Understanding GPCR signalling in mechanosensing and intestinal barrier function

Supervisory team:
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Host institution: University of Bristol, University of the West of England; UWE
Submit applications for this project to the University of Bristol

Project description:

A fundamental challenge in biology is understanding how our cells sense, respond, and adapt to a variety of microenvironmental stresses. Mechanisms of cellular adaptation are crucial for maintaining healthy tissue homeostasis, as their failure undermines tissue fitness and contributes to age-related diseases such as chronic inflammation and cancer. The human gut is lined with epithelial cells that form a physical barrier between our bodies and the outside world. A key challenge for these cells is how to maintain the integrity of this barrier in response to mechanical stress — the biophysical cues such as stretch, compression and pressure that occur as food is pushed through our gut. In recent years, mechanical forces have emerged as key regulators of cell behaviour through downstream activation of the transcriptional co-regulators YAP/TAZ. However, the primary sensors of mechanical stresses upstream of YAP/TAZ activation in this context remain poorly characterised.

An important way that cells sense and respond to changes in their environment is through G protein-coupled receptors (GPCRs). We recently identified an orphan GPCR that couples to YAP/TAZ activation in intestinal epithelial cells during microenvironmental stress. However, what this receptor senses remains unknown. Excitingly, newly acquired phosphoproteomics data suggest this receptor signals to proteins involved in cell-cell junctions, extracellular matrix adhesion, and Rho GTPase activity. Since these pathways are known to be closely interlinked and important in epithelial barrier function and mechanobiology, we hypothesise that this GPCR is a critical mechanosensor that controls barrier integrity in response to biophysical stress.

In a multidisciplinary research programme using 3D organoid culture and 2D mechanosensing models of the intestinal epithelium, you will investigate how this GPCR shapes normal intestinal homeostasis and epithelial barrier function in response to mechanical stress. Loss of function organoid models will be generated using CRISPR-Cas9, which will be combined with integrative omics (RNA-seq and proteomics) for characterisation of the GPCR-regulated transcriptome and proteome. Training will be provided in omics and bioinformatics as well as advanced cell biology techniques including organoid culture, live cell imaging, confocal microscopy, RNAi and CRISPR-Cas9. You will carry out your research in modern laboratories supported by cutting edge microscopy and proteomics facilities.

Understanding the role of this GPCR in mechanosensing and barrier function will pave the way for the identification of drug targets that could prevent the breakdown of healthy tissue homeostasis and/or promote tissue regeneration in a number of disease contexts.

Please note: *This project in collaboration with the University of Bristol and the University of the West of England (UWE) is subject to a* ***joint degree award****. Successful applicants will be registered at both these institutions, and graduates will be awarded a joint degree from these two institutions upon successful completion of the PhD programme.*