

COMMENTARY

Uncovering interleukin-7 in celiac disease through a human autoimmune organoid model: A commentary

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Abstract

This commentary describes an innovative air-liquid interface (ALI) duodenal organoid system for studying celiac disease (CeD). Derived from patient biopsies, this model uniquely preserves the native tissue microenvironment, including epithelial, stromal, and diverse tissue-resident immune cells, overcoming the limitations of conventional cultures and animal models. When stimulated with gluten peptides, the organoids replicate key pathological features of CeD, such as epithelial cell death mediated by cytotoxic T cells. Research has identified interleukin-7 (IL-7), secreted by mesenchymal cells, as a critical and previously underappreciated mediator of this gluten-induced autoimmune attack. This discovery highlights IL-7 as a promising therapeutic target and establishes the ALI organoid platform as a powerful tool for investigating complex epithelial-immune interactions in other autoimmune and infectious diseases, drug screening, and personalized medicine.

Keywords: Organoids; Celiac disease; Immune-epithelial interactions; Interleukin-7; Therapeutic targeting

1. Introduction

Organoids are three-dimensional, self-organizing *in vitro* models derived from stem cells or tissue fragments. They have become transformative instruments in studying human physiology and disease.¹ In contrast to traditional two-dimensional cell cultures, organoids replicate the functional dynamics, cellular heterogeneity, and architectural complexity of native tissues. This technology has acquired significant momentum in autoimmune research, where the interactions between epithelial, stromal, and immune compartments are essential for pathogenesis. The necessity of models that preserve these interactions

is exemplified by celiac disease (CeD), an autoimmune disorder characterized by an immune response to gluten that specifically targets the duodenal mucosa.² Historically, *in vitro* studies of CeD have been restricted by several factors.³ Researchers could not cultivate affected epithelium with tissue-resident immune cells. Conventional enteroids and animal models failed to overcome this limitation. This divide was bridged by the study conducted by Santos *et al.*,⁴ which developed an air-liquid interface (ALI) duodenal organoid system that preserves native immune populations (Figure 1).⁴ Their work transcends technical innovation to establish a new paradigm: organoids as self-

contained human immune niches capable of recapitulating autoimmune pathogenesis without artificial immune reconstitution. By preserving the native tissue-immune unit, this model resolves a fundamental limitation in autoimmunity research—the inability to study tissue-resident immunity in dynamic, long-term cultures.

2. Technical description

The application of organoids is contingent upon their distinctive ability to maintain the *in vivo* tissue microenvironment. In the pathogenesis of CeD, the duodenal mucosa is damaged by human leukocyte antigen (HLA)-DQ2/DQ8-restricted immune responses triggered by gluten-derived peptides. This complex multicellular interplay, fundamental to human disease, is absent in models such as gliadin-treated cell lines or HLA-transgenic rodents. Conventional enteroids exclude immune and mesenchymal cells, whereas murine models necessitate artificial overexpression of cytokines such as interleukin (IL)-15 to mimic disease pathogenesis. In contrast, the ALI organoid system cultures intact endoscopic biopsy fragments, better replicating the native tissue environment. This approach maintains the epithelium, mesenchyme, and tissue-resident immune cells as an integrated unit. The immune cells include T cells, B cells, natural killer (NK) cells, and myeloid subsets. This integrated system circumvents the limitations of previous models by preserving immune diversity, including T cell receptor (TCR) and B cell receptor (BCR) repertoires that closely reflect those found in patient biopsies, while leveraging the self-renewal capacity of intestinal stem cells. Consequently, ALI organoids offer a human-relevant substrate for dissecting gluten-dependent immune activation, as they preserve the spatial organization and functional crosstalk of the duodenal mucosa.

The methodology of Santos *et al.*⁴ emphasizes the technical complexity of contemporary organoid systems. Duodenal biopsies from CeD patients (active disease or remission) and non-CeD controls were minced and embedded in collagen matrices under ALI conditions. Using Wnt-3a, epidermal growth factor, Noggin, and R-spondin1-based media, the cultures sustained epithelial proliferation and, critically, maintained diverse CD45⁺ hematopoietic cells for over a year—a feat unattainable in conventional explant cultures. To simulate the disease, they treated the organoids with HLA-DQ2.5-restricted gliadin peptides, using class II-associated invariant chain peptides as a control. Flow cytometry and cytokine profiling quantified epithelial apoptosis, cytotoxic marker expression, and antitransglutaminase 2 (TG2) autoantibody production, while single-cell RNA sequencing (scRNA-seq) mapped immune subset activation. Functional studies validated mechanistic pathways through the use of neutralizing

antibodies (anti-major histocompatibility complex [MHC]-II, anti-NK group 2 member D [G2C/D]) and recombinant IL-7. In addition, immunohistochemistry was performed on patient biopsies to corroborate clinical relevance.

3. Key findings

The investigation findings shed light on the complex relationship between epithelial destruction and gluten-specific immunity. Gliadin induced apoptosis in HLA-DQ2.5⁺ CeD organoids, which was characterized by cleaved caspase-3⁺ epithelium and villus atrophy—pathognomonic features of active CeD. This mechanism necessitated MHC-II-mediated antigen presentation, as blockade abrogated epithelial damage. It was facilitated by cytotoxic CD8⁺ intraepithelial lymphocytes that expressed NKG2C/D receptors, which recognize stress ligands on epithelial cells. The scRNA-seq analysis demonstrated a comprehensive activation of the immune network. In CD8⁺ T cells, gliadin upregulated cytotoxic genes (granzymes, *PRF1*), while in myeloid cells, chemokines (CCL3-5, CCL20) and cytokines (IL-2, IL-15) were associated with the pathogenesis of CeD. Notably, plasma cells within organoids secreted anti-TG2 autoantibodies, which mirrored the serological hallmark of CeD. The most significant discovery was the identification of IL-7 as a gluten-inducible effector. The finding that IL-7 originates from the lamina propria mesenchyme, rather than hematopoietic cells, reframes our understanding of the tissue microenvironment's role in orchestrating the autoimmune attack. This insight prompts new hypotheses: is mesenchymal activation a primary event following gluten exposure, and what signals trigger this specific IL-7 response? The study showed that IL-7 was necessary and sufficient for epithelial apoptosis by modulating NKG2C/D expression on CD8⁺ T cells, cementing it as a pivotal—and previously underappreciated—therapeutic target. The role of IL-7 in the progression of the disease was further substantiated by clinical biopsies, which confirmed its upregulation in active CeD, particularly in mesenchymal compartments.

4. Limitations and future potential applications

The ALI organoid system is far-reaching and surpasses CeD; however, key limitations must be acknowledged. Three constraints require particular attention. The first is the HLA-restricted dependency. The system's reliance on donor biopsies introduced inherent variability in HLA genotypes and immune cell populations, which may affect experimental reproducibility. The second is the donor-specific immune drift. While immune populations are maintained long-term, their precise stability and potential for phenotypic drift over extended culture periods

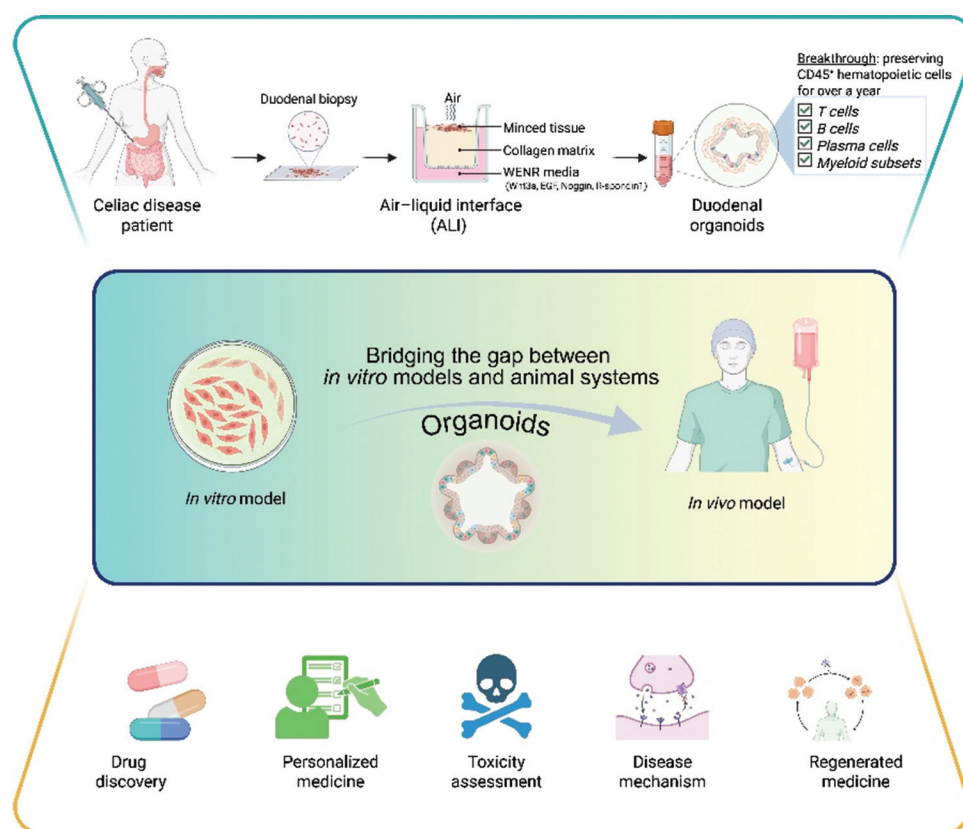


Figure 1. Schematic of endoscopic biopsies cultured using air-liquid interface in collagen/WENR media and its significance and advantages. Image created using BioRender. Hu, A. (2025). <https://BioRender.com/so3nntr>.

warrant further investigation. Finally, the simplified microenvironment. The absence of luminal microbiota, vascularization, and neural inputs overlooked their potential modulatory roles in CeD pathogenesis. These limitations may potentially be addressed through several promising approaches. Induced pluripotent stem cell-derived organoids with clustered regularly interspaced short palindromic repeat (CRISPR)-engineered HLA haplotypes could provide a pathway toward standardizing genetic backgrounds, thereby reducing donor variability and potentially enhancing experimental reproducibility. Cryopreserved immune cell banks might offer a solution for stabilizing donor-derived lymphocyte populations, addressing concerns regarding long-term phenotypic drift, and supporting more consistent immune repertoire analyses across experiments. Additionally, microfluidic integration of patient-specific microbiome samples or endothelial networks represents an avenue for reconstructing critical aspects of the luminal and vascular microenvironment currently absent in the model.

Beyond CeD, this platform demonstrated broad applicability across multiple domains. For personalized medicine, HLA-matched organoids could predict patient-specific responses to gluten-free diets or biologics, enabling tailored interventions. In autoimmune research, the

system's ability to recapitulate autoantibody production (e.g., anti-TG2-like responses) provides new avenues to model B cell pathology in conditions like lupus or rheumatoid arthritis. For infectious diseases, it offers unique capabilities to simulate mucosal pathogen interactions—such as *Helicobacter pylori* persistence in gastric tissue or SARS-CoV-2 entry mechanisms in airways. Notably, the platform's proficiency in modeling tissue-resident immunity renders it particularly valuable for disorders relying on epithelial-immune crosstalk, including type 1 diabetes and inflammatory bowel disease, while its long-term stability further facilitates pharmacodynamic studies of novel therapeutics targeting IL-7, NKG2C/D, or gluten detoxification pathways.

5. Conclusion

The broader significance of the work by Santos *et al.*⁴ is its redefining of organoid technology as a bridge between defective animal systems and reductionist *in vitro* models. Beyond CeD, this system offers a template for modeling other HLA-linked autoimmune disorders (e.g., type 1 diabetes, multiple sclerosis) where epithelial-stromal-immune triads drive pathology. It further challenges the field to reconsider mesenchymal cells as active orchestrators—not passive bystanders—in autoimmune attacks, prompting

new hypotheses about stromal sensing of environmental triggers. Identifying IL-7 as a gluten-inducible effector recontextualizes CeD pathogenesis and highlights immediate therapeutic opportunities. Given that therapies targeting the IL-7 pathway are already in clinical development for other autoimmune diseases,⁵ this finding provides a strong rationale for repurposing such agents for CeD. This discovery underscores the power of organoid systems to reveal actionable therapeutic targets that are obscured in conventional models. Moreover, the platform's adaptability and scalability, which are exemplified by its compatibility with high-throughput screening, cytokine modulation, and CRISPR editing, are indicative of a revolution in precision medicine. Organoid systems can integrate neural, vascular, and microbiome components, simplifying the complexities of human physiology. This, in turn, can expedite translating mechanistic insights into clinical therapies. The platform is also invaluable for modeling other disorders of the epithelial-immune interface. For example, it could be adapted to study host-pathogen interactions in infectious diseases like *Helicobacter pylori* gastritis or to model the environmental triggers of inflammatory bowel disease. Key challenges remain, such as standardizing stromal components and integrating luminal microbiota to fully replicate the gut ecosystem. However, as the field progresses, refining these integrated human organoid systems—for instance, by incorporating vascular and neural components—will bring us closer to recapitulating the full complexity of human physiology, expediting the translation of mechanistic insights into clinical therapies for autoimmune disorders, as well as neurological research,⁶ anticancer therapy,⁷ tissues repair,⁸ and personalized treatment,⁹ paving the way for precise therapies.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

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Ethics approval and consent to participate

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Consent for publication

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