH FACTORS, NUTRIENTS AND CANCER JUNIOR GROUP

Junior Group Leader
Nabil Djouder

Post-Doctoral Fellow
Hugo Bernard

OVERVIEW

The incidence of metabolic disease and cancer has increased to epidemic proportions, possibly due to hypernutrition and a more sedentary life style with less energy expenditure. Our laboratory studies the molecular mechanisms of disease associated with the deregulation of growth factor and nutrient signalling pathways. Identifying new components of the growth factor and nutrient cascades, as well as elucidating their role and functions *in vivo* by generating new genetically engineered mouse models (GEMMs), will help us to better understand how nutrient overload can induce metabolic disorders and cancer.

Thus, using cell biological and biochemical techniques, combined with *in vivo* mouse models and human data, our lab devotes efforts to the development of innovative mechanism-based therapeutics to potentially treat metabolic dysfunctions and cancer.

"Our research focus is to generate mouse models recapitulating human disease associated to nutrient overload in order to guide research perspectives and applications."

Research concepts from our laboratory

- → Metabolic alterations initiate tumorigenesis prior to genomic instability.
- → Inhibition of de novo NAD+ synthesis functions a non-oncogene addiction pathway in liver and pancreas cancer.
- → Oncogene-induced NAD+ depletion in DNA damage.

Graduate Students
Marta Brandt, Almudena Chaves, Amanda Garrido, Ana Teijeiro

Technician
Eva Martínez (since March) (PEJ)*

Student In Practice
Tatiana Grazioso (*Universidad Complutense de Madrid*)

**Plan de Empleo Joven* (Youth Employment Plan)

RESEARCH HIGHLIGHTS

We have a particular interest in studying gastrointestinal track disorders. Our work in this area focuses on metabolic organs such as the liver, intestine and pancreas, as these 3 organs are physiologically interconnected and influenced through their exocrine and/or endocrine functions and microbiota (FIGURE). Our task is thus to generate new mouse models mimicking human disease and to study mechanisms and events iniating disease development. We also use patient-derived xenograft models and organoids to translate our findings into clinical perspectives. Guided by experimental mouse models combined with the use of human data, we aim to provide a comprehensive study for a rational approach towards the development of novel mechanism-based therapeutics to prevent, ameliorate and treat diseases.

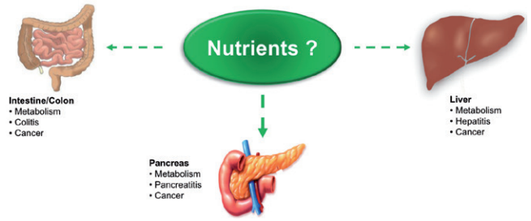

Figure Milestones in growth factors and nutrients research in my laboratory. The scheme illustrates our present and future research. Time and effort are dedicated to better understand how misregulation in growth factor and nutrient signalling pathways can lead to gastrointestinal track disease development.

Identifying new components of growth factor and nutrient signalling cascades

We identified 2 components of the growth factor and nutrient signalling cascades regulating the mTORC1 pathway: Uncoventional prefoldin RPB5 interactor (URI) (Djouder *et al.*, 2007) and Microspherule protein 1 (MCRS1) (Fawal *et al.*, 2015).

Uncoventional prefoldin RPB5 interactor (URI): URI is member of the R2TP/URI-prefoldin like complex, which contains not only prefoldin subunits but also RNA polymerase binding subunit (RPB5), ATPases/helicases RuvB-like protein 2 (RUVBL2, also known as 48- kDa TATA box-binding protein-interacting [TIP48] or reptin) and RuvB-like protein 1 (RUVBL1, also known as 49-kDa TATA box-binding protein-interacting [TIP49] or pontin) and co-chaperones such as heat shock protein 90 (HSP90). URI is a downstream component of the growth factor and nutrient signalling pathways. It is phosphorylated by S6K1 and has an oncogenic role in ovarian cancer and HCC development.

Microspherule protein 1 (MCRS1): MCRS1, in an amino acid-dependent manner, maintains Rheb at lysosome surfaces, connecting Rheb to mTORC1. MCRS1 depletion promotes Rheb/TSC2 interaction, rendering Rheb inactive and delocalising it from lysosomes to recycling endocytic vesicles, leading to mTORC1 inactivation.

Generation of genetically engineered mouse models

- → 2 conditional knock-outs (URI and MCRS1 loss-of-function).
- → 3 knock-ins (over-expression of URI (wt), URI (S371A) and MCRS1).

Research achievements

- → Inflammatory cues and nutrient overloads up-regulate hepatic URI.
- → URI is an oncogene initiating NASH and HCC.
- → Nicotinamide riboside to prevent liver and pancreas cancers.
- → MCRS1 activates mTORC1 in response to amino acids.
- → URI is the first identified OGT regulator in response to glucose fluctuations.
- → Glucose depletion can induce oncogenic signals through OGT/c-MYC regulation.
- → c-MYC is oncogenic and tumour suppressive depending on nutrient availability. ■

PUBLICATIONS

- *Burén* S, Gomes AL, Fawal MA, Teijeiro A, Yilmaz M, Tummala KS, Perez M, Rodriguez-Justo M, Campos-Olivas R, Megias D, Djouder N (2016). Regulation of OGT by URI in Response to Glucose Confers c-MYC-Dependent Survival Mechanisms. *Cancer Cell* 30, 290-307.
- Gomes AL, Teijeiro A, Burén S, Tummala KS, Yilmaz M, Waisman A, Theurillat JP, Perna C, Djouder N (2016). Metabolic Inflammation-Associated IL17A Causes Non Alcoholic Steatohepatitis and Hepatocellular Carcinoma Development. *Cancer Cell* 30, 161-175.
- Djouder N (2016). Adaptive survival mechanism to glucose restrictions. *Oncoscience* 3, 302-303.
- Garrido A, Brandt M, Djouder N (2016). Transport to Rhebpress Activity. *Small GTPases* 7, 12-15.