GROWTH FACTORS, NUTRIENTS AND CANCER JUNIOR GROUP

Junior Group Leader
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Research concepts from our laboratory
- Metabolic alterations initiate tumorigenesis prior to genomic instability.
- Inhibition of de novo NAD+ synthesis functions as a non-oncogene addiction pathway in liver and pancreas cancer.
- Oncogene-induced NAD+ depletion in DNA damage.

OVERVIEW

The incidence of metabolic disease and cancer has increased to epidemic proportions, possibly due to hypernutrition and a more sedentary lifestyle 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 in order to guide research perspectives to nutrient overload in order to guide research perspectives.

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

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RESEARCH HIGHLIGHTS

We have a particular interest in studying gastrointestinal tract 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 initiating 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.

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: Unconditional prefoldin PRPS interactor (URI) (Djouder et al., 2007) and Microspherule protein 1 (MCRS1) (Fawal et al., 2015).

Unconditional prefoldin PRPS interactor (URI): URI is a member of the R2TP/URI-prefoldin like complex, which contains not only prefoldin subunits but also RNA polymerase binding subunit (PRPS), 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 cancers.

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 de-localising it from lysosomes to recycling endocytic vesicles, leading to mTORC1 inactivation.

Publications

Spanish National Cancer Research Centre
CNIO
CANCER CELL BIOLOGY PROGRAMME
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Student in Practice
Tatiana Gavrais (Universidade Complutense de Madrid)
Yván de Grano (Junior Youth Employment Plan)

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.