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EDITORIAL

A Perfect Match: Explant and Organoid Systems Help Study Cytokines in Sickness and Health

A plethora of inflammatory cytokines have been implicated in various gastrointestinal (GI) tract disorders, but there still is limited knowledge regarding the mechanisms underlying the interaction between epithelial and immune cells that lead to major disturbances in GI mucosa homeostasis.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Jarry et al[1] showed that one of the type I interferons, interferon α (IFN-α), induces apoptosis and promotes intestinal epithelial barrier disruption by activating the inflammasome. The investigators used a 3-dimensional model of human normal colonic mucosa explant culture, an ex vivo system that not only maintains the architecture of the tissue but also contains various mucosal resident cells that can interact to trigger an innate immune response. They used this tissue culture model to dissect a sequence of cellular and molecular events triggered by IFN-α. First, they found that IFN-α disturbs homeostasis in the human normal colonic mucosa by rapidly inducing apoptosis of entire crypts, but this response was variable among tissue fragments from different patients because in 21% of the cases IFN-α had no apoptotic effect. Interestingly, these observations indicated that their ex vivo model was able to recapitulate the heterogeneity of cancer patients' responses to IFN-α–based treatment regarding intestinal disorders as a side effect.[2]

This study continued by elucidating mechanisms involved in IFN-α–induced apoptosis in the human intestinal mucosa, considering not only the epithelium itself, but other mucosal resident cells preserved in colonic explants and their interactions. IFN-α induced a Th1 response, with increased numbers of T box expressed in T cells (T-bet)-positive cells in the lamina propria along with augmented levels of IFN-γ. By using different inhibitors of the inflammasome pathway in the explant cultures, they were able to determine a sequence of events leading to intestinal barrier disruption. Such studies are complicated in animal models because of variables such as routes of drug delivery, drug clearance and half-life, confounding systemic effects of drugs, and difficulties in synchronizing cellular responses in the tissue to determine an unequivocal succession of causal events. Their data showed the following cascade: IFN-α activates caspase-1 in epithelial and mononuclear cells that produce interleukin (IL)18 and induces IFN-γ secretion by T-bet$^+$ T lymphocytes in the lamina propria, causing epithelial cell apoptosis and subsequent intestinal barrier disruption.

The human normal colonic explant culture allowed Jarry et al[1] to investigate how IFN-α affects intestinal mucosa homeostasis through a cross-talk between epithelial and immune cells and describe the mechanisms involved. The possibility of a direct effect of IFN-α in the human colonic epithelium, however, cannot be discarded completely. The investigation of a direct effect of cytokines on GI epithelial cells has been neglected over the years, with investigators instead concerned primarily with how cytokines are produced by and interact with immune cells. One reason for our blind spot about direct epithelial cell production of and response to cytokines could be the lack of in vitro models that allow dissection of the various cellular players involved. Recently, this issue was addressed by using another type of 3-dimensional model, the organoid culture composed exclusively of epithelial cells. Mouse small intestinal organoids have been used to show that IFN-γ directly induces degranulation and apoptosis of Paneth cells, which are not affected by other cytokines studied, including IL22.[3] Nevertheless, IL22 influences mouse and human small intestinal organoids in a different way by directly promoting proliferation of intestinal stem cells.[4] The epithelial response to chronic inflammation has been assessed by exposing mouse colonic organoids to IL1β, IL6, tumor necrosis factor α, LPS, and flagellin for 60 weeks, resulting in persistent nuclear factor-κB activation and epithelial cell transformation.[5] The possibility of investigating interactions between different mucosal cells is an important characteristic of the explant culture used by Jarry et al,[1] while questions that require a still complex, but more isolated, epithelial-focused system benefit from organoids. Therefore, associating both explant and organoid models can help elucidate the molecular and cellular mechanisms involved in the interplay between the GI epithelium and immune cells, by determining the precise roles of intermediate cytokines in the maintenance and disturbance of tissue homeostasis.

Establishing systems wherein human primary cells can be cultured in varying complexity from pure epithelial organoids to mixed cultures of several tissue types is exciting because we now can begin to determine the role of genetic variability in cytokine response. Such variability among human beings might help explain why patients respond differently to pathogens and to drugs, which eventually should allow us to better understand how to target therapy in a more precise way (ie, precision medicine).

LUCIANA H. OSAKI, PhD
JASON C. MILLS, MD, PhD
Division of Gastroenterology
Department of Medicine
Department of Pathology and Immunology
Department of Developmental Biology
Washington University
St. Louis, Missouri

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Correspondence
Address correspondence to: Jason Mills, MD, PhD, Division of Gastroenterology, Washington University, 660 South Euclid Avenue, Campus Box 8124, St. Louis, Missouri 63110. e-mail: jmills@wustl.edu.

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