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Review

The role of immunomodulators on intestinal barrier homeostasis in experimental models

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SUMMARY

The intestinal epithelium is composed of specialized epithelial cells that form a physical and biochemical barrier to commensal and pathogenic microorganisms. However, dysregulation of the epithelial barrier function can lead to increased intestinal permeability and bacterial translocation across the intestinal mucosa, which contributes to local and systemic immune activation. The increase in these parameters is associated with inflammatory bowel disease, physical exercise under heat stress, intestinal obstruction, ischemia, and mucositis, among other conditions. Lately, there has been growing interest in immunomodulatory nutrients and probiotics that can regulate host immune and inflammatory responses and possibly restore the intestinal barrier. Immunomodulators such as amino acids (glutamine, arginine, tryptophan, and citrulline), fatty acids (short-chain and omega-3 fatty acids and conjugated linoleic acids), and probiotics (*Bifidobacterium*, *Saccharomyces*, and *Lactobacillus*) have been reported in the literature. Here, we review the critical roles of immunomodulatory nutrients in supporting gut barrier integrity and function.

1. Introduction

The term intestinal barrier refers to the ability of the intestinal epithelium to separate intraluminal substances from the rest of the human body. The intestinal epithelium is a polarized single layer of cells that constitutes the largest and most important selective barrier against the external environment (Fig. 1). In addition to its known function of nutrient absorption, it also plays roles in immune response.

The specialized architecture of the intestinal epithelium maintains a selective barrier by forming interconnected protein networks between enterocytes; these networks, known as desmosomes, adherens junctions, and tight junctions, prevent the absorption of many potentially harmful substances. These networks involve transmembrane proteins that associate with adjacent cells and adaptor proteins that connect to the cytoskeleton. Substances can permeate the epithelium by two pathways, transcellular and paracellular routes, as shown in Fig. 1. Absorption mainly occurs via the transcellular pathway when molecules are hydrophobic. Passage via the paracellular route is regulated by tight

Non-standard abbreviations: BT, bacterial translocation; DAI, disease activity index; IP, intestinal permeability; sIgA, immunoglobulin A, secretory; TNF, tumor necrosis factor; NF-κB, nuclear factor-κB; NO, nitric oxide; HSP, heat shock protein; iNOS, inducible NO synthase; KC, keratinocyte-derived chemokine; DSS, dextran sodium sulfate; IκBα, inhibitor protein of IκBα; SCFA, short-chain fatty acid; CLA, conjugated linoleic acid; TBT, tributyrin; ω-3, omega-3; COX-2, cyclooxygenase-2; TNBS, 2,4,6-trinitrobenzene sulfonic acid; PPARs, peroxisome proliferator-activated receptors; PUFAs, polyunsaturated fatty acids.

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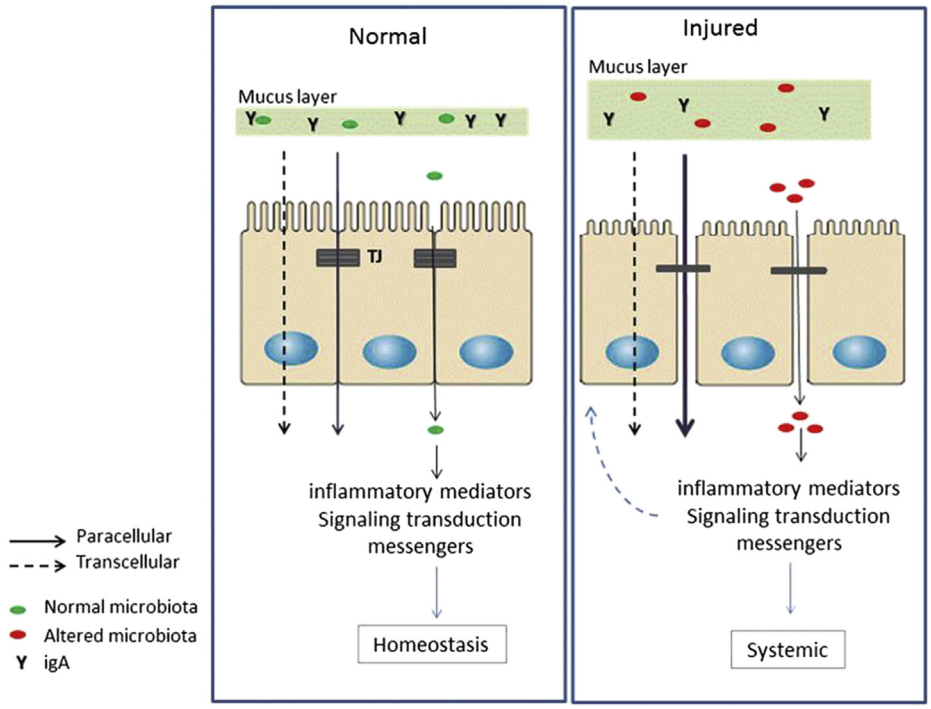

Fig. 1. Intestinal barrier in homeostasis and in the injured state. The intestinal barrier is composed of a single cell layer of epithelial cells. Apical junctions (e.g., tight junctions, TJ) that bind epithelial cells and regulate the movement of paracellular antigens and substances across the intercellular space between epithelial cells (———). If an injury occurs, this space can increase, facilitating the passage of harmful substances, which leads to a cascade of biochemical events that result in inflammation and/or apoptosis. Transcellular permeability is associated with the movement of antigens and molecules from the lumen into the mucosa through intestinal epithelial cells (- - - -). Enterocytes and other specialized cells secrete mucins that create the mucus layer. Intestinal epithelial cells secrete IgA in homeostasis, but when an injury occurs, this production is altered.

junctions located between the apical lateral membranes of adjacent enterocytes that react to stimuli like pathogens, commensal bacteria, and bacterial products such as lipopolysaccharides (LPS). Tight junctions selectively regulate the movement of fluids, nutrients, microbes, and toxins across the epithelium and thereby set up an efficient semi-permeable barrier [1]. The establishment and maintenance of tight junctions is crucial for both cellular polarity and epithelial barrier function of the intestinal epithelium.

Epithelial cells permit a small amount of luminal antigens, such as bacteria, to transcellularly cross the epithelium to extraintestinal sites (e.g., liver, spleen, kidney, and bloodstream) via endocytosis; this process is known as bacterial translocation (BT). Low levels of BT are normal and activate a host's immune system. However, when this barrier undergoes damage, it results in increased intestinal permeability (IP) and BT across the intestinal mucosa, which can contribute to the release of systemic inflammatory mediators, induction of signaling transduction messengers, and activation of immunological cells, leading to the development of inflammation and sepsis. Various stress conditions, for instance, physical exercise under heat stress [2], intestinal obstruction [3], and cancer treatment are usually associated with increased IP and BT. Furthermore, changes in intestinal microbiota colonization can cause irritable bowel syndrome [5], inflammatory bowel disease [6], and mucositis [7] involving alterations of the intestinal epithelium.

Host defense is responsible for distinguishing commensal microorganisms from pathogens. Enterocytes secrete immune mediators to react with antigens, such as antibacterial peptides, immunoglobulin A, secretory (sIgA), and chemokines [9]. Cytokines, such as the proinflammatory cytokines interferon-gamma (IFN-γ) and tumor necrosis factor (TNF), as well as anti-inflammatory interleukins (IL)-4, IL-5, IL-9, and IL-13, are also produced as immune mediators in response to injury. Furthermore, the presence of the mucus layer also acts as a protective feature of the intestinal barrier, interacting with bacterial surfaces, and eliminating bacteria by peristalsis [8].

Nuclear factor (NF)-κB is a signaling messenger that regulates the activity of cytokines and other biological defenses. Its activation is stimulated by bacteria, viruses, cytokines, and oxidative stress, as well as ionizing radiation and chemotherapeutic agents [4,7,10]. Because of its different target genes, NF-κB has been linked with the pathogenesis of several diseases.

The recent benefits of immunomodulatory nutrients and probiotics have been demonstrated to modulate host immune and inflammatory responses and restore the intestinal barrier after injury. Immunomodulators such as amino acids [2,3,11–13], fatty acids [14–16], and probiotics [17,18], have been reported in the literature.

2. Amino acids

Amino acids are essential substrates for the synthesis of different nitrogenous compounds such as proteins. They serve as important physiologic fuels for the small intestinal mucosa and important substrates for synthesis of many products, including nitric oxide (NO) and polyamines. Recent studies have showed important therapeutic functions for certain amino acids such as glutamine (Table 1), arginine (Table 2), tryptophan [19], and citrulline [13] in gut-related diseases [20].

2.1. Glutamine

Glutamine is a nonessential amino acid with many functions. For example, it is quantitatively the most important fuel for the intestinal tissue and immune cells, it is a key precursor for the intestinal synthesis of glutathione [21], and is important for intestinal surface integrity [22–24].