Title: Unraveling Early and Late Immune Landscapes in Celiac Disease Using Spatial Transcriptomics

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Abstract

Celiac disease (CD) is characterized by circulating serum transglutaminase 2 (TG2) autoantibodies and small bowel mucosal damage hallmarked by villous atrophy, crypt hyperplasia and immune cell infiltration. Due to the slow progression of intestinal damage, some patients may exhibit elevated serum antibodies while maintaining normal intestinal morphology. This condition, termed potential celiac disease (PCD), is thought to represent an early stage in CD pathogenesis. While numerous transcriptomics studies in CD exist, traditional methods lack the ability to capture tissue context, challenges that spatial transcriptomics can address.

This study aimed to characterize spatial gene expression differences between CD, PCD, and healthy controls to better understand different stages of CD pathogenesis.

Using GeoMx Spatial Transcriptomics, we analyzed duodenal biopsies from CD patients (n=10), PCD patients (n=2), and controls (n=5). Regions of interest (ROIs) were selected from villus and crypt focusing on both epithelium and lamina propria.

Our results show distinct inflammatory changes in CD compared to controls, as well as between PCD and controls. CD samples exhibited upregulation of genes involved in antigen presentation and immune surveillance (e.g., IGHG1-5, HLA-E), indicating chronic inflammation. PCD samples displayed more innate immune response genes (e.g., IFI6, IL32) compared to controls, reflecting early-stage immune activity. This study represents the first comprehensive mapping of transcriptomic alterations in CD, demonstrating spatial transcriptomic shifts as the disease progresses, with detectable changes already present in the PCD stage.