Proton-pump Inhibitors Modulate Gene Expression Profiles in Esophageal Epithelium and Microbiome

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Introduction

- Proton-pump inhibitors (PPIs) are commonly used in children to manage gastroesophageal reflux disease and eosinophilic esophagitis
- PPIs are also used in children with upper gastrointestinal symptoms and without a formal diagnosis and with normal esophagus
- However, the impact of PPIs exposure on otherwise normal pediatric esophagus has not been reported.

Aim and Hypothesis

- ❖ To investigate the association between the PPI exposure and the esophageal epithelial gene expression and microbiota in children with normal esophagus.
- ❖ To examine if differences in the host esophageal epithelial gene expression were driven by underlying esophageal epithelium cell type composition.
- ❖ Hypothesis: We hypothesized that PPI exposure alters the normal pediatric esophageal epithelial transcriptional profile in a cell-type dependent manner and impacts the local microbiome.

Methods

- We sequenced and analyzed PPI naïve (PPI- = 7) and PPI treated (PPI+ = 10) esophageal biopsies obtained from children with normal esophagus on endoscopy and normal esophageal histology.
- Metatranscriptomics approach optimized for low bacterial load human samples was used to capture host epithelial gene expression and microbial transcriptome.
- To assess whether observed gene expression changes could be related to the cell types composition in the biopsies, deconvolution analysis was performed using xCell.

Results

- The median (interquartile range) age of our cohort was 14 (12-16) years, with female (63%) and Caucasian preponderance (89%)
- Seven (37%) were PPI naïve (PPI-) and 10 (63%) were on a PPI (PPI+) and were similar in terms of their demographics and clinical features.

Results

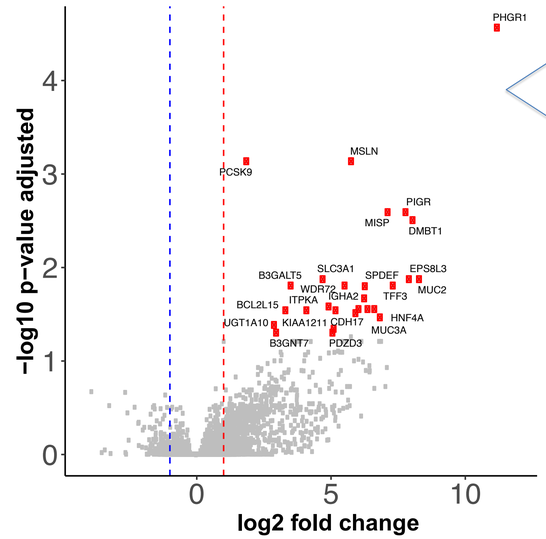


Fig 1: Volcano plot showing differentially expressed host genes between children on PPI and children not on PPI. We use a threshold of log2 fold change >1 and adjusted $p < 0.05$ to call the genes that are up- or downregulated. The upregulated genes that satisfy the threshold are shown in red dots.

Fig 2: Heatmap showing specific cell types derived using deconvolution of bulk RNA-sequencing data.

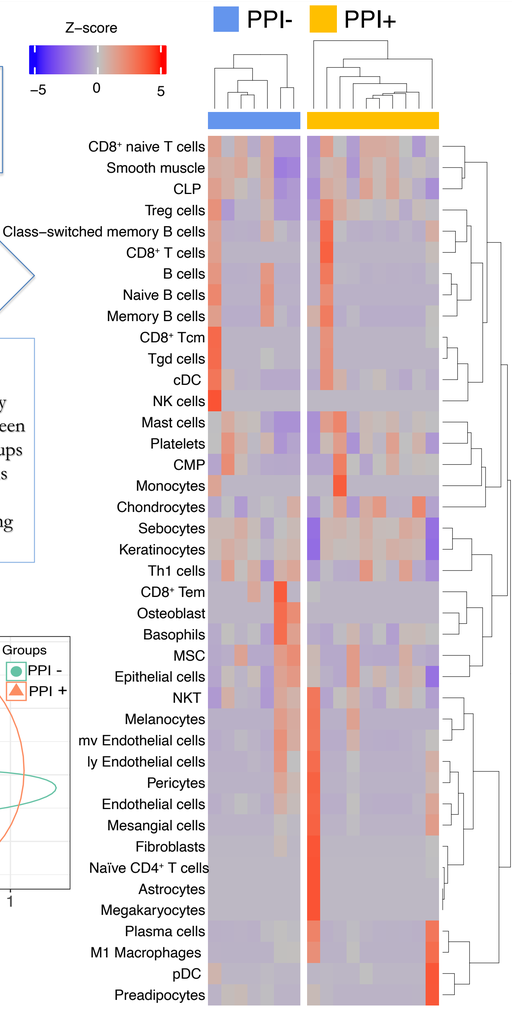
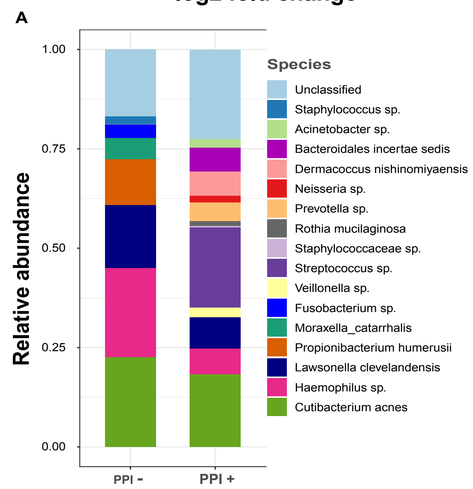
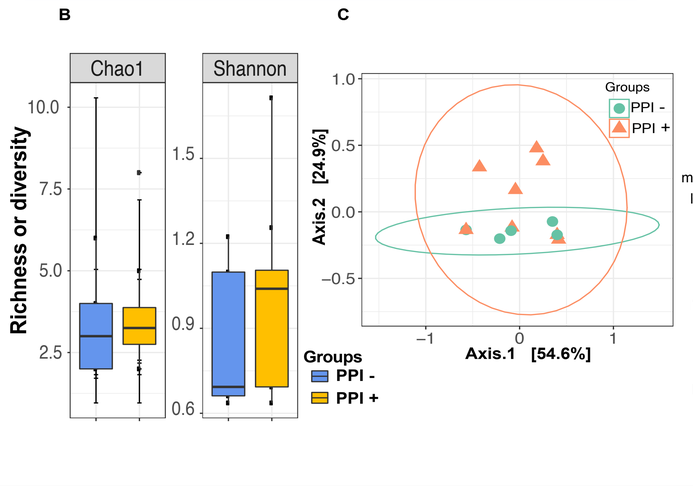


Fig 3: (A) color-coded bar plot shows the average relative abundance of microbial taxa identified in the esophagus in PPI- and PPI+ groups. (B) Richness and alpha diversity of the esophagus microbiome. Alpha diversity and richness (measured by Shannon and Chao1 index) are compared between the PPI- and PPI+ groups. Differences in alpha diversity between the groups were not significant. (C) A principal coordinate analysis plot of Bray-Curtis dissimilarities (beta-diversity) over the first two-axis is shown. Overall, the microbiome community composition was not significantly dissimilar among the PPI+ and PPI- groups.





Conclusions

- In children with normal esophagus, PPI exposure is associated with upregulation of esophageal mucosal homeostasis and epithelial cell function genes in a cell-type independent manner and altered esophageal microbiome. Studies are warranted to validate our findings and to investigate if the causal effect of PPIs on the normal esophageal epithelium and microbial communities.

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