Microbial Depletion in Mouse Colitis Models Impairs Intestinal Wound Healing and Damage Response Gene Expression

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Background

- Inflammatory Bowel Disease (IBD) is a multifactorial disease characterized by chronic epithelial injury and impaired healing in response to inflammatory and microbial stimuli. Current interventions for IBD focus on treating chronic inflammation, while regenerative interventions remain an unmet clinical need.
- **Damage response genes or DRGs** are part of an epithelial cellular gene expression pattern that is upregulated after an injury (Nusse et al., 2018).
- TGF-β1 and YAP/TAZ signaling are important for DRG expression during wound healing (Yui et al., 2018; Chen et al., 2023).
- **Microbial factors and the role of the microbiota during wound healing, specifically linking the role of DRGs responsible for enhancing regenerative effects, remain understudied.**

My objective is to elucidate the role of the microbiota during intestinal wound healing by studying regenerative mechanisms in the epithelium and to determine microbial factors that enhance regenerative mechanisms. ***I hypothesize that intestinal microbiota promotes colonic wound healing post-DSS injury.***

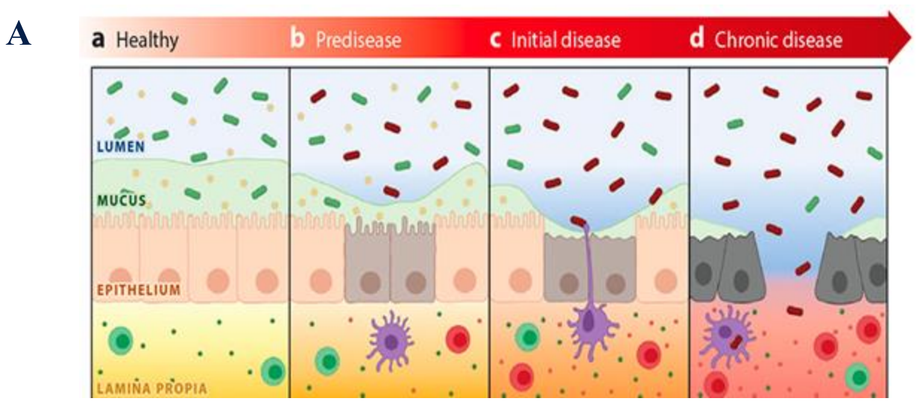


Fig.1 Intestinal injuries in IBD and wound healing in the colon. (A) Modified schematic by Shan et al., 2023. Microbial shifts over time in IBD epithelial injuries.

Results

Microbial depletion delays epithelial regeneration in the colon

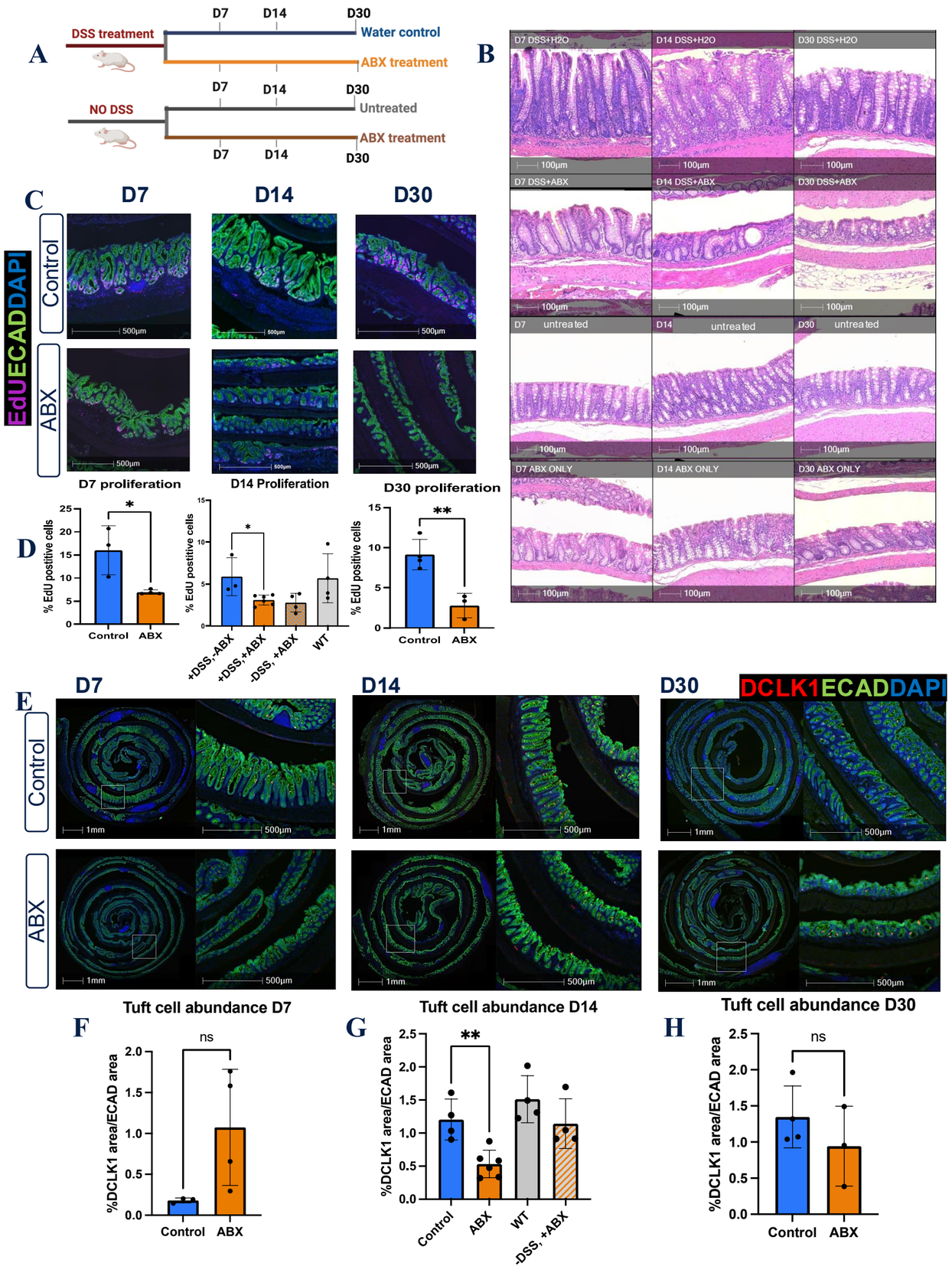


Fig. 2 (A) Experimental design. (B) H&E images of middle-distal colonic crypts during regeneration. (C, D) Proliferation 7,14, and 30 days after DSS treatment in antibiotic (ABX) treated vs. water controls and whole tissue quantifications. (E, F, G, H) Tuft cell abundance over time in mice depleted of microbiota (ABX) and water controls.

Repair-associated mechanisms and DRGs decrease in microbiome-depleted mice

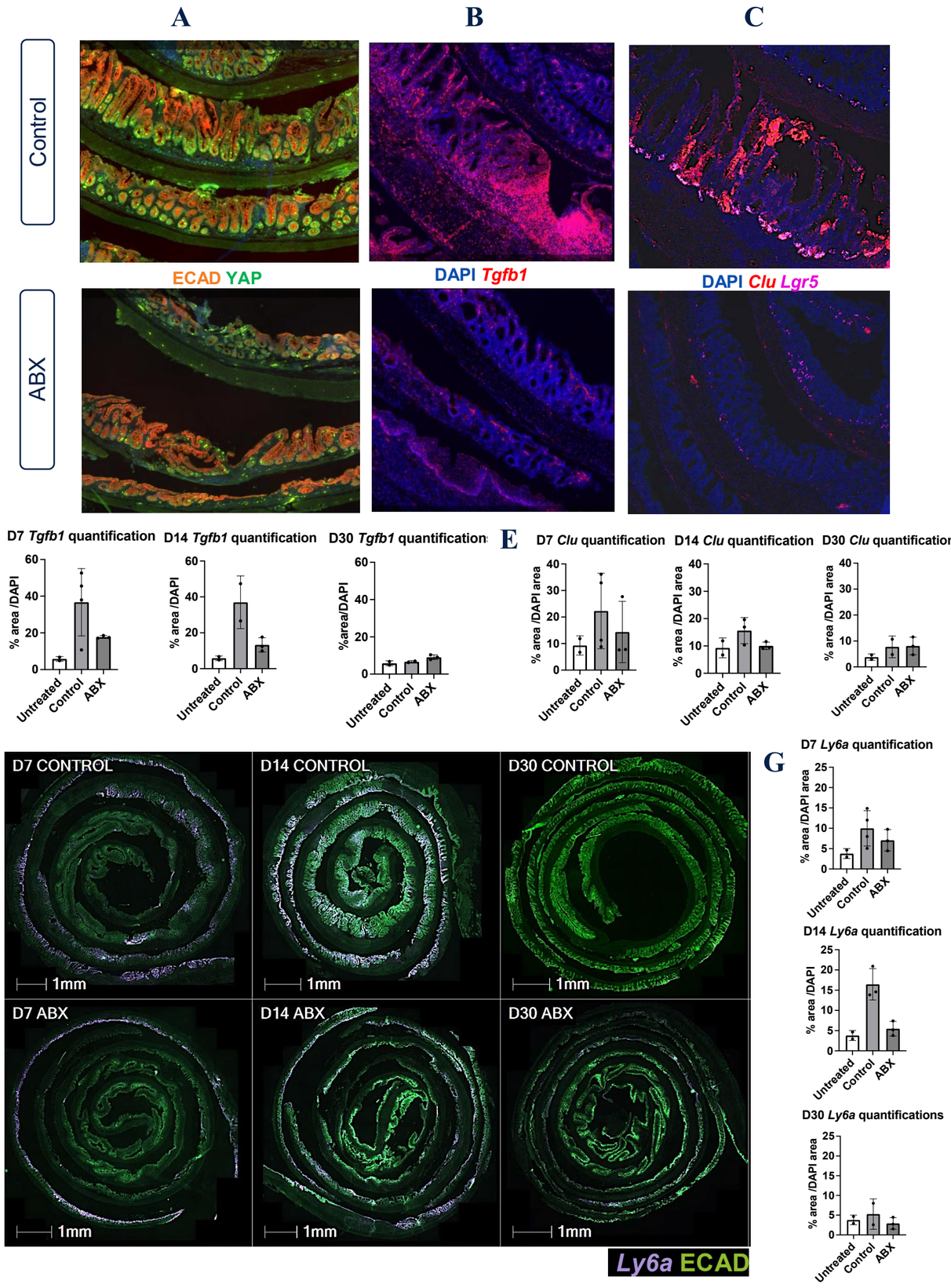


Fig. 3 (A, B, C) Colonic crypts during the repair phase,14 days after DSS treatment. YAP IF stain in control vs. ABX-treated mice. *Tgfb1*, *Clu, Lgr5 in situ* hybridization representative images. (D, E, G) Whole tissue *in situ* hybridization quantifications over time of mice with (ABX) and without microbial depletion (control). Images A-C taken at 20x. (F) Representative images of regional differences of DRG *Ly6a* over time in control and ABX-treated mice.

Propionate is sufficient to induce damage response organoid morphology *in vitro*

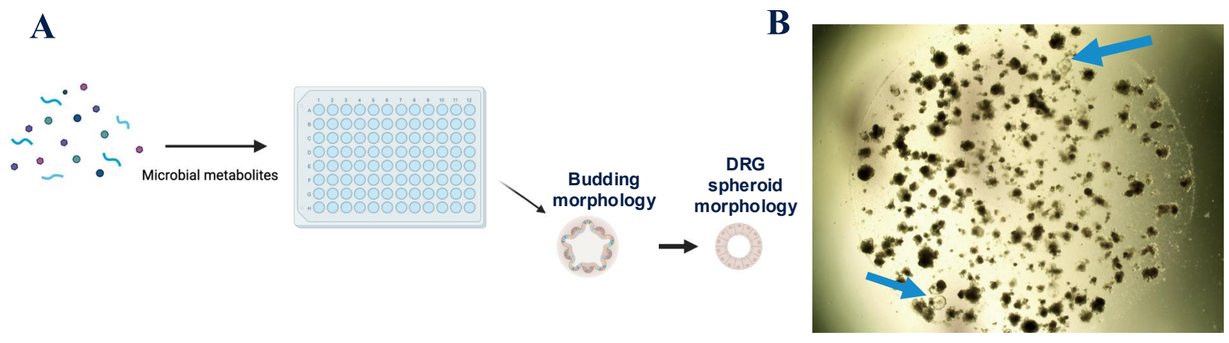
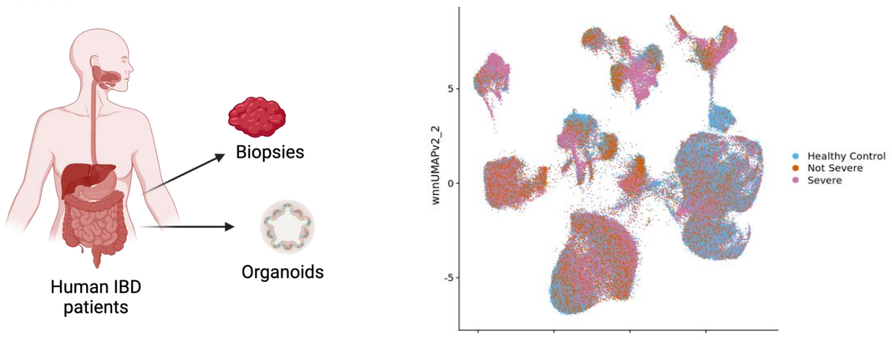


Fig. 4 (A) *In vitro* metabolite screen experimental design. (B) Spheroid morphology of propionate-treated organoids at 70 hrs. Images taken at 10x.

Conclusion and Future Directions

- The microbiome is important for intestinal regeneration and expression of DRGs.
- The investigation of DRGs has not been extensively explored in IBD patients and disease severity.
- Future mechanistic studies are required to determine how microbes contribute to epithelial DRG expression.



Schematics created using BioRender.com

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