Disclosure of Interest None Declared.

REFERENCE

**PTH-020** FACTORS INFLUENCING ABNORMAL GLAND MORPHOGENESIS IN COLORECTAL CANCER (CRC) - TRANSLATIONAL STUDIES
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Introduction Disruption of colorectal gland formation characterises high grade, aggressive CRCs but causal mechanisms remain unclear. Glandular morphogenesis can be modelled in three-dimensional (3D) culture systems that enable investigation of specific oncogenic signals. We have shown that the tumour suppressor PTEN regulates 3D glandular morphogenesis in a Caco-2 colorectal organotypic model system through effects on the Rho-GEF cdc42. Cdc42 is activated by specific guanine nucleotide exchange factors (GEFs) and influences gland lumen formation by regulation of apical membrane (AM) assembly. PTEN knockdown inhibits cdc42, disrupts AM integrity and induces a vacuolar, multilumen glandular phenotype evocative of high grade CRC. While PTEN has catalytically-active or -inactive functional domains relevant to phosphatidylinositol 3-kinase (PI3K) activity, Caco-2 gland development was unaffected by PI3K signalling.

Methods We used wild type PTEN-expressing Caco-2 cells and isogenic stable PTEN knockdown Caco-2 (KD) clones in two- (2D) and three-dimensional (3D) cultures as model systems. Cell membrane localization of specific cdc42 GEFs was investigated by cell fractionation and immunoblot. Effects of catalytically-active or -inactive PTEN mutants on cdc42 activity and/or AM integrity during 3D morphogenesis were investigated by transfection and confocal microscopy. Apical membrane integrity was assessed in human CRC by semiquantitative score of the AM marker, NHERF-1. CRC gland morphology was assessed by a validated grading system.

Results PTEN expression enhanced cell membrane recruitment of cdc42 GEFs with a specific role in 3D morphogenesis (Tuba, ITSN2). PTEN mutants containing an intact catalytically-inactive C2 domain enhanced cdc42 activity, restored AM integrity and rescued defective morphogenesis of 3D PTEN-KD Caco-2 cultures. Conversely, a C2 domain construct mutated at its CBR3 lipid-binding motif was ineffective. Fundamental attributes of the model system viz. associations between AM integrity and gland morphology were conserved and had prognostic significance in human CRC.

Conclusion PTEN deficiency impairs GEF membrane recruitment, cdc42 activation, apical membrane assembly and CRC glandular morphogenesis in a predictive colorectal cancer model system. PTEN-cdc42 regulatory pathways influence AM integrity and colorectal glandular morphogenesis. Dissection of these networks may identify molecular targets for novel therapy, aimed at high grade CRC.

Disclosure of Interest None Declared.

**PTH-021** MAGNETIC ANAL SPHINCTER – A NOVEL SURGICAL OPTION FOR MANAGEMENT OF FAECAL INCONTINENCE
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Introduction Magnetic anal sphincter (MAS) is a novel surgical option for faecal incontinence. It has been developed by the University of Dundee and licensed by a Danish company. It is a 40 mm diameter, 13 mm thick cylinder made of titanium and is lined with anodised stainless steel mesh. MAS works by restoring the depth of the anal canal, reducing the rectal capacity and increasing rectoanal inhibitory reflex (RAIR). The aim of this pilot study was to assess safety and feasibility of MAS in patients with faecal incontinence.

Methods A single surgeon inserted MAS in 6 patients; 3 with idiopathic faecal incontinence and 3 with faecal incontinence following surgery for colorectal cancer. The procedure was performed under general anaesthesia with simultaneous biofeedback. One patient had a biopsy of the anal margin and one patient had a diverting colostomy. All patients were followed up at 1, 3, 6 and 12 months.

Results MAS was inserted successfully in all patients, with evidence of anal sphincter activity. In one patient the magnet was inserted high in the anal canal and this was corrected during the first post-operative follow up visit. One patient had a perineal haematoma, one had anal ulceration and one patient had anal pain.之 None Declared.