

TRANSGENIC MICE WITH FLUORESCENT PROGLUCAGON-EXPRESSING CELLS

Dr Fiona Gribble and Dr Frank Reimann have developed transgenic mice with fluorescently labelled proglucagon-expressing cells.

Uses

- Paves the way for exploration into mechanisms underlying GLP-1, PYY and glucagon release
- Potential to identify targets in these cells that could be exploited therapeutically for treatment of diabetes and obesity
- Isolated cells suitable for electrophysiology, fluorescence calcium imaging, and expression analysis studies

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Background

Enteroendocrine L cells secrete a number of physiologically important peptides, including glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), peptide YY (PYY) and oxyntomodulin. Each of these hormones is under evaluation for potential therapeutic applications in humans.

GLP-1 is a gut hormone and a neuropeptide produced from the glucagon precursor proglucagon, which is expressed by the alpha-cells of the pancreatic islets, the endocrine L cells of the intestine and by neurons located at specific sites in the brain. It is secreted in response to food intake and is a prime candidate for manipulation in development of new therapies for obesity and diabetes.

Technology

Dr Fiona Gribble and Dr Frank Reimann at the University of Cambridge have made a transgenic mouse model in which cells expressing proglucagon are labelled by the yellow fluorescent protein, Venus. This will enable detailed characterisation of proglucagon-expressing cells needed to fuel progress of this research field and targeting these cells provides exciting therapeutic opportunities

In the gut, Venus-positive cells were found to increase in density along the intestinal axis from the duodenum to the colon. In pancreatic islets, Venus fluorescence colocalised with proglucagon immunostaining, confirming the identity of the labelled cells as glucagon-producing α cells. Islet cells from the transgenic mice could be separated by flow cytometry into relatively pure populations of α and β cells and a mixed population of δ and pancreatic polypeptide (PP) cells. GLP-1 expressing neurones in the brainstem were also found to be labelled with fluorescent protein.

The fluorescently tagged cells are suitable for patch clamping, single-cell dynamic calcium imaging, and cell sorting, providing a range of new and powerful techniques to interrogate the function of this enteroendocrine cell type.

Figure 1: Venus labelled L cell in the small intestine (Bar = 20 μ m)

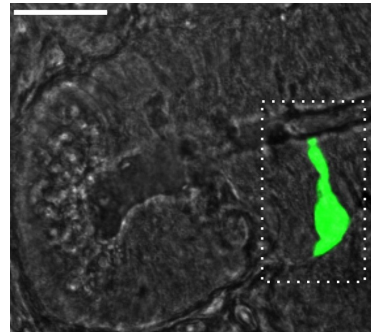
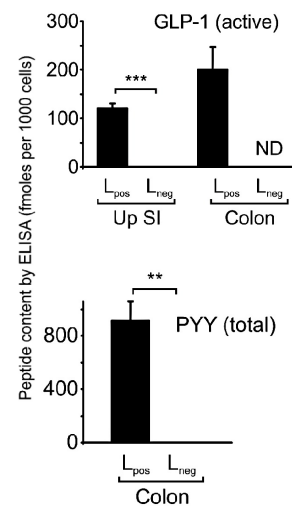


Figure 2: GLP-1, and PYY peptide contents in L_{pos} and L_{neg} cells from the small intestine (upper half, Up SI) or colon, as indicated, collected by FACS sorting and measured by ELISA.



Publication

Glucose Sensing in L Cells: A Primary Cell Study. *Cell Metabolism* 2008 8(6):532

Commercialisation

These mice are available for internal research purposes on a non-exclusive basis and we are seeking licensees to apply these mice to their own research.