

**RAS-RAF AND PI3K-AKT INTRACELLULAR SIGNALLING: CANDIDATE PATHWAYS FOR POST-BOWEL RESECTION ADAPTATION?**

Roland Partridge<sup>1,2</sup>, Rachel Ridgeway<sup>3</sup>, Claudio Murgia<sup>3</sup>, Owen Sansom<sup>3</sup>, Jamie Davies<sup>1</sup>

<sup>1</sup>Centre for Integrative Physiology, University of Edinburgh, Edinburgh, UK, <sup>2</sup>Royal Hospital for Sick Children, Edinburgh, UK, <sup>3</sup>Beatson Institute For Cancer Research, Glasgow, UK

**Aim:** The intracellular signalling pathways responsible for mediating adaptation of the intestine following bowel resection are not well understood. This study explores a genetic mutant with small bowel structural changes similar to those observed during post-resection intestinal adaptation. Factors with potential to augment post-resection adaptation in light of this are discussed.

**Method:** A Villin-Cre-ERT2 Pten<sup>-/-</sup> Braf<sup>V600E</sup> mouse model was investigated. Administration of tamoxifen results in conditional activation of the Ras-Raf and PI3K-AKT intracellular signalling pathways, by silencing Pten and activating Braf in Villin-expressing intestinal epithelia cells. Mice in the experimental group (n=2) were activated by intra-peritoneal administration of tamoxifen, and a control group consisted of non-activated littermates (n=3). Intestines were harvested from the mice at 35 days post-activation and a total of 50 H&E stained cross-sections were analysed for intestinal morphology.

**Results:** Activation of the Ras-Raf and PI3K-AKT pathways in the intestinal epithelia resulted in significant morphometric changes in the bowel. Within the epithelia there was an increase compared to littermate non-activated controls in: (*median (interquartile range) Mann Whitney p-value*): Villus height: 384µm (340-415µm) vs 185 µm (159-201µm); p<0.001. Crypt depth: 64µm (63-69µm) vs 43µm (41-47µm); p<0.001. Crypt density (no crypts per 100µm of bowel circumference): 5.8 (4.9-6.1) vs 4.2 (4.0-4.4); p<0.001. There was also an increase in the bowel circumference: 4.0mm (3.9-4.3) vs 3.5mm (3.2-3.7); p<0.001, and length of the small bowel: 45.0cm (43.4-49.5cm) vs 38.0cm (36.8-39.6cm); p=0.035.

**Conclusion:** Conditional activation of the Ras-Raf and PI3K-AKT pathways in intestinal epithelium induces morphological changes in the small intestine similar to those seen following bowel resection. This suggests a possible role for these pathways during intestinal adaptation that may be amenable to manipulation. From this work we propose small molecule Pten inhibitors as candidate intestinotrophic agents to augment post-resection intestinal adaptation.