Understanding transcriptional control of autophagy during epithelial homeostasis and microenvironmental stress

Supervisory team:
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Submit applications for this project to the University of Bristol

Project description:

A fundamental challenge in biology is understanding how cells respond and adapt to environmental changes to maintain tissue homeostasis. Intestinal epithelial cells lining the gut are continually subjected to microenvironmental stresses. They use adaptive signalling to tolerate these stresses, and failures in these mechanisms can undermine tissue fitness and gut barrier function, contributing to age-related diseases including inflammation and cancer.

One physiological stress encountered by intestinal epithelial cells is reduced oxygen availability (hypoxia). This occurs under homeostatic conditions due to fluctuating metabolic demands and counter-current blood flow. Cells sense and respond to oxygen deprivation by switching on hypoxia-inducible factors (HIFs), transcription factors that increase the expression of genes involved in adaptive processes, such as autophagy, an essential stress response pathway. Autophagy transcriptional control in the gut is also influenced by Wnt/beta-catenin signalling, and by YAP, a Hippo pathway effector that induces a transcriptional programme favouring cell survival and tissue regeneration. We have recently discovered an exciting new regulatory axis involving the induction of an uncharacterised G-protein coupled receptor (GPCR) that signals via YAP to enable hypoxic cell survival. Newly acquired data from genetic loss-of-function studies indicate that this receptor may suppress Wnt/beta-catenin signalling to trigger the autophagy response during hypoxia. We suspect that failure to activate this signalling axis may uncouple the Wnt/beta-catenin and autophagy pathways, compromising the adaptive cellular response and resulting in tissue damage.

This project will determine the role of this new GPCR during normal intestinal homeostasis and upon exposure to physiological hypoxia, focusing on its interactions with the Wnt/beta-catenin and Hippo/YAP pathways. In a multidisciplinary research programme using ex-vivo 3D organoid culture models of the intestinal epithelium, you will investigate how this GPCR shapes normal epithelial homeostasis and the response to low oxygen stress. Loss of function organoid models will be generated using CRISPR-Cas9 for stem cell and differentiation assays, for autophagic flux and metabolic analysis. This will be combined with integrative 'omics' characterisation of the GPCR-regulated transcriptome/proteome using RNA-seq and quantitative proteomic approaches, respectively. Training will be provided in advanced cell biology and 'omics' techniques, including stem cell culture, widefield and confocal microscopy, bioinformatics, and CRISPR-mediated genome editing, in modern laboratories supported by cutting edge microscopy and proteomics facilities.