

Understanding how cellular stress tunes junctional plasticity to drive barrier homeostasis

Project ID: 3623

Supervisory team

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Registered institution: University of the West of England (UWE)

Host institutions: University of the West of England (UWE)/Cardiff University

Project description: Epithelial tissues such as the intestine and pancreas form protective barriers that must stay intact throughout life. To achieve this, damaged or excess cells are continuously removed by a process called cell extrusion. During extrusion, individual cells are actively expelled from the epithelial layer while neighbouring cells remodel their junctions to close the gap and maintain barrier continuity. This process maintains epithelial homeostasis. Recent findings suggest that extrusion is influenced by differences in mechanical forces between cells, alongside factors such as crowding. However, we still do not fully understand how environmental stress changes cell adhesion and mechanical signalling to influence whether cells are retained or eliminated. Unpublished data from our labs suggest that an orphan G protein-coupled receptor (GPCR) could play a role in this process. Cells lacking this receptor retain expression of the key adhesive protein E-cadherin under stress and show less activation of the mechanosensitive transcriptional co-activator YAP. We hypothesise that this receptor coordinates stress-dependent changes in cell junctions and mechanical signalling to regulate cell extrusion and barrier homeostasis. This project will:

1. Discover how this GPCR regulates E-cadherin trafficking and junctional turnover during microenvironmental stresses such as hypoxia and mechanical stretch.
2. Explore whether the GPCR is required for extrusion of unfit cells using RAS-mutant models (testing EPHA2-dependence) and examine Wnt5a-Hippo (YAP/TAZ) crosstalk using live-cell imaging in epithelial monolayers and intestinal organoids.
3. Investigate how the GPCR influences YAP activity and actomyosin contractility, linking adhesion dynamics to mechanotransduction, and assess its effects on tight junctions and cell polarity.

Initial experiments will test for GPCR-dependent changes in junctions and extrusion; these findings will guide targeted pathway studies and validation in organoids. Comparing receptor depletion with re-expression will test whether observed changes depend specifically on the GPCR. Tracking individual junctions before, during and after extrusion will establish the sequence of events, helping distinguish changes that precede cell removal from those accompanying closure of the gap. The project combines live-cell, super-resolution and fluorescence lifetime imaging microscopy (FLIM), RNAi/CRISPR approaches and barrier function assays. Quantitative image analysis and modelling of E-cadherin trafficking will help distinguish changes in junctional turnover from changes in protein abundance. You will receive complementary training in epithelial cell biology, advanced microscopy and quantitative analysis at Cardiff University and UWE Bristol. The project will provide new insight into how epithelial tissues adapt their junctions and coordinate cell removal while maintaining a protective barrier.

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.