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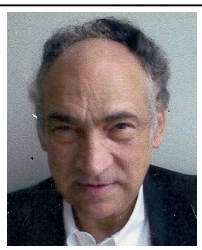
Intestinal Barrier Dysfunction in Human Pathology and Aging

Marcel Cerqueira César Machado and Fabiano Pinheiro da Silva



Marcel C.C. Machado

Emergency Medicine Department, University of Sao Paulo, Brazil

Fabiano P. da Silva

Abstract: ***Background:*** The intestinal barrier is a layer that constitutes the most important barrier against the external environment. It can be partially disrupted in several frequent scenarios, leading to autoimmune and inflammatory diseases. Translocation of intestinal luminal contents into the intestinal mucosa may induce inflammatory disorders and therefore tissue injuries. Disruption of the intestinal barrier may induce local and systemic injuries and may play a role in inflammatory bowel disease, liver diseases, the aging process and in the systemic inflammatory response syndrome, including lung, heart and brain dysfunctions.

Conclusion: Here, we discuss how the maintenance of it selectively permeability is crucial to adequate absorption of nutrients, electrolytes and water while maintaining effective host defense properties in order to avoid not intestinal injury, systemic inflammation and distant organ damage.

Keywords: Intestinal barrier, inflammation, bacterial translocation.

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INTRODUCTION

The intestinal barrier is the interface between the organism and the content of the intestinal lumen. The luminal content is mainly constituted of 500–1500 different bacterial species with 10–100 trillion bacteria [1]. Intestinal microbiota differ between people and between species. The main factors that regulate intestinal microflora are age, health status, diet and genetic factors (antimicrobial peptides) [2, 3]. The intestinal epithelial barrier is the border between intestinal microbiota and the organism. It is a complex anatomical structure that comprises an uninterrupted monolayer of epithelial cells held together by intercellular junctional complexes that maintain highly selective permeability, prohibiting the migration of microbiota elements and other luminal content (food, antigens and others deleterious substances) into the intestinal mucosa [4, 5]. Besides the epithelial line, there is a mucous layer of mucin glycoprotein secreted by goblet cells that acts as a physical agent between the intestinal lumen and the epithelial layer [6, 7].

The intestinal mucosa is formed by a layer of epithelial cells strongly held together by a junctional complex of molecules that ensures impermeability to mucosal bacteria, toxins and other toxic substances. Paneth cells, which produce antimicrobial peptides, enteroendocrine cells and stem cells are part of this complex, in addition to IgA-producing B lymphocytes, macrophages and other inflammatory cells in the sub mucosa (Fig. **1**). Underlying these cells are cells similar to astrocytes, the glial cells of the gut. Several studies have demonstrated the importance of these cells in maintaining intestinal barrier integrity. These cells produce a number substances that act in a paracrine manner and whose net effect is to protect the intestinal mucosa. One protein, glial cell-derived neurotrophic factor, can inhibit the expression of pro-inflammatory cytokines such as IL-8, TNF and myeloperoxidase, and inhibit apoptosis in intestinal mucosal cells [8].

*Address correspondence to this author at the Faculdade de Medicina da Universidade de São Paulo, Laboratório de Emergências Clínicas (LIM-51), Av. Dr. Arnaldo, 455 sala 3189, CEP 01246-000, São Paulo - SP, Brazil; Tel: +55 11 3061 8480; Fax: +55 11 3061 8480;
E-mail: mccm37@uol.com.br

Translocation of the contents of the intestinal lumen into the intestinal mucosa may induce inflammatory disorders and therefore tissue injuries [9]. Disruption of the intestinal barrier may induce local and systemic injuries and may play a role in inflammatory bowel disease, liver diseases, aging processes and in systemic inflammatory response syndrome, including lung, heart and brain dysfunctions. The intercellular junctional complex comprises several proteins, including claudins, occludin and zona occludens, which are important to maintain the selective permeability of the intestinal mucosa. Intestinal epithelial cell damage, disruption of the intercellular junctional complex and regeneration difficulty were reported to be involved in bacterial translocation and systemic damage in acute systemic inflammatory states [10]. The importance of the enteric nervous system in the maintenance of intestinal barrier function has been recently stressed [11]. There is an interplay between intestinal barrier dysfunction and systemic inflammation, as intestinal barrier dysfunction leads to systemic inflammation and systemic inflammation results in intestinal barrier dysfunction. Antimicrobial peptides are a component of the animal innate immune system, being expressed on mucosal surfaces, including the gastrointestinal tract. Antimicrobial peptides, besides their antimicrobial activity, regulate intestinal mucin and tight junction protein expression and microbiota composition, and are therefore important to the maintenance of intestinal barrier function [12].

INTESTINAL BARRIER DYSFUNCTION AND INTESTINAL INFLAMMATORY DISEASES

Previous reports have shown that host innate immune signaling can modulate intestinal bacteria and therefore influence host susceptibility to colitis. Patients with intestinal inflammatory diseases (ulcerative colitis and Crohn's disease) seem to develop intestinal damage in the absence of a specific pathogen. Genetic studies in patients with inflammatory bowel disease demonstrated that innate immunity may play an important role in the pathogenesis of inflammatory bowel disease [13, 14]. Several reports have shown that the innate immune system mediates the interaction between the intestinal microbiota and the organism, being essential for intestinal inflammatory responses to pattern recognition receptors (PRR), including toll-like receptors (TLR). Members of the innate immune

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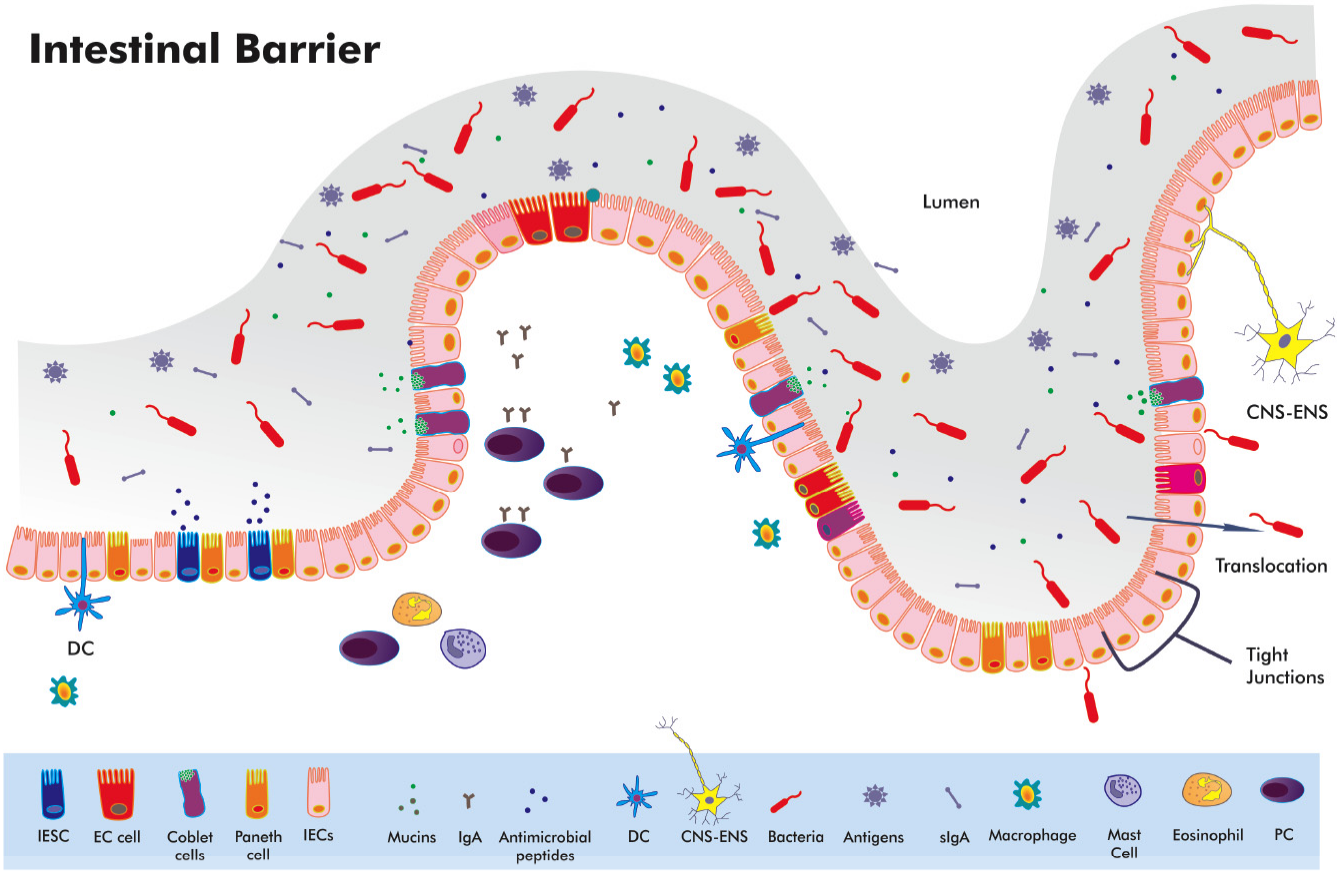

Fig. (1). Schematic drawing illustrating the inflammatory responses and cellular repair mechanisms of intestinal mucosa in the presence of bacterial translocation. IEC: intestinal epithelial cell; IESC: intestinal stem cell; EC: enterochromaffin cell; DC: dendritic cell; CNS-ENS: central nervous system-enteric nervous system; PC: plasma cell; IgA: immunoglobulin A; sIgA: secretory IgA.

system are important locally to maintain the balance between microbiota and the host [15, 16]. A recent publication demonstrated that increased epithelial TLR4 signaling was associated with disruption of the intestinal barrier and increased density of mucosa-associated bacteria and bacterial translocation. Furthermore, increased epithelial TLR4 signaling was associated with altered expression of antimicrobial peptide genes and altered epithelial cell differentiation [17].

INTESTINAL BARRIER DYSFUNCTION AND SYSTEMIC INFLAMMATION

The concept that the intestines may be a reservoir for systemic inflammation developed many years ago [18]. It was reported several decades ago that hypovolemic shock damages the intestinal barrier and induces translocation of intestinal contents into the bloodstream [19]. This translocation happens even without anatomical damage to the intestinal mucosa. The loss of intestinal macromolecular barrier function in the hypovolemic state was reported in several experimental studies. Intestinal barrier dysfunction has been observed in aortic dissection [20], aortic surgery [21], Pringle maneuver [22], acute pancreatitis [23, 24], hemorrhagic shock [25], in burns [26] and in septic shock [27]. Discussion on the relevance of bacterial translocation in the pathogenesis of systemic inflammatory responses and multiple organ dysfunction has been recently reported. It has been established that loss of intestinal barrier function with systemic spread of gut-derived harmful substances (non-microbial, pro-inflammatory and others) may cause a septic condition, and contribute to distant organ failure [28]. In acute pancreatitis, a relationship was found between bacteremia, infected necrosis, organ failure and intestinal barrier dysfunction [29].

Intestinal fatty acid binding protein (IFABP) is 15 kDa protein located at the tips of intestinal mucosal villi and can leak into the bloodstream following enterocyte damage [30]; therefore, serum levels of IFABP can be used as a marker of intestinal dysfunction. Serum IFABP is elevated in severe attacks of acute pancreatitis [24], in sepsis [27] and in hepatic surgery using the Pringle maneuver [22]. Recent unpublished data from our laboratory suggests that hypotension during hepatic surgery is followed by increased IFABP serum levels, indicating that even a mild decrease in arterial pressure may damage intestinal epithelial cells.

INTESTINAL BARRIER DYSFUNCTION AND LIVER DISEASES

The anatomical location of the liver confers important functions to this organ related to the intestinal microbiota. The connection between the gut and liver makes the liver vulnerable to translocation of intestinal lumen contents to the portal vein. Intestinal mucosa provides the first line of defense, and the liver the second, to harmful substances that may escape intestinal detection. As mentioned, PRR (including TLR members of the innate immune system) are important for maintaining a local balance between microbiota and the host.

PRR, mainly TLR, have been reported in the liver itself as providing additional mechanisms of detection related to translocation of intestinal contents. Several liver cells express TLR that have been recognized as critical factors in the pathogenesis of chronic

liver disease. These TLR respond to endotoxin stimulation, producing pro-inflammatory cytokines such as TNF-α, IL-6 and IFN-γ. Endotoxin translocation, secondary to intestinal barrier dysfunction, may therefore induce liver damage [31]. The relationship between alcoholic liver disease and intestinal barrier dysfunction has been discussed previously [32, 33].

Data from several studies have demonstrated that alcohol, through the metabolite acetaldehyde, can damage the intestinal barrier by disrupting the intercellular junctional complex [34], resulting in increased plasma endotoxin levels. Recent reviews examining the effects of alcohol on the intestines have been reported [32, 33]. Additionally, studies have reported that intestinal barrier function is altered in patients with severe liver damage and this can affect patient survival [35]. It is therefore conceivable that hepatic lesions can reduce the function of the liver as the second line of defense to harmful substances that escape intestinal detection and may induce a systemic inflammatory response that induces secondary intestinal barrier dysfunction.

INTESTINAL BARRIER DYSFUNCTION: HEART, LUNGS AND BRAIN CONNECTIONS

Some reports suggest that intestinal barrier dysfunction may be associated with coronary heart disease. Patients with inflammatory bowel disease seemed to have more frequent coronary heart disease when compared with a match control group in one study [35].

A recent report established a connection between intestinal microbiota metabolism of phosphatidylcholine and atherosclerosis [36]. Additionally, patients with myocardial dysfunction may have an altered intestinal microcirculation resulting in intestinal barrier dysfunction [37], with the translocation of bacterial and other harmful products further increasing pro-inflammatory cytokine production and contributing to cardiac dysfunction. A recent report addresses the interplay between intestinal barrier dysfunction and chronic heart failure [38].

Data on the interaction between the heart and gut are still preliminary, and further studies are needed before a definitive link between these two important systems can be made and fully understood [39].

With regard to the lungs, a recent report suggests a correlation between increased permeability of gastrointestinal mucosa and moderate to severe asthma [40].

In acute severe intestinal barrier dysfunction, such as that which occurs in sepsis or systemic inflammatory syndrome, several reports have linked lung damage and the development of adult respiratory distress syndrome and multiple organ failure syndrome with bacterial and other harmful products that have translocated into systemic and portal circulation, further increasing secretion of several pro-inflammatory cytokines [41, 42].

Some studies have reported the possibility of brain and gut interactions, especially in Parkinson's disease, with intestinal barrier dysfunction and with excessive stimulation of the innate immune system inducing systemic inflammation and brain damage [43, 44]. However, the causes of altered intestinal permeability in brain diseases are not fully established, and require further study [45]. A recent report suggests a possible relationship among psychological stress, intestinal barrier dysfunction and irritable bowel syndrome [46] (Fig. **2**).

INTESTINAL BARRIER DYSFUNCTION AND AGING

Aging is associated with increased morbidity and mortality from systemic inflammation, as observed in acute pancreatitis, sepsis and other inflammatory disorders [47]. Although some authors attribute this increased vulnerability to comorbidities in the elderly [48], others have reported that advanced age is an independent prognostic factor in these situations [49].

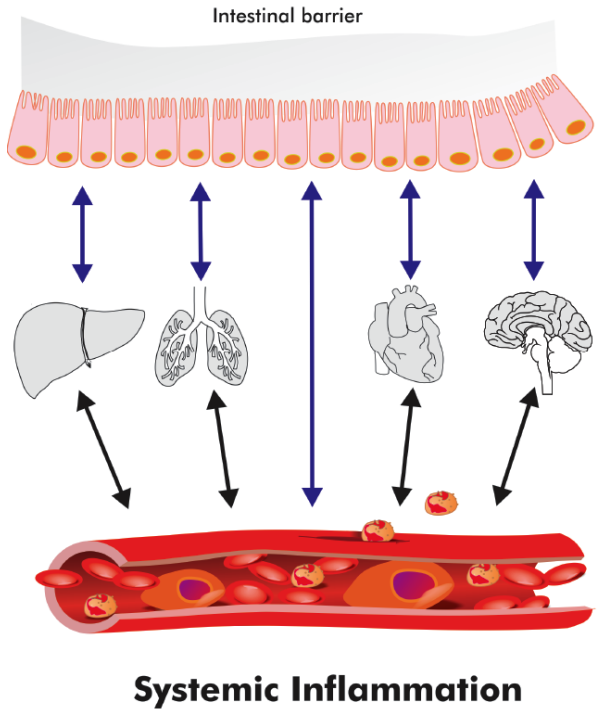

Fig. (2). Effects of bacterial translocation in different organs and causing systemic inflammation.

The mechanisms behind a poor prognosis are not fully elucidated. Some possibilities have been suggested, among them is the possibly of a previous presence of a pro-inflammatory state in the elderly [50] or specific changes in organs, including the lungs, which could release a second wave of cytokines during a systemic inflammatory process that would further worsen systemic inflammation [51]. Another possibility is the presence of increased intestinal lesions and, consequently, higher bacterial translocation in the elderly. This concept is based on the fact that the elderly, despite presenting local lesions similar to those observed in young patients, have more severe acute pancreatitis [49], and gut barrier dysfunction has been implicated as the primary cause of bacterial translocation and multiple organ failure in this population [52].

The causes of most dysfunction in gut barrier in the elderly in the presence of systemic inflammatory processes are not well established. Cytokine production in elderly patients with sepsis is similar to that of younger patients [53, 54]. Clinically, we have observed that elderly patients undergoing major surgery initially proceed with excellent recovery, which may be unexpected from the risk/size of the intervention, but later develop a severe inflammatory response, frequently associated with poor outcomes. This delay in the explosive production of cytokines (such as IL-6) has been observed in elderly patients undergoing different surgical interventions [55]. A recent publication reported that lung cells from older animals after exposure to endotoxin produced pro-inflammatory cytokines at a later stage but for a longer duration when compared with cells from young animals [56]. These findings support our observations, and those of other authors [55], on elderly patients' responses to surgical trauma. Increased cytokine production was also observed in mononuclear cells from elderly patients *in vitro* when compared with the young [57].

These and other findings suggest that aging may not promote an increased inflammatory response but rather a delayed or prolonged pro-inflammatory response. This pro-inflammatory state may be the result of some kind of deregulation of the genes involved in inflammatory response processes [54].

TLR4 was found to show increased expression and CD14 has been observed in elderly patients with sepsis when compared with a younger population [58]. This stronger inflammatory response in the elderly is probably a result of changes in the innate immune system. Changes in adipose triglyceride lipase in older animals was related to an increased inflammatory response [59].

A previous study demonstrated that heat shock protein 70 modulates the inflammatory response in sepsis, preventing apoptosis of intestinal cells and systemic inflammation, and is expressed to a lesser degree in the elderly [60]. This may go some way to explaining the intestinal barrier dysfunction observed in these patients.

The pro-inflammatory state observed in aging populations may be related to dysfunction of the intestinal barrier, and therefore to increased bacterial translocation. An increased pancreatic infection rate was observed in older animals with acute pancreatitis [61]. This finding was also observed by our group in a study on elderly animals with acute pancreatitis [62].

Given that administration of agents to block platelet-activating factor reduces bacterial translocation [63], it is plausible that the pro-inflammatory response characteristically observed in the elderly is responsible for increased intestinal inflammation and tissue damage, with more severe dysfunction of the intestinal barrier and increased bacterial translocation.

In experimental studies by our group, we observed greater production of pro-inflammatory cytokines and reduced production of anti-inflammatory cytokines in the bowels of older rats subjected to acute pancreatitis when compared with a young population. It is possible that increased intestinal inflammation due to age itself is responsible for the majority of intestinal barrier dysfunction and increased bacterial translocation, and thus increased systemic lesions [10].

Recently, we evaluated the presence of antimicrobial peptides in the intestinal wall of older mice and young rats subjected to acute pancreatitis. Surprisingly, we found a greater production of defensins in the older animals [64]. This finding is contrary to the hypothesis that aging leads to immunosuppression. Antimicrobial peptides are an important part of innate immunity and are reasonably well preserved on the evolutionary scale, being present in most living species. Despite having as their main action an antimicrobial effect, such substances regulate many immune functions.

Dysfunction of the intestinal barrier in complex inflammatory diseases may be related to systemic responses. In a previous clinical study that investigated plasma levels of 6-FABP (a fatty acid binding protein), protein was found to localize in intestinal villi and escaped into peripheral circulation in cases of intestinal lesions. We observed an increase in 6-FABP in the peripheral circulation of patients with sepsis and septic shock, and it proved to be an excellent marker of intestinal injury in this situation [27]. Although we have no robust data yet about the causes of most intestinal barrier dysfunction in elderly patients with systemic infections, the experimental and clinical findings in patients with acute pancreatitis suggest that changes to the intestinal barrier may be responsible for the increased vulnerability seen in the elderly. Experimental work by our group showed greater Cox-2 gene expression in the gut of older rats with acute pancreatitis compared with young rats, indicating increased intestinal inflammation. Increased expression of genes related to intercellular junction proteins were also observed in young rats, suggesting that, in situations of intestinal damage, young animals are better able to restore intestinal barrier integrity than older ones [10].

The intestinal microbiome in the elderly, particularly in centenarians, shows marked differences from the young [65], and has been the subject of abundant clinical work, including as a possible therapeutic target in several complex diseases.

The intestinal microbiome varies due to environmental factors and diet [2], and it is possible that it could be adjusted or manipulated under various conditions; for example, in preparation for surgical procedures. In a recent experimental study using older animals with atrophy of the intestinal mucosa, damage to intercellular junctions and increased intestinal bacterial count were observed [66]. The intestinal barrier thus can already present functional and architectural changes in the elderly during systemic inflammation, as well as changes in the intestinal microbiome. And these pre-existing changes can add up, caused by systemic inflammation resulting from infection, trauma or surgery. Knowledge of the changes might be able to be used to minimize the effects of gut barrier dysfunction in these circumstances. It is possible that early enteral nutrition before surgical procedures or for systemic infections could substantially reduce damage to the intestinal barrier [67]. The delivery of macromolecules can preserve bowel function while maintaining a near normal immune response [68]. While such care is important for patients in general, it may be especially important for the elderly in reducing intestinal barrier dysfunction and systemic repercussions.

Recent work has demonstrated that plasma levels of intestinal alkaline phosphatase are associated with intestinal barrier integrity, suggesting that the administration of this enzyme could maintain or restore the integrity of intestinal mucosa [69]. There is the need, however, for controlled studies to verify the usefulness of this type of treatment. This particular paper again emphasized the importance of enteral feeding to maintain the integrity of intestinal mucosa [69].

Glial cells of the intestine produce glial-derived S-nitrosoglutathione (GSNO), a substance with antioxidant and protective effects on intestinal mucosa. The protective effect seems to be related to increased expression of the intercellular junction proteins ZO-1 and occludin. These data and our own experimental observations with older animals suggest a possible defect in intestinal glia in elderly patients, with an increase in the production of inflammatory cytokines through the reduced production of GSNO, glial cell-derived neurotrophic factor and other important substances used in barrier integrity maintenance. Indeed, the administration glial cell-derived neurotrophic factor restores intestinal barrier ablation in transgenic mice with intestinal glia [8].

The data available gives support to the hypothesis that previous alterations of the intestinal barrier in the elderly are exacerbated during systemic inflammation processes. There is the possibility that therapeutic interventions may have a favorable influence on the intestinal barrier in elderly, thus reducing systemic effects and mortality in the systemic inflammatory processes observed in this population.

CONCLUSION

The dysregulation of intestinal barrier functions has been associated with several inflammatory and immune disorders. It promotes sustained systemic inflammation through the leakage of bacterial products, cell debris and other danger signals into the bloodstream, causing local and distant cell death and promoting significant organ damage.

Therapeutic strategies aimed at maintaining intestinal integrity are crucial, in conjunction with systemic drugs, for the resolution of the pathological processes discussed in this article. Disruption of the intestinal barrier may be the driver maintaining systemic inflammation, and both conditions need to be targeted, because one tends to sustain the other and perpetuate critical illnesses.

CONFLICTS OF INTEREST

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M.C.C.M. reviewed the literature and wrote the first draft. F.P.S. helped him to reach the final version.

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