Understanding receptor-mediated mechanosensing and signalling in cell barrier function during tissue homeostasis and stress responses

Supervisory team:
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Host institution: University of Bristol, University of the West of England (UWE)

Submit applications for this project to 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 receptor (ligands currently unknown) 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 receptor is a critical mechanosensor that controls barrier integrity in response to biophysical stress.

In a multidisciplinary research programme using cutting-edge techniques such as live-cell imaging, 3D organoid culture and 2D mechanosensing models of the intestinal epithelium, you will investigate how receptor-mediated signalling shapes normal intestinal homeostasis and epithelial barrier function in response to mechanical stress. Genetic loss of function models will be generated using CRISPR-Cas9, which will be combined with integrative omics (RNAseq and proteomics) for characterisation of receptor-mediate gene signatures. Training will be provided in omics and bioinformatics as well as advanced cell biology techniques including organoid culture, IncuCyte 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 receptor 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 including inflammation and cancer.

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.*

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.