Piezo2 loss promotes colorectal tumorigenesis by enhancing Wnt activity

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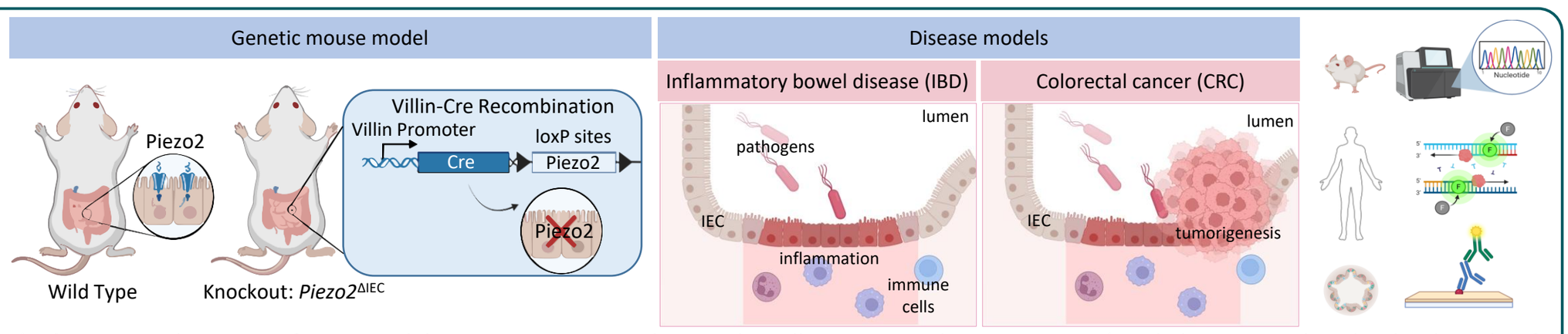
Introduction

Piezo channels are increasingly recognized as key regulators of epithelial physiology; however, their roles in intestinal epithelial cells (IECs) and gastrointestinal disease remain unclear. Here, we investigated the function of epithelial Piezo2 in gut homeostasis and its contribution to pathology.



Methods: Mice with IEC-specific *Piezo2* deletion were generated using the Villin-Cre recombination system[1] and characterized in depth. The role of epithelial Piezo2 in intestinal disease was investigated using established mouse models of Inflammatory Bowel Disease (IBD) and Colorectal Cancer (CRC). In addition, publicly available RNA-sequencing datasets from CRC patients were analyzed.

Figures generated with Biorender and Figurelabs.

Results

Figure 1. The lack of Piezo2 in IEC does not affect the intestinal homeostasis

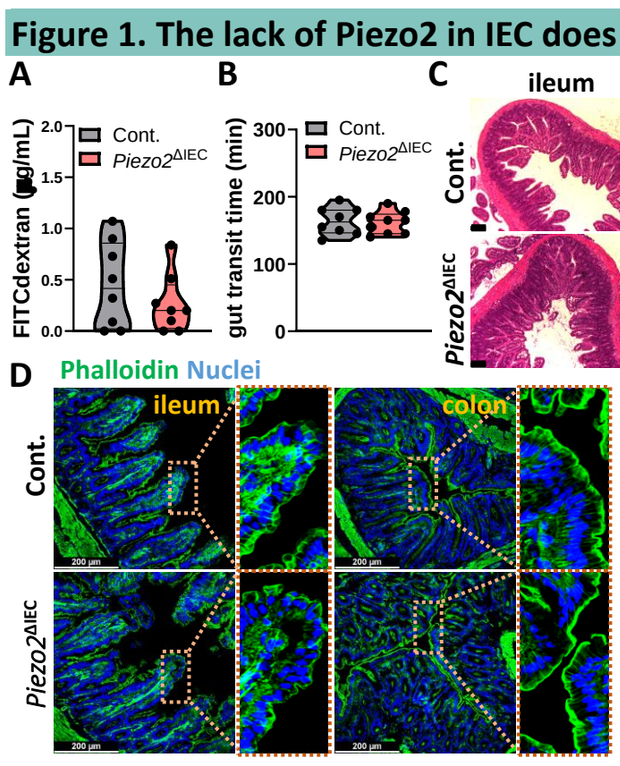


Figure 1.
(A) Gut permeability in control and *Piezo2*ΔIEC mice, measured by the serum concentration of orally administered FITC-dextran.
(B) Whole gut transit time measured in control and *Piezo2*ΔIEC mice.
(C) Representative pictures and overall histological score of ileal and colonic tissues.
(D) F-actin fiber staining using Phalloidin (in green) in ileum and distal colon (n = 5).
Statistical analyses were performed using the unpaired t-test.

Figure 2. Piezo2 acts as tumor suppressor in colorectal cancer

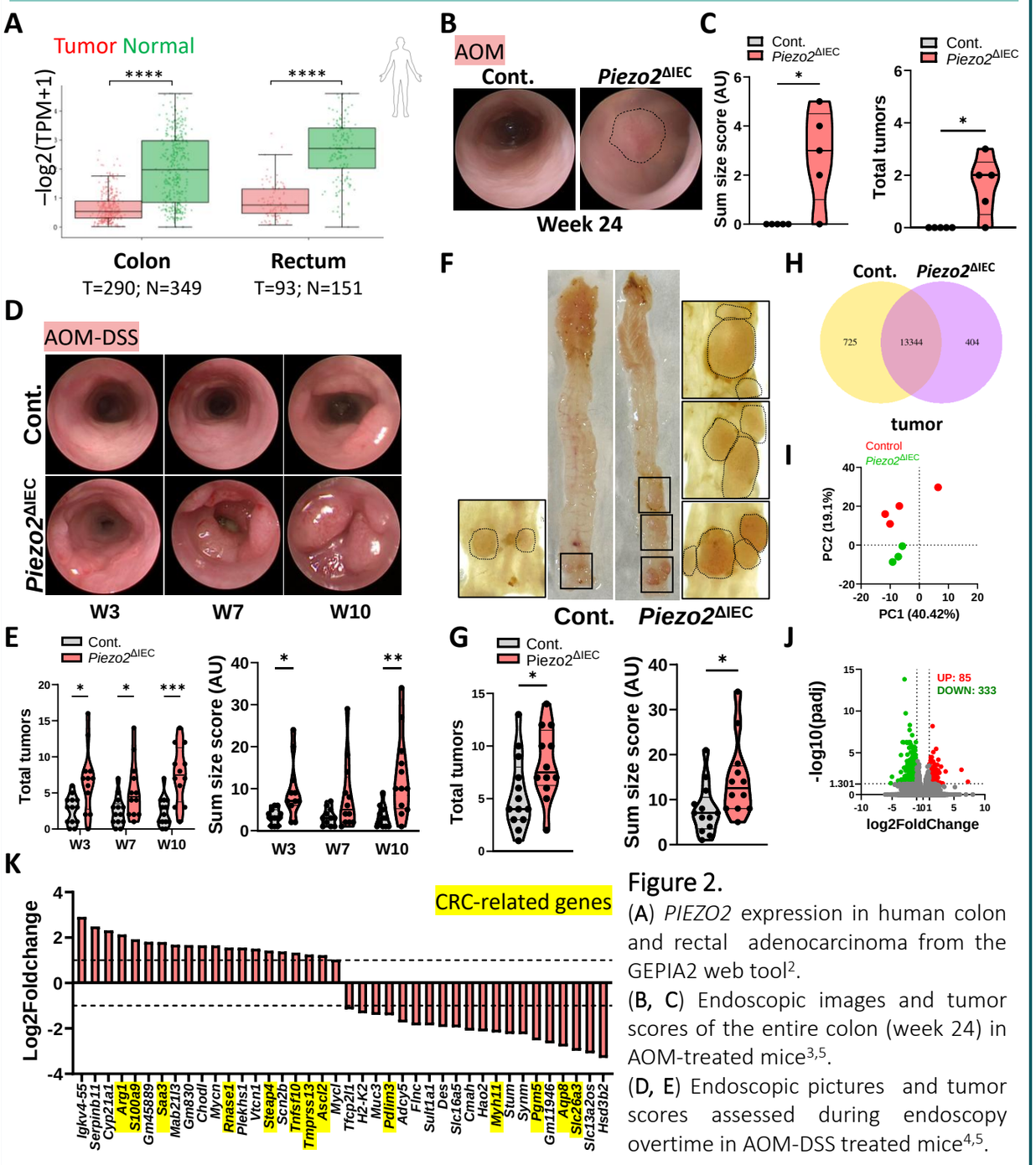


Figure 2.
(A) *PIEZO2* expression in human colon and rectal adenocarcinoma from the GEPIA2 web tool[2].
(B, C) Endoscopic images and tumor scores of the entire colon (week 24) in AOM-treated mice[3,5].
(D, E) Endoscopic pictures and tumor scores assessed during endoscopy overtime in AOM-DSS treated mice[4,5].
(F, G) Representative pictures and tumor scores of the entire colon in AOM-DSS treated mice, week 10.
(H) Venn diagram of sequenced genes between control and *Piezo2*ΔIEC tumors.
(I) Principal Component Analysis (PCA) 2D score blot of control and *Piezo2ΔIEC* tumors.
(J) Volcano plot showing 28.186 sequenced genes with |log2FC| > 0. Dashed lines indicate the thresholds for adjusted p = 0.05 and log2FC = ±1.
(K) Top 20 upregulated and top 20 downregulated genes (adjusted p < 0.05) from (J), with CRC-related genes highlighted in yellow.
(H-K) Bulk RNA-sequencing data from size-matched tumors collected from AOM-DSS-treated control mice (n = 4) and *Piezo2*ΔIEC mice (n = 3).
Statistical analyses were performed using the unpaired t-test (C, G) and 2way ANOVA (E)

Conclusion

Piezo2 is dispensable for the maintenance of intestinal epithelial integrity under homeostatic condition, but functions as a tumor suppressor in the colon by modulating Wnt/β-catenin signaling. These findings identify a previously unrecognized role for Piezo2 in regulating intestinal tumorigenesis and suggest that Piezo2 may represent a promising therapeutic target in colorectal cancer (CRC).

Figure 3. Impact of Piezo2 deficiency on intracellular ion homeostasis in IECs

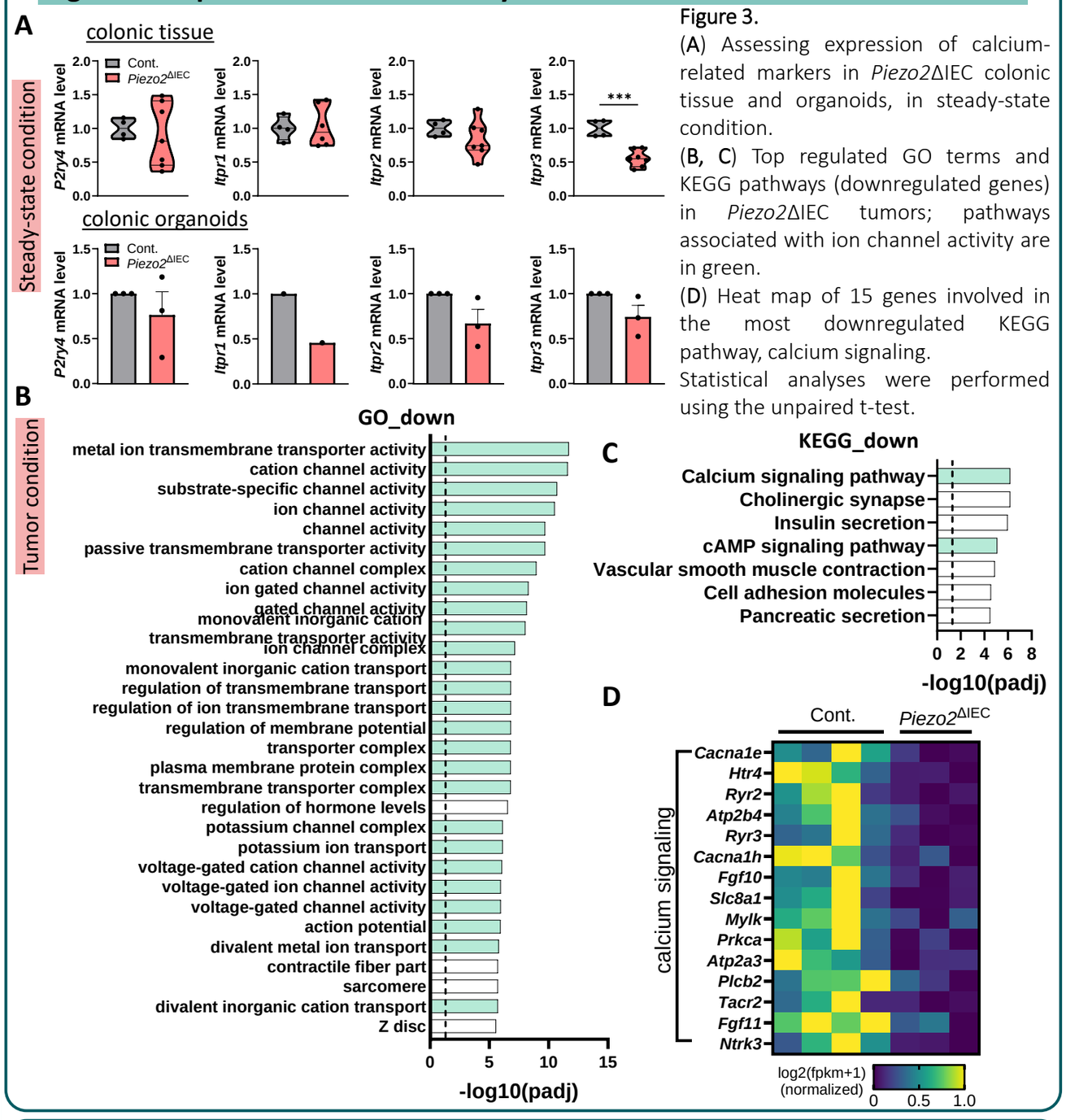


Figure 3.
(A) Assessing expression of calcium-related markers in *Piezo2*ΔIEC colonic tissue and organoids, in steady-state condition.
(B, C) Top regulated GO terms and KEGG pathways (downregulated genes) in *Piezo2*ΔIEC tumors; pathways associated with ion channel activity are in green.
(D) Heat map of 15 genes involved in the most downregulated KEGG pathway, calcium signaling.
Statistical analyses were performed using the unpaired t-test.

Figure 4. Lack of Piezo2 leads to the activation of Wnt signaling pathway

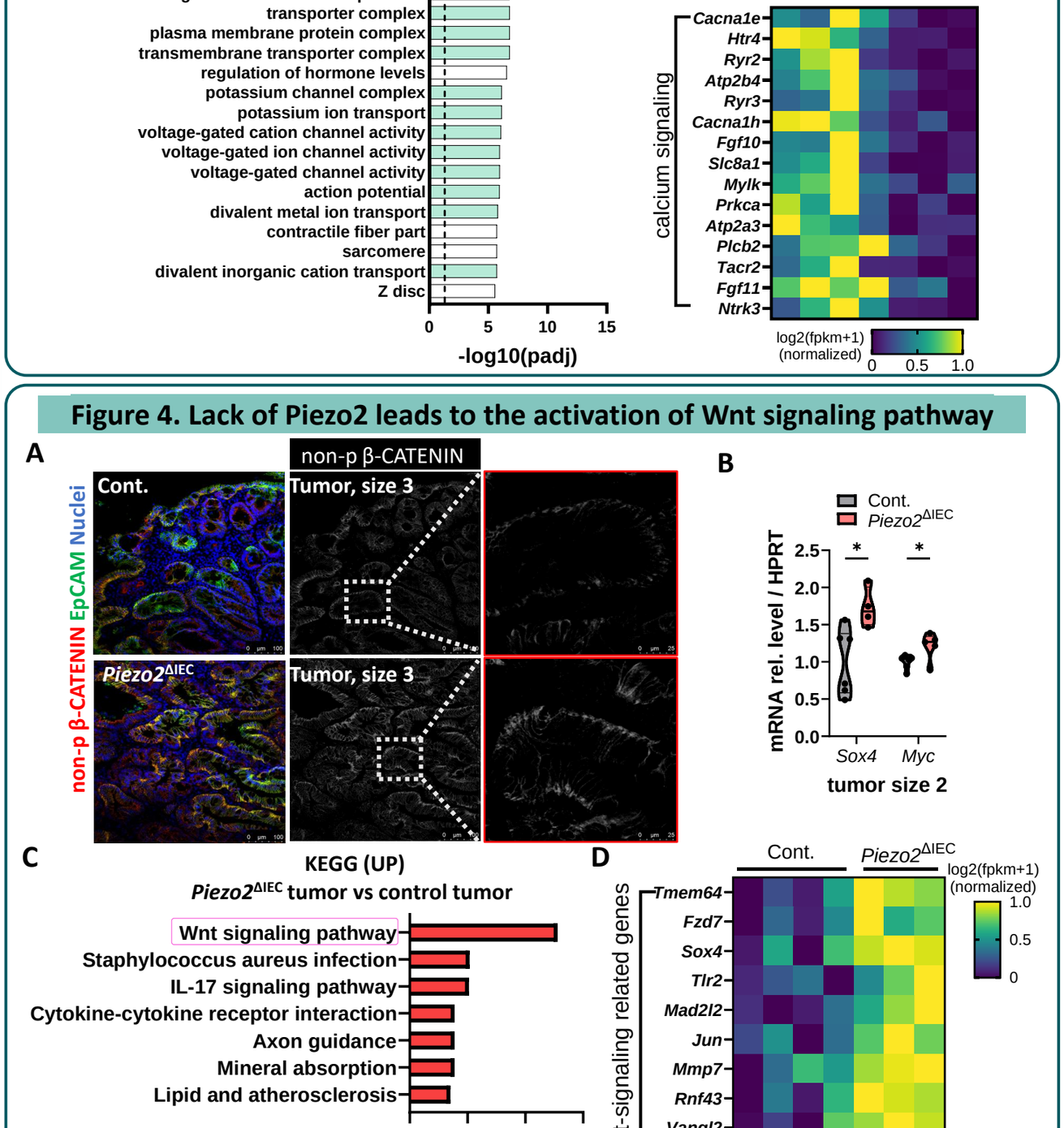


Figure 4.
(A) Non-phosphorylated β-catenin expression assessed by immunofluorescence staining, costained with nuclei and intestinal epithelial cell marker (EpCAM).
(B) Gene expression (qPCR) of Sox4 and Myc from control and *Piezo2*-deficient tumors.
(C) Wnt signaling pathway was identified as the most upregulated KEGG pathway.
(D) Heat map of significantly altered genes involved in the Wnt signaling pathway.
(E, F) Representative images of *Piezo2*-deficient organoids cultured in medium supplemented with reduced Wnt surrogate-Fc fusion protein. Normalized organoid area over time is shown in (F).
Statistical analyses were performed using the multiple unpaired t-test.

References:
1. el Marjou F, Janssen KP, Chang BH, et al., Genesis 2004; 2. Tang Z, Kang B, Li C, et al., Nucleic Acids Res 2019; 3. Neufert C, Heichler C, Brabletz T, et al., Nature Protocols 2021; 4. Tanaka T, Kohno H, Suzuki R, et al., Cancer Sci 2003; 5. Becker C, Fantini MC, Neurath MF, Nature Protocols 2006.

*Statistical significance are indicated as follows: * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001.*

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