Imaging Platform for IBD Drug Discovery

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Overview

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal (GI) tract, resulting in its damage and gut barrier dysfunction. These chronic conditions are treatable but not curable, dramatically decrease the patient's quality of life and affect approximately 1.6 million Americans. The teams of Profs. Geiger and Elinav designed a high-throughput screening platform for molecules that affect the intestinal epithelial barrier and identified specific molecules that can be used as potential drugs to treat IBD.

Background and Unmet Need

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis (UC), is characterized by chronic inflammation of the gastrointestinal (GI) tract, resulting in its damage. These chronic conditions are treatable but not curable, dramatically affecting the patient's quality of life, and may impose a significant financial burden. IBD affects as many as 1.6 million Americans, with 70,000 new cases of the diseases diagnosed each year.

IBD is associated with dysfunctions of the intestinal barrier, generating a "leaky gut" that enhances permeability and translocation of microbial molecules through the intestinal barrier. This process increases the risk for mucosal infection and leads to the systemic inflammation that characterizes the disease.

Therefore, there is an urgent need to devise strategies to counteract the detrimental systemic consequences of gut barrier dysfunction.

The Solution

The groups of Profs. Geiger and Elinav have established a high-throughput screening platform to identify small molecules that modulate epithelial tight-junctions (TJs) and barrier function, which can be further developed into IBD therapeutics.

Technology Essence

The intestinal barrier is composed of a monolayer of epithelial cells held tightly together to their neighbors and to the underlying extracellular matrix. This monolayer is sealed by complexes of multiple adhesive transmembrane molecules, called tight junctions (TJs) and focal adhesions (FAs). The teams of Profs. Elinav and Geiger established an imaging-based, quantitative, high-throughput screen to identify molecules that disrupt or stabilize intestinal epithelial TJs and barrier function in vitro. This was achieved by imaging the structure of TJs and FAs in cultured cell lines (i.e., CaCo-2, Figure 1). The system was quantified and validated using known disruptors, such as tumor necrosis factor (TNF), interleukin 1b (IL-1b), and bacterial lipopolysaccharide (LPS). The researchers then widened their search to screen for thousands of barrier-modulating compounds among libraries of human secreted molecules (i.e., cytokines, growth factors, hormones), microbiota-related molecules, and various other small molecule drug libraries. These screens led to discovering multiple TJ disruptors (i.e., putrescine) and stabilizers (i.e., taurine) that affected CaCo-2 monolayers. The teams validated their findings using in vivo mouse models, demonstrating that putrescine administration induced a leaky gut phenomenon during intestinal autoinflammation and infection. Importantly, coadministration of a stabilizer, taurine, significantly reversed the disruptive effect of putrescine on intestinal barrier function during enteric infection (Figure 2)1, suggesting that these drugs can be developed to treat gut barrier impairment in IBD patients.

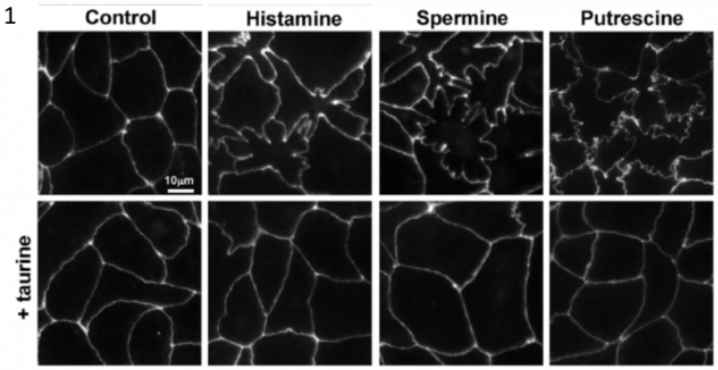

Figure 1 – CaCo-2 cells treated with indicated disruptors alone or in combination with taurine (a stabilizer), fixed, and stained for ZO1 to visualize TJs.

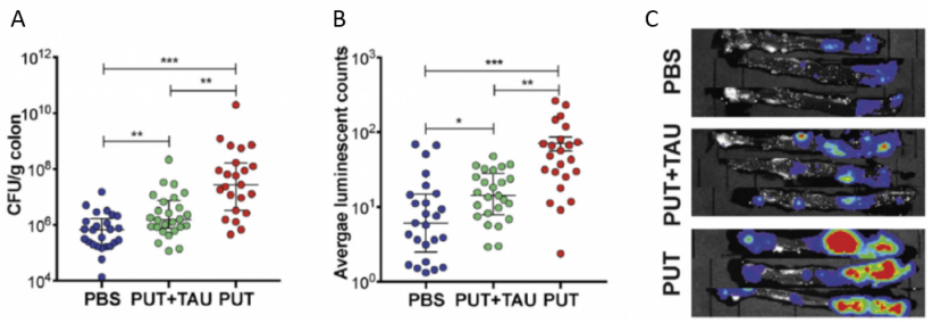

Figure 2 – Restoration of the disruptive effect of putrescine by taurine supplementation in mice with *C. rodentium* infection. Wild-type mice treated with phosphate-buffered saline (PBS), putrescine (PUT), or putrescine plus taurine (TAU) were infected with *C. rodentium*. (A) Colony-forming units (CFUs) recovered from colonic tissue, (B) ex vivo colonic bioluminescence quantification, and (C) imaging and on day seven after infection.

Applications and Advantages

- A high-content screening platform for identifying agents that affect gut barrier stability which could be developed to drugs for the treatment of:
    - IBD (e.g. Chron's disease, ulcerative colitis)
    - Uncontrollable inflammation which results from microbiota- and food antigen- associated disease

Development Status

The teams have designed a high-throughput screening platform and identified molecules that disrupt and stabilize intestinal epithelial TJs and barrier function. The platform's utility in identifying epithelial barrier function modulators was independently validated in two in vivo colon inflammation models (DSS colitis and Citrobacter rodentium infection).

References:

Grosheva I, Zheng D, Levy M, et al. High-Throughput Screen Identifies Host and Microbiota Regulators of Intestinal Barrier Function. Gastroenterology. 2020;159(5):1807-1823. doi:10.1053/j.gastro.2020.07.003

Patent Status

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