GROWTH FACTORS, NUTRIENTS AND CANCER GROUP

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OVERVIEW

Our laboratory devotes effort to understand the molecular mechanisms linking environmental stresses to disease pathogenesis. Research in the last decade has focused mainly on understanding the functions and roles of newly discovered mutated genes in the development of cancer and associated disorders. However, the exposure to environmental factors, through the regulation and expression of virulent eukaryotic proteins, has often been an ignored permanent challenge for an organism.

Based on the integration of experimental mouse models, combined with the use of state-of-the art technologies and human data, we aim to provide a comprehensive study for a rational approach towards the development of novel mechanism-based therapies to prevent and treat diseases.

"We aim to understand mechanisms of disease by generating new mouse models that recapitulate pathological features of human syndromes in order to guide early prevention and treatment."

RESEARCH HIGHLIGHTS

Poor diets (under-nutrition, micronutrient deficiencies, over-nutrition, high-fat and low-fibre diets, etc.), alcohol consumption, ionising radiation, bacteria and virus infections, etc., are risk and pathogenic factors for disease development. How these environmental factors can alter the host's eukaryotic epithelial cells to cause various pathologies, potentially progressing to cancer, remains largely unknown. Finding new genes affected by environmental stressors, and understanding their functions and role in disease development, may pave the way for future therapies. In our lab, we therefore focus on the identification and understanding of mechanisms of likely causal links between environmental stresses and pathologies in order to develop new preventive and therapeutic options.

Unconventional prefoldin RPB5 interactor (URI)

The responses of eukaryotic cells to a variety of environmental stresses involve changes in the expression profile of molecular chaperones. These chaperones are essential to engage protective mechanisms to ensure cellular and protein homeostasis caused by injurious environmental stimuli. In our lab, we focus on studying the roles and functions of the unconventional prefoldin RPB5 interactor (URI), a member of the prefoldin chaperone family, whose expression is modulated by various pathogenic environmental factors. Principally, lessons from genetically engineered URI gain- and loss-of-function mouse models taught us that high URI expression may lead to uncontrolled protein substrate regulation, and decreased URI may induce over-functioning of protein clients – both conditions may lead to various pathologies.

Microspherule protein 1 (MCRS1)

We also recently discovered MCRS1 (Microspherule protein 1) with scaffolding activities regulating mTORC1 activity in response to amino acids.

Mechanisms of gastrointestinal tract disease

Our interest is therefore driven by the discovery of URI and MCRS1 proteins, both regulated by environmental stressors, which may compromise their functions and activate pleiotropic circuits supporting non-oncogene addiction functions and dependence, provoking severe outcomes. Using URI and MCRS1 mouse models generated in our lab, combined with cutting-edge technologies, we are studying mechanisms of disease predominantly associated to the gastrointestinal tract, often related to pathogenic environmental factors (ionising radiation, bacteria, viruses and poor diet), with the objective of developing new strategies for treatment. Our research is mainly focussed on the study of intestinal, gastric, pancreatic and liver disorders (FIGURE).

In this regard, we made the following discoveries:

- → Inflammatory cues up-regulate hepatic URI, which inhibits *de novo* NAD^+ synthesis causing DNA damage and thereby initiating hepatocellular carcinoma (HCC). Replenishing the pools of NAD^+ by using nicotinamide riboside prevents HCC. Our data suggest that metabolic alterations initiate tumorigenesis prior to genomic instability.
- → Nutrient overload increases hepatic URI, which results in NAD^+ deficit-induced DNA damage that activates metabolic inflammation-associated IL-17A to cause non-alcoholic steatohepatitis (NASH) and HCC. Boosting NAD^+ by using nicotinamide riboside or blocking IL-17A axis prevents NASH and HCC.
- → Hepatocellular carcinoma originates from transformed hepatocytes, whereas hepatic progenitor cells give rise to benign lesions including regenerative nodules and adenomas.
- → Cells exposed to prolonged inadequate glucose concentrations elicit first a protective and adaptive response to optimise glucose utilisation and suppress death, in order to give to the cells an opportunity to recover from metabolic stress. OGT regulation by URI is a sophisticated mechanism conferring c-MYC-dependent survival functions in response to glucose fluctuations.
- → MCRS1 has oncogenic and tumour suppressive activities by regulating mTORC1. Inhibition of mTORC1 via MCRS1 deletion in the intestine protects from APC loss-dependent tumorigenesis, whereas it promotes colitis-induced colorectal cancer (CRC). Our work reveals mTORC1 oncogenic and tumour-suppressive roles in intestinal epithelium and avenues to optimised and personalised therapeutic regimens for CRC.

We intend to make significant progress over the next few years in order to elucidate mechanisms of disease associated to the digestive system. This will be made possible thanks to the specific environment at the CNIO providing state-of-the-art facilities and access to key technological platforms with advanced technologies, as well as the availability of various genetically engineered mouse models generated in our lab, patient-derived xenograft models, organoids, cell biological and biochemical techniques, and the large number of omics and human data. ■

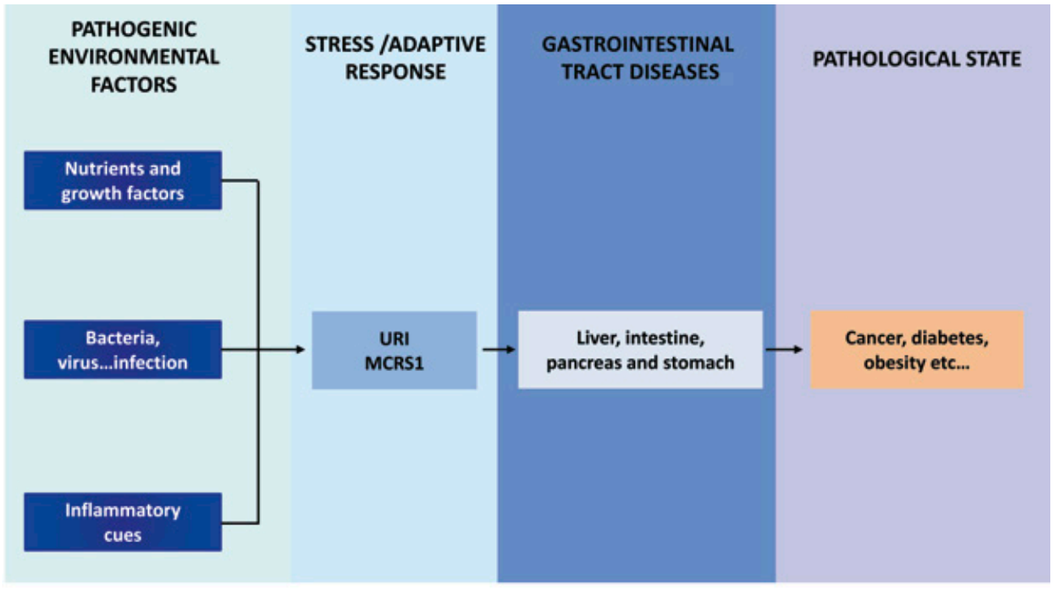

Figure Representation of our research directive. Our lab is mainly interested in understanding how pathogenic environmental factors lead to disease associated to the gastrointestinal tract. Molecular chaperones are essential to engage protective mechanisms to ensure cellular and protein homeostasis caused by injurious environmental stimuli. Environmental stress modulates thus URI and MCRS1 expressions to maintain cellular homeostasis or cause disease development.

PUBLICATIONS

- Brandt M, Grazioso TP, Fawal MA, Tummala KS, Torres-Ruiz R, Rodriguez-Perales S, Perna C, Djouder N (2018). mTORC1 inactivation promotes colitis-induced colorectal cancer but protects from APC loss-dependent tumorigenesis. *Cell Metab* 27, 118-135.
- Youssif C, Cubillos-Rojas M, Comalada M, Llonch E, Perna C, Djouder N, Nebreda AR (2018). Myeloid p38α signaling promotes intestinal IGF-1 production and inflammation-associated tumorigenesis. *EMBO Mol Med* 10, e8403.

Book Chapters

- Djouder N (2018). Prefoldins: the new chaperones. Djouder, N (ed.); Advances in Experimental Medicine and Biology, vol. 1106. Springer Nature. ISBN 978-3-030-00736-2; ISBN 978-3-030-00737-9 (eBook).
- Chaves-Pérez A, Thompson S, Djouder N (2018). Roles and Functions of the Unconventional Prefoldin URI, vol. 1106:95-108. In: Advances in Experimental Medicine and Biology. Springer Nature. ISBN 978-3-030-00736-2; ISBN 978-3-030-00737-9 (eBook).

AWARDS AND RECOGNITION

- Member of the European Society for Clinical Nutrition and Metabolism (ESPEN).