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CLASS I PI3K ISOFORM REGULATES NOD1/2 MEDIATED BACTERIAL AMINO ACID SENSING PATHWAY AND CONTROL GUT HOMEOSTASIS UNDER INFLAMMATORY CONDITIONS

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Phospoinositide-3-kinases (PI3Ks) are important evolutionarily conserved lipid kinases, regulating organismal pathways essential for cell growth, division, proliferation, and are often deregulated in cancer and inflammation. Colorectal and gastric cancers are reported to have high rates of activating mutations in the ubiquitously expressed gene encoding PI3Kα. PI3Ks regulate PRR-driven innate immune responses however how PI3Kα couples to intestinal epithelial cell (IEC) functions and gut homeostasis is not well understood. Intestinal epithelium is the largest and fastest regenerative tissue with protective barrier-type function. Disruption of the intestinal barrier due to genetic and/or environmental factors results in inflammatory bowel disease (IBD). NOD2 is the first identified susceptibility gene in IBD, and regulates innate immune responses to bacteria-derived dipeptides. In IECs, NOD1/2 was reported to regulate intestinal stem cell renewal and contribute to wound healing response. Since PRR signalling plays an important role in IEC division and self-renewal under stress conditions, upon injury and infection, we investigated whether IEC-intrinsic PI3Kα regulates NOD1/2 signalling and is involved in responses to gut protective responses, following gut injury. Herein by genetic and pharmacological targeting in vivo and in vitro, we showed that PI3Kα couples to NOD1/2 pathways, activated by bacterial dipeptides and induces mTOR signalling, analogous to nutrient sensing of eukaryotic amino acids. Strikingly, conditional inactivation of PI3Kα in adult mice result in lethality shortly following DSS-induced injury, while not showing gross differences in inflammation. Our findings demonstrate PI3Kα is an essential in intestinal integrity, function and IEC-intrinsic PI3Kα coupling to NOD1/2 mediated mTOR signalling adds a new layer to the complexity to the symbiotic host microbiome interactions even under stressful conditions.

Biography

Laura Medrano Gonzalez has completed her degree in Genetics from Universitat Autonoma de Barcelona. During her four year degree, she was awarded with an international studentship to work in Professor Andy Waters' research group at the Institute of Infection, Immunity and Inflammation, University of Glasgow. After her experience studying a protein complex related to sexual development of malaria's parasite, she was accepted at Imperial College London to pursue her research career with an MSc in Immunology. During her Master's-project, she joined Professor Peter Openshaw's laboratory in order to perform independent research, experimental setup and analysis focusing on B-cell responses against RSV. She joined Dr Ezra Aksoy's pioneering research group working in mucosal immunity and inflammation at the William Harvey Research Institute. She is currently a PhD candidate investigating the isoform-selective roles of PI3Ks and innate immune receptor signalling in the intestinal epithelial cells (IECs) and has presented her research data in several international conferences.

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