Class I PI3Kα isoform regulates NOD1/2 mediated bacterial amino acid sensing pathway and control gut homeostasis under inflammatory conditions.

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Abstract (not more than 300 words)

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 result 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 show 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 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.

Keywords— *Intestinal epithelium, NOD signalling, proliferation, intestinal injury and regeneration.*

Professional Biography (100-150 words)

Laura Medrano-Gonzalez completed her Genetics-degree at Universitat Autonoma de Barcelona. During her 4-year degree, Laura 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, Laura was accepted at Imperial College of London to pursue her research career with an MSc in Immunology. During her master's-project, Laura joined Professor Peter Openshaw's laboratory in order to perform independent research, experimental setup and analysis focusing on B-cell responses against RSV. Laura 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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Any Comments: I heard about this conference thanks to Sara Wallner, who contacted me through Linkedin and encouraged me to attend. I believe that my attendance to this conference would be beneficial for my project as well as for my career progression as a competitive researcher and lecturer in cell biology and immunology.

Desired presentation: _ Oral / _ Poster

Track Name : Track 17: Mucosal immunology

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