Leaky gut – concept or clinical entity?

Eamonn M.M. Quigley

Purpose of review
This article evaluates the current status of the gut barrier in gastrointestinal disorders.

Recent findings
The gut barrier is a complex, multicomponent, interactive, and bidirectional entity that includes, but is not restricted to the epithelial cell layer. Intestinal permeability, the phenomenon most readily and commonly studied, reflects just one (albeit an important one) function of the barrier that is intimately related to and interacts with luminal contents, including the microbiota. The mucosal immune response also influences barrier integrity; effects of inflammation *per se* must be accounted for in the interpretation of permeability studies in disease states.

Summary
Although several aspects of barrier function can be assessed in man, one must be aware of exactly what a given test measures, as well as of its limitations. The temptation to employ results from a test of paracellular flux to imply a role for barrier dysfunction in disorders thought to be based on bacterial or macromolecular translocation must be resisted. Although changes in barrier function have been described in several gastrointestinal disorders, their primacy remains to be defined. At present, few studies support efficacy for an intervention that improves barrier function in altering the natural history of a disease process.

Keywords
claudin, intestinal barrier, occludin, permeability, tight junction, zonulin

INTRODUCTION

A casual survey of the popular press and various other media could lead one to believe that a 'leaky gut' presents a major threat to mankind and forms the basis for many epidemics that threaten to engulf the populace of North America and Western Europe. Disorders as diverse as food intolerance, fibromyalgia, chronic fatigue syndrome, and autism are thought to owe their symptomatology to a defect in the gut wall that allows various vile humors to enter the circulation and poison the unwary host. The purveyors of these dire dictums view the barrier as a single-cell thick, epithelial layer with disruption of intercellular connections leading to increased permeability and consequent access to the blood stream for various noxious chemicals, intact bacteria and a host of dietary and microbial components; this train of events then proclaimed, usually unsupported by any data, as the primary abnormality in a host of diseases. Various diets and therapies are then dutifully recommended based on their ability to 'strengthen' the barrier and restore permeability to physiological levels. Among those agents touted for their 'barrier-restoring' properties are a number of strategies that can modulate the microbiota, most notably probiotics. Here again the volume of claims outstrips solid clinical evidence by a country mile. The goal of this review is several fold. Firstly, it will define the gut barrier, describe its components and examine how the luminal microbiota interacts with it. Secondly, it will critically assess techniques that have been developed to measure gut barrier function in man and, in so doing, determine whether they are reproducible and sufficiently sensitive to detect changes in disease and in response to an intervention. Thirdly, it will evaluate, based on evidence, the role of gut barrier dysfunction in various diseases and disorders and, finally, it will examine whether interventions can rectify impaired barrier function and, thereby, influence the natural history of any disease

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KEY POINTS

- The ultrastructure and biology of the epithelial barrier have been revealed in considerable detail.
- Tools to study barrier function in man are available, but each is highly specific for a particular barrier component.
- Although barrier dysfunction has been described in a number of disorders, its role in their pathogenesis remains to be defined.
- The gut barrier is a target for novel therapies; the promise of this approach is yet to be realized.

or disorder. This assessment will pay particular attention to comparing and contrasting results obtained in animal models with those in the human disease/disorder.

THE GUT BARRIER – BASIC BIOLOGY

A passing glimpse at the considerable literature relating to the gut barrier and permeability makes it abundantly clear that these are highly complex issues and certainly not ones amenable to simplistic reduction [1–5]. In defining these concepts some take a very strict and focused approach regarding barrier and permeability as interchangeable terms both referring 'exclusively to changes in the flux of solutes and fluids across the epithelium' [5]. Others take a broader view and adhere to the concept originally advanced by Cummings who described the barrier as 'the complex structure that separates the internal milieu from the luminal environment' [6]. This latter approach is much more inclusive and encompasses entities that may have little or no role in regulating permeability but may contribute to the integrity of the gut and, thereby, the individual in other ways [7▪▪]. In this approach, as will become abundantly clear, the barrier and permeability are not interchangeable terms. Indeed, multiple factors contribute to the barrier, in the broadest meaning of the term, and include the mucus layer (or layers), peptides with protective and often antibacterial functions that are secreted into the mucus layer (e.g., defensins, lysozyme, and Reg3), the unstirred water layer, and the epithelium [2,4,7▪▪]. Other factors play an important role in the protection of the epithelium from potential invaders within its local (luminal) environment: the host immune response [including the production of immunoglobulin A (IgA), cytokines, chemokines, and mast cell proteases] as well as neuro-endocrine responses [leading to the generation of 5-hydroxy tryptamine (5-HT), histamine, cannabinoids, among others] [2,4,7▪▪]. As long as one is aware of these differing approaches to the definition of the barrier and of its relationships to permeability (the target of so many of our measurements, especially, *in vivo* in man) one can understand the relevant and related literature.

The gut barrier must be viewed as a dynamic entity capable of interacting with and responding to various stimuli. Furthermore, in terms of ultrastructure and function, the barrier demonstrates significant regional variation along the gut with the colonic barrier being much tighter (i.e., less permeable) than the small intestine. Variations in permeability are also evident on a much more local level; in the small intestine pore size increases from just 4–5 Å at the villus tip to over 20 Å at the base of the crypt [4]. Interactions with the microbiota are especially important and must be viewed as bidirectional; the microbiota influences the barrier and elements of the barrier can impact on the microbiota [8,9▪,10,11]. There are, in effect, two mucus layers, a much thicker and loosely adherent outer layer where bacteria and bacterial products are abundant, and an inner firmly adherent layer where bacteria are sparse; these layers also vary considerably in dimension along the gut; the depth of both layers is greatest in the colon and much less so in the jejunum. It should also be stressed that the relative dimensions of the mucus layers and the epithelium are typically grossly misrepresented in pictorial renditions of the gut barrier with the mucus layer depicted as a narrow band atop a large enterocyte; in reality, the mucus layer can reach a depth of over 800 microns which is not much less than the height of an entire villus (range 500–1600 microns).

Conceptually, the term barrier may also be somewhat of a misnomer and may fail to adequately reflect the critical role of the 'barrier' as a conduit for bidirectional exchange between the lumen, the epithelium, and the sub-epithelial compartments. This may not only be essential for the absorption of fluid, electrolytes, and nutrients but also to enable the gut-associated lymphoid tissue to 'get to know' its commensal microbiota and develop a tolerant relationship with it. Dynamic interactions are key to barrier function. Indeed, observations derived from experimental models of colitis indicate that mild increases in intestinal permeability can lead to the activation of immunoregulatory pathways and, thereby, play a protective role [12].

At the ultrastructural level, much interest has surrounded the integrity of cell–cell junctions in the epithelium (Fig. 1). The space between cells (which governs the paracellular pathway for fluid and electrolyte fluxes) is regulated by structures that interlink enterocytes in the one-cell layer thick

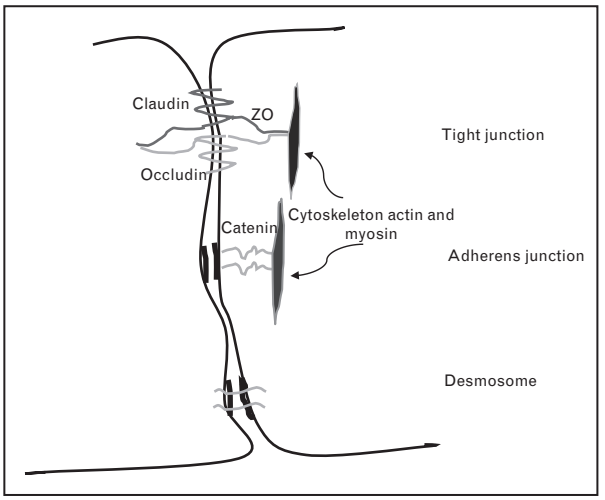

FIGURE 1. A schematic representation of the intercellular connections that facilitate the paracellular pathway. ZO, zonulin, zona occludens protein.

epithelium. On the apical aspect, cells are linked by tight junctions (zona occludens) and adherens junctions; on the basolateral aspect cells are linked by desmosomes. Given the critical role of the paracellular pathway in fluid and electrolyte absorption, the basic ultrastructure and biology of the tight junctions have been the focus of considerable interest [1–3]. Several families of membrane proteins contribute to a network of strands and grooves: occludins, claudins, and junctional adhesion molecules. These, in turn, attach to scaffolding proteins (zonula occludens proteins; ZO) and, through them, to the cytoskeleton of the enterocyte. The zonula adherens features cadherins (such as e-cadherin) that also link to the cytoskeleton via catenins (e.g., α-catenin 1 and β-catenin). Finally, gap junctions facilitate exchange of small molecules between cells.

The interactions between these proteins are highly complex and vary along the length of the gut. Furthermore, different members of the same family may exert very different actions; for example, although claudins 1, 3, 4, 5, and 8 serve to enhance the barrier, claudins 2, 7, 10, and 23 tend to weaken it and increase permeability [1,2]. Not only are these junctions intimately related to the cytoskeleton of the enterocyte but they are also interactive with the endothelium, submucosal immune cells, as well as the luminal environment. For example, the proinflammatory cytokines TNFα and IL-13 have important but different effects on the paracellular pathway [5]. Although TNFα increases flux by reorganizing of the tight junction to lead to a route that has low capacity and is nonselective (so-called leak pathway), IL-13 through upregulation of claudin-2 forms a paracellular cation and water channel that is high capacity and charge, and size selective (the so-called pore pathway) [5].

It is very important to understand that even when disrupted, the paracellular pathway is not capable of transporting very large molecules, not to mind permitting access to whole bacteria [7▪▪]. This is a fundamental issue; most in-vivo studies involve an assessment of the paracellular pathway and when increased permeability is discovered, wild extrapolations to bacterial translocation are made. Other routes/pathways such as epithelial gaps provided by apoptotic enterocytes or transcytosis across an intact cell must be invoked to explain such phenomena [7▪▪,13].

ASSESSING BARRIER INTEGRITY AND FUNCTION

Several techniques have been developed to assess the function of the barrier (and/or intestinal permeability) [4,14,15,16▪▪]. Some of the more commonly employed techniques, their site of action, and shortcomings are listed on Table 1. Of these, the most widely employed is the lactulose/mannitol test [17]. In interpreting results of this test one must be fully aware of the several factors that can influence results. As both lactulose and mannitol are metabolized by the colonic microbiota, they are not of use in assessing colonic permeability, thus their limitations in ulcerative colitis or irritable bowel syndrome (IBS) (if the colon is your target organ). Intestinal transit, intestinal surface area, epithelial cell integrity (cell death or damage may permit transport across nonparacellular routes), and kidney function may also impact on results. The techniques listed on Table 1 relate exclusively to permeability for fluid and electrolytes and small molecules (the barrier as equivalent to permeability). Many other approaches have been taken to assess barrier function in its broadest sense. Some have attempted to provide evidence of bacterial translocation; a phenomenon that can be readily demonstrated in a variety of animal models but that has proven so difficult to validate in man. Attempts to confirm the translocation hypothesis and to demonstrate its relevance to such disorders as shock, severe burns, and advanced liver disease have been hampered by problems inherent to the various assays, such as that for lipopolysaccharide, for example. Another approach is to measure bacterial metabolites, such as butyrate, that have been shown to enhance colonic barrier function. A variety of assays, such as those for citrulline, fatty acid binding protein (FABP), and claudin-3 have been proposed as measures of epithelial cell damage [7▪▪,15]. The structural and ultrastructural integrity of the barrier

Table 1. Tests of barrier function

Test	Molecules	Site	Material	Problems
Ex-vivo permeability				
Using chamber	Water, ions, sugars, etc.	Specific	Biopsy	Invasive
In-vivo permeability				
Lactulose/mannitol	Oligosaccharides of different molecular weights	Small intestine	Urine	Time consuming
Sucralose	Sucralose	Colon	Urine	Time consuming
Sucrose, glucose	Sucrose or glucose	Stomach	Urine	Time consuming
PEG 4000/400	PEGs	Gut	Urine	Time consuming
^{51}Cr-EDTA	^{51}Cr-EDTA	Gut	Urine	Radio activity

Cr-EDTA, chromium 51 labeled-ethylene diamine tetracetic acid; PEG, polyethylene glycol.

can also be assessed by conventional histologic methods and electron microscopy and immunohistochemistry. Other biomarkers, such as fecal levels of calprotectin, alpha-1 antitrypsin, defensins, and secretory immunoglobulin A may provide more indirect insights into epithelial integrity and/or the presence of processes that could impair barrier function [7▪▪,15].

What is critical in the interpretation of all of these tests is to understand exactly what they measure and what they do not measure; in this way pathophysiological leaps of faith and conclusions that are quite simply incorrect can be avoided.

Factors independent of the test or its performance characteristics can also muddy the results of permeability tests. Thus, high fat, high fructose, 'Western' diets increase permeability as does alcohol ingestion [18–20,21▪]. Other dietary issues are also relevant: vitamin A deficiency and changes in diet or the colonic microbiota that lower butyrate levels will also impair barrier function and increase permeability. Furthermore, though supportive data are derived virtually exclusively from animal models, the ingestion of prebiotics and probiotics could, in contrast, enhance barrier integrity [22,23].

GUT BARRIER FUNCTION IN DISEASE

Table 2 lists some of the many diseases/disorders where impaired barrier function has been described and a role in pathophysiology proposed [4,5,7▪▪,14,24–27,28▪▪,29–31,32▪,33,34]. In assessing the significance of a finding of increased permeability in a given disorder one must be aware of the limitations of current data so succinctly summarized by Odenwald and Turner who emphasized the following critical points [5]:

(1) Altered permeability may be an epiphenomenon; for example, any inflammatory process may impair barrier integrity and several other luminal and systemic factors, such as dietary components, bile acids, allergens, stress, and physical activity can independently influence barrier function.
(2) Experimental animal models have shown that impaired barrier function (e.g., genetically determined defects in barrier components) do not, in isolation, lead to the emergence of a disease phenotype [35].
(3) Increased permeability is not necessarily deleterious [12].
(4) As of now, there is no convincing evidence that an intervention that restores or improves barrier function in man can alter the natural history of a given disease or disorder. Though some encouraging data have emerged regarding the use of larazotide acetate, a regulator of tight junctional function [36], as adjunctive therapy in celiac disease [37▪▪], tight junctional regulation remains an exciting goal rather than an already attained achievement in human disease [38,39].

Table 2. Diseases and disorders associated with altered intestinal barrier function

Enteric infections and infestations
Shock, burns, trauma (multiorgan failure syndrome)
Inflammatory bowel disease
Obesity and metabolic syndrome
Type 1 diabetes
Human immunodeficiency virus infection
Liver disease
Graft vs. host disease
Celiac disease
Irritable bowel syndrome
Pancreatitis

Nonetheless, there are substantial pieces of circumstantial evidence that point to a more fundamental role for the barrier in certain disease states. In both inflammatory bowel disease (IBD) and celiac disease, for example, increased intestinal permeability has been demonstrated in clinically unaffected first-degree relatives [40,41▪]; in IBD this finding has been linked to the possession of genetic mutations linked to IBD [40]. In another chronic intestinal disorder, IBS, a predisposition to develop IBS *de novo* following an episode of bacterial gastroenteritis has been linked to genes that code for components of the gut barrier [42]; others have observed upregulation of a certain mRNA, miR-29a which has been demonstrated to regulate permeability through an effect on glutamine metabolism, in IBS [43▪,44]. Studies from animal models of liver diseases such as alcoholic liver disease and nonalcoholic fatty liver disease provide convincing evidence for interactions between the microbiota, barrier function, the inflammatory response, and the initiation and perpetuation of the various components of the liver disease [28▪▪,29–31]. Tantalizing as these observations are, they have yet to be described in man.

CONCLUSION

What then is the status of 'the leaky gut'? It is evident that this term should not be used as it is totally misleading in the context in which it is most commonly employed. Strictly speaking, this term should be restricted to those situations where epithelial tight junctional function is impaired resulting in increased flux across the paracellular route; a phenomenon, though accessible to measurement *in vivo* in man, has little to do with the diseases and disorders in which a 'leaky gut' is thought to play a role. In this instance the very concept is well holed below the water line and truly leaking from every pore.

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Conflicts of interest

There are no conflicts of interest.

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