

GROWTH FACTORS, NUTRIENTS AND CANCER GROUP

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OVERVIEW

Research over the last 20 years has focused mainly on understanding the functions and roles of newly discovered mutated genes in the development of cancer and associated diseases. However, it remains largely unknown how environmental factors can alter the host’s eukaryotic epithelial cells to cause various pathologies that can progress to cancer. Identifying likely causal links between environmental stresses and diseases that progress to cancer will help to elucidate mechanisms of disease and to identify targets with preventive and therapeutic value for treating frequent lethal human disorders with increased worldwide incidence and unmet medical needs.

In our laboratory, we focus on understanding the mechanisms of diseases associated with the ingestion of toxic diets or nutrient overload that can lead to obesity and associated disorders, including diseases of the digestive system. We have a particular interest in liver disease, including non-alcoholic steatohepatitis and cirrhosis, and their progression to hepatocellular carcinoma (HCC), one of the most aggressive and lethal liver cancers. We also study intestinal disorders that can lead to colorectal cancer. Our ultimate goal is to guide the design of new medicines.

“We continuously strive to generate new and unique preclinical mouse models to elucidate the mechanisms of diseases and capture the complexity of human disorders, with a particular focus on diseases associated with obesity and the digestive tract.”

RESEARCH HIGHLIGHTS

Our research interest is mainly driven by the discovery of two components initially identified in our laboratory to be downstream targets of the growth factor and nutrient signalling cascades: the **URI (Unconventional prefoldin RPB5 Interactor)** and **MCRS1 (Microspherule protein 1)** proteins. URI and MCRS1 are respectively part of 2 independent protein complexes: the **URI prefoldin-like** and the **non-specific lethal (NSL) complexes**. Importantly, URI and MCRS1 expression turned out to be also regulated by environmental factors (nutrients, radiations, bacteria, viruses, etc.), which may compromise their functions and activate pleiotropic circuits supporting complex cell signalling networks, thereby provoking severe outcomes.

Using genetically engineered mouse models generated in our lab for URI and MCRS1 gain- and loss-of-functions, combined with other model systems and cutting-edge technologies and human data, our laboratory has devoted substantial efforts over the last years to determine the molecular, cellular, and pathophysiological mechanisms that link environmental stresses to obesity and disease pathogenesis of the digestive system, with the aim of developing more effective therapeutic strategies. In particular, we have focused on diseases associated to the liver, intestine, and pancreas, as these organs are primarily impacted by environmental stressors, including nutrient overload, but are also physiologically interconnected through their exocrine and/or endocrine functions. In this regard, the following highlights summarise our major achievements during 2022:

- The liver has an exceptional ability to regenerate itself to maintain tissue homeostasis, but this process can be impacted by stress signals, potentially leading to liver cancer. We have reviewed the mechanisms of hepatic regeneration under homeostasis or upon injury (Rigual *et al.*, *Trends Cancer*, 2022).
- Additionally, we have developed a novel murine model that mimics the pathological features of cirrhosis, and uncovered a new function of MCRS1 in regulating histone acetylation, maintaining gene expression and liver homeostasis. The loss of MCRS1 in hepatocytes activates the bile acid/FXR axis in liver fibroblasts, a significant event in cirrhosis development, with important implications for treatment (Garrido *et al.*, *J Hepatol*, 2022).
- We have also determined the mechanisms of regeneration of the intestinal epithelium and demonstrated that URI+ cells play a crucial role in maintaining intestinal homeostasis by controlling R-spondin 1 levels, supporting Lgr5^{high} intestinal stem cell proliferation. These findings highlight the unexpected role of transit-amplifying cells in controlling Lgr5^{high} intestinal stem cell proliferation (Chaves-Peréz *et al.*, *J Exp Med*, 2022).

Future work

Obesity is becoming one of the most increasingly growing risk factors for liver and intestinal disorders, including cancer. By employing multi- and inter-disciplinary approaches, including the use of preclinical mouse models generated in our laboratory combined with human data, we will continue to determine the mechanisms of diseases associated with obesity. In particular, with a special focus on diseases of the digestive system, we aim to: find out what goes wrong in diseased and cancerous tissues; understand how organs can regenerate; potentially engineer new tissues; and, if regeneration goes awry, determine how it contributes to cancer. Our ultimate goal is to help guide the design of new medicines against obesity and its associated disorders (FIGURE 1). ■

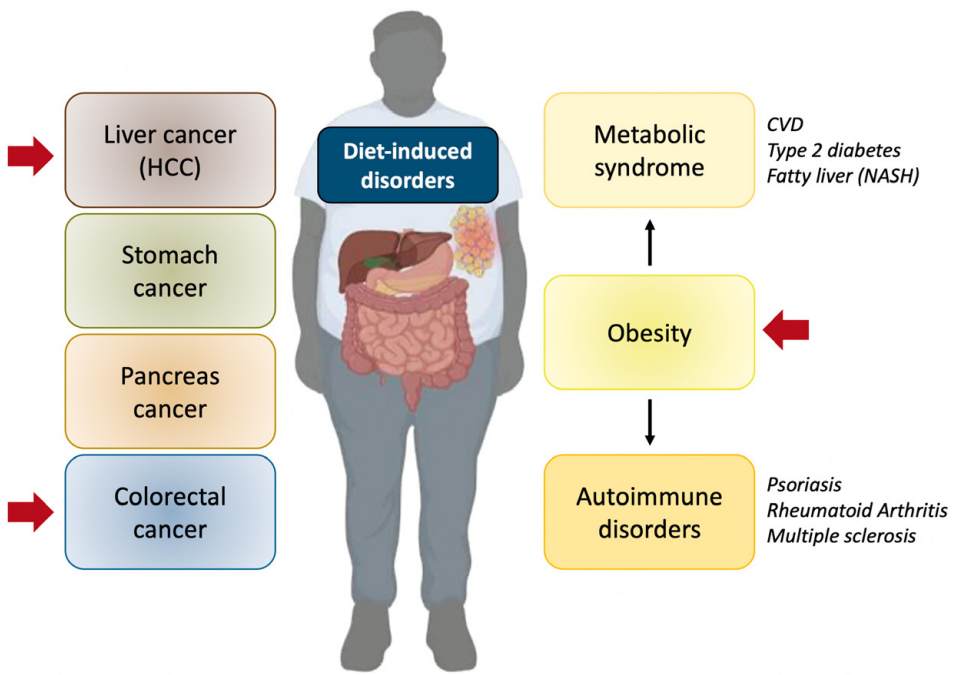


FIGURE 1 Representation of some of our research directions. Obesity is one of the most increasingly growing risk factors for liver and intestinal disorders, including cancer. By employing multi- and inter-disciplinary approaches, including the use of preclinical mouse models generated in our lab combined with human data, we aim to: find out what goes wrong in diseased tissues; understand how organs can regenerate; potentially engineer new tissues; and, if regeneration goes awry, determine how it contributes to disorders. Our final goal is to guide the design of new medicines against obesity and its associated disorders, including metabolic, liver and intestinal diseases. CVD: cardiovascular diseases. NASH: Non-alcoholic steatohepatitis.

PUBLICATIONS

Chaves-Pérez A, Santos-de-Frutos K, De la Rosa S, Herranz-Montoya I, Perna C, Djouder N (2022). Transit-amplifying cells control R-spondins in the mouse crypt to modulate intestinal stem cell proliferation. *J Exp Med* 219, e20212405.

Garrido A, Kim E, Teijeiro A, Sánchez Sánchez P, Gallo R, Nair A, Matamala Montoya M, Perna C, Vicent GP, Muñoz J, Campos-Olivas R, Melms JC, Izar B, Schwabe RF, Djouder N (2022). Histone acetylation of bile acid transporter genes plays a critical role in liver cirrhosis. *J Hepatol* 76, 850-861.

Rigual MDM, Sánchez Sánchez P, Djouder N (2022). Is liver regeneration key in hepatocellular carcinoma development? *Trends Cancer*. PMID: 36347768.

AWARDS AND RECOGNITION

- BBVA grant Award in Biomedicine 2022, Spain.
- Spanish national grant from the Ministry of Science and Innovation (*Retos* 2022).
- Member of the European Association for the Study of Diabetes (EASD).