PARIETAL CELL-SPECIFIC SLC26A9 DELETION DRIVES SPEM VIA SPERMIDINE-STAT3-MEDIATED EXPANSION OF APOE+PDGFRA+ FIBROBLASTS

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UEG Week Barcelona 2026 | Presentation

Digestive Oncology | Stomach & H. Pylori | Mechanisms & Personalised Medicine | Immunology | Oesophagus

October 18, 2026

Parietal cell-specific deletion of Slc26a9 in mice drives SPEM formation through epithelial-fibroblast-immune cell crosstalk mediated by spermidine-Stat3 signaling and expansion of Apoe+Pdgfra+ cancer-associated fibroblasts.

KEY POINTS

- Selective deletion of Slc26a9 in parietal cells caused significant depletion of parietal cells and expansion of SPEM cells in Slc26a9 knockout mice, as demonstrated by single-cell RNA sequencing.
- Slc26a9 deletion expanded a novel Apoe+Pdgfra+ fibroblast subtype that exhibited marked upregulation of cancer-associated fibroblast marker genes including Col12a1, Col27a1, Col6a3, and Tgfbi, validated by Western blot and immunofluorescence.
- Non-targeted metabolomics revealed disrupted beta-Alanine metabolism and significantly increased tissue spermidine levels in Slc26a9-deficient mice; in vitro spermidine stimulation induced Stat3 phosphorylation and Apoe upregulation in primary fibroblasts, an effect abolished by Stat3 phosphorylation inhibitor.
- Cell-chat analysis and immunofluorescence demonstrated that Apoe+Pdgfra+ fibroblasts interact with macrophages via the Col6a5-Sdc4 ligand-receptor pair to drive M2 macrophage polarization, with Col6a5 co-localizing with Apoe and Sdc4 co-localizing with M2 marker CD163.
- The study identifies targeted Slc26a9 deletion in parietal cells as the critical initial step instigating epithelial-fibroblast-immune cell crosstalk that drives SPEM, a key precancerous gastric lesion.

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