

The Role of the Gut Barrier Function in Health and Disease

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The intestinal tract contains the body's largest interface between a person and his or her external environment. The complexity of its function is obvious when thinking that at the same time the intestine must serve two opposite functions; the selective permeability of needed nutrients from the intestinal lumen into the circulation and into the internal milieu in general and, on the other hand, the prevention of the penetration of harmful entities including microorganisms, luminal antigens, and luminal proinflammatory factors. The latter function is known as barrier function [1].

The gut barrier function is comprised by three major lines of defence [2]: 1) The biological barrier, which is made up of normal intestinal flora (gut microbiota) responsible for colonization resistance; 2) The immune barrier, which is composed of gut associated lymphoid tissue (GALT), effector and regulatory T cells, IgA producing B (plasma) cells, group 3 innate lymphoid cells, and, resident macrophages and dendritic cells in the lamina propria; and 3) The mechanical barrier, consisting of the closed-lining intestinal epithelial cells and by the capillary endothelial cells. The epithelial and endothelial cells come into the closest possible contact in the most apical part of the lateral cell membranes ("kissing points") by specific structures named "tight junctions" (TJs), which interconnect the cells and restrict the passage of ions, molecules and cells through the paracellular space [2, 3].

The term "bacterial translocation" (BT), was first described by Berg and Garlington in 1979, as the phenomenon of passage of viable bacteria from the gastrointestinal tract through the epithelial mucosa into the lamina propria and then to the mesenteric lymph nodes and possibly other normally sterile organs [4]. This initial definition was later widened to include the translocation of non-viable bacteria or their products, namely pathogen-associated molecular patterns (PAMPs), with main representative the intestinal endotoxin. BT occurs in healthy in-

dividuals in a low rate of 5-10%, serving two main physiological roles; the antigenic exposure of the gut immune system to be prepared for an effective immune response in case of extensive pathogen invasion, and the development of immune tolerance to several microbial antigens of commensal microflora [5-7].

The intestinal barrier is compromised in several disease states leading to an increased level of BT associated with infectious complications and promotion of a systemic inflammatory response that aggravates the pathophysiological consequences of the underlying disease [8-13]. There are three main pathophysiological groups of intestinal barrier failure associated with pathologic conditions:

1) The intestinal barrier failure observed in surgical patients subjected to major operations for diverse reasons (major liver resections, bowel resections for malignancy, bowel transplantation, aortic aneurysm repair). In this group of patients, increased BT is associated with increased postoperative infectious complications [5, 11, 14-17]. The connecting mechanism is translocation of gut-derived pathogens through a dysfunctional mucosal barrier to the mesenteric lymph nodes, the portal vein and the systemic circulation, eventually leading to postoperative infections [18]. Also, this is the mechanism by which the necrotic pancreas becomes infected in patients with severe necrotic pancreatitis [19].

2) The second group includes critically ill patients, severely injured or septic, hospitalized in intensive care units. Increased gut permeability is associated with the development of systemic inflammatory response and multiple organ dysfunction syndrome (MODS) in these patients. However, the connecting pathophysiological link of gut barrier failure and MODS does not seem to be the classical process of BT [18]. Current pathogenetic aspects support the "gut-lymph" theory of sepsis and MODS. According to this theory, microbes and/or their products, through a dysfunctional gut barrier, first gain access to the intestinal submucosa activating the intestinal immunological system of defence. An intestinal proinflammatory response further aggravates intestinal injury and danger-associated molecular patterns (DAMPs) are released in the mesenteric lymphatics, carried to the lung and the systemic circulation, stimulating Toll like receptors-4 and perhaps other pattern recognition receptors (PRR) in a fashion similar to bacteria, thus eventually promoting injurious effects in diverse organs [20]. Therefore, the gut becomes a pivotal proinflammatory organ promoting deleterious effects in even distant organs, through release of DAMPs, without the need of systemic bacterial translocation [18, 20].

3) The third group of intestinal barrier dysfunction involves

Manuscript submitted May 31, 2018, accepted June 7, 2018

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doi: <https://doi.org/10.14740/gr1053w>

stable patients with chronic pathologic conditions that present a low-grade translocation of enteric microbes and immunostimulatory bioproducts from the gut lumen first in the lamina propria and thereafter in the systemic circulation, promoting a chronic immune activation associated with disease progression and/or development of complications and comorbidities from other organs [1, 21, 22]. This intestinal barrier dysfunction group encompasses patients with HIV infection, liver cirrhosis, chronic viral hepatitis B or C, non-alcoholic steatohepatitis or non-alcoholic fatty liver disease, patients with inflammatory bowel diseases, celiac disease, irritable bowel syndrome, obesity and diverse autoimmune conditions [1, 21-23]. For example, in HIV infection, intestinal barrier dysfunction, BT and chronic immune activation have been associated with cardiovascular, neurocognitive and lymphoproliferative comorbidities, despite effective viral suppression with modern antiretroviral treatment; and in liver cirrhosis intestinal barrier dysfunction has been associated with all of its complications, namely spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, variceal bleeding, progression of liver injury and hepatocellular carcinoma [21, 22].

In conclusion, the Hippocratic quote “all disease begins in the gut” seems to be true, over 2,000 years later, for diverse pathological conditions. Our knowledge on the pivotal role of the intestinal barrier and gut microbiota in health and disease has been majorly developed and constitutes currently a scientific field of intense research. Clinicians should not neglect considering this central pathophysiological role of the gut and should apply all necessary preventive measures to protect the integrity of their patients’ intestines in diverse intestinal and extra-intestinal diseases. Future research with application of modern systems biology approaches, namely using genomics, transcriptomics and proteomics might lead to specific and potentially individualized pharmacological targets for intervention to control intestinal hyperpermeability.

Conflict of Interest

None of the authors has any conflict of interest to report that may be related to this submission.

Author Contributions

All authors contributed equally.

Funding

No funding by any private or public party was received for this Editorial.

Abbreviations

TJ: tight junctions; BT: bacterial translocation; PAMPS: pathogen-associated molecular patterns; DAMPs: danger-associated

ated molecular patterns; PRR: pattern recognition receptors; MODS: multiple organ dysfunction syndrome

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