Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Mucosal permeability and mast cells as targets for functional gastrointestinal disorders

Åsa V Keita[1] and Johan D Söderholm[1,2]

The intestinal mucosa is constantly exposed to harmful luminal content, and uptake is closely controlled and regulated by neuro-immune factors. If control is broken, it might lead to ongoing enhanced mucosal permeability, potentially resulting in functional gastrointestinal disorders. The importance of mast cells in the regulation of the mucosal barrier has become obvious, and increased numbers and more activated mast cells have been observed in irritable bowel syndrome, functional dyspepsia and gastroesophageal reflux disease. To target the disturbed mucosal permeability, directly or via mast cells, is therefore currently of major interest. For example, administration of mast cell stabilizers and probiotics have shown promising effects in patients with functional gastrointestinal disorders.

Addresses
[1] Department of Clinical and Experimental Medicine, Division of Surgery, Orthopedics and Oncology, Linköping University, Linköping, Sweden
[2] Department of Surgery, County Council of Östergötland, Linköping, Sweden

Corresponding author: Keita, Åsa V (asa.keita@liu.se)

Current Opinion in Pharmacology 2018, **43**:66–71

This review comes from a themed issue on **Gastrointestinal**

Edited by **Giovanni Sarnelli** and **Jan Tack**

https://doi.org/10.1016/j.coph.2018.08.011

Introduction

The intestinal barrier is one of the largest interfaces between the outer world and the human internal milieu. The intestinal mucosa is constantly exposed to luminal content, but under normal conditions only small amounts of antigens and bacteria pass through the epithelium and further interact with the cells of the innate and adaptive immune system. The ability to protect from harmful luminal content and to control the mucosal permeability is defined as *intestinal barrier function*. If the control of the intestinal barrier is broken, by for example enteric infections, it leads to enhanced mucosal permeability and disturbances in epithelial–immuno-neural interaction. A normal host can downregulate this response when the triggering event has been resolved. In a susceptible host ongoing enhanced mucosal permeability may result in mucosal damage, contributing to the development of for example inflammatory bowel disease or functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS), functional dyspepsia (FD) and gastroesophageal reflux disease (GERD). The importance of mast cells (MCs) in the regulation of mucosal barrier has previously been demonstrated by several groups. In this review, we will focus on the role of MCs in the regulation of mucosal permeability and mucosal permeability as target for FGIDs.

Mucosal permeability in FGIDs

Intestinal mucosal permeability is defined as the non-mediated intestinal passage of medium-sized hydrophilic molecules, that is passage of molecules down a concentration gradient without the assistance of a carrier system. However, from a pathogenesis perspective the terms 'mucosal permeability' or 'mucosal barrier function' also includes the transcellular route for macromolecules and microorganisms. Under normal conditions, the paracellular route is impermeable to protein-sized molecules and thus constitutes an effective barrier to antigenic macromolecules. During intestinal disorders alterations of both the paracellular and transcellular route have shown to be of major importance.

IBS

Several studies have demonstrated an increased intestinal permeability in IBS patients [1–4]. The underlying mechanisms include alterations in tight junction protein expression, localization or function, changes in the microbiota, presence of active inflammation and/or presence of pro-inflammatory cytokines and increased cell-shedding [5]. A recent large-scale genome-wide association meta-analysis revealed regulation of ion channel activity as the most likely pathway affecting IBS risk [6]. The identified genes include *FXDY1*, *FXDY3*, *FXDY5* and *FXDY7*, which encode for ion channels involved in regulation of tight and adherent junctions. In line with this, *CDH1*, encoding for the adherens junction protein E-cadherin, was previously recognized as a risk gene for postinfectious-IBS [7]. These studies implicate function of the apical junctional complex as an important factor in IBS pathogenesis. In addition, Zhou *et al.* [8•] recently demonstrated that oral glutamine administration restores intestinal permeability (lactulose/mannitol ratio) to normal in patients with postinfectious-IBS-D. Since glutamine is known to effect claudin-1 tight junction protein

[9], authors speculate that glutamine improves permeability through restoration of tight junction proteins.

It has become evident from IBS animal models, such as maternal separation [10] and chronic stress [11], that both the paracellular and transcellular pathways are involved in barrier dysfunction. For example, changes in paracellular permeability include a reduction of zonula-occludin-1 (ZO-1), disruption of apical claudin-1, occludin and ZO-1 [12,13] and an increased proteasome-mediated degradation of occludin [14]. Jejunal biopsies from IBS-D patients showed an upregulation in genes involved in epithelial barrier function, that is genes regulating cingulin and claudin-2, and simultaneously an upregulated expression of these proteins [15]. In addition, bowel dysfunction, perceived stress and number of MCs correlated with the upregulated genes and their respective target proteins. Studies on transcellular permeability are few. Lee *et al.* [16] showed increased transcellular permeability in rectal biopsies of IBS-D patients and, recently, we found increased transcellular passage to live bacteria in colonic biopsies of IBS-M, C and D patients compared to healthy subjects [17••], highlighting the involvement of the transcellular route also in humans. Interestingly, there is also some evidence that visceral hypersensitivity in IBS patients may be linked to a barrier dysfunction. Repeated application of IBS-C fecal supernatant into colon of mice triggered abdominal pain that was linked to enzymatic degradation of occludin and increased permeability [18].

FD

A study by Vanheel *et al.* [19] was the first one to demonstrate impaired duodenal mucosal barrier function in patients with FD. This was shown by reduced transepithelial resistance (TER), increased paracellular passage, and altered expression of several proteins of the apical junction complex. Further, the expression changes correlated with impaired duodenal integrity and low-grade inflammation. In a follow-up study [20•], activation of mucosal MCs and eosinophils was found in FD patients, however, no association to impaired paracellular permeability was found.

GERD

GERD is differentiated into erosive (ERD) and nonerosive reflux disease (NERD). Patients suffering from ERD have endoscopic visible breaks of the esophageal mucosal integrity [21]. Almost 70% of the patients with GERD symptoms do not display these mucosal changes in conventional esophagogastroduodenoscopy and are thus given the diagnosis NERD.

Increased permeability or abnormal TER can be induced by gastric acid affecting the apical membranes and the junctional complexes of the *stratum corneum*, the main components of esophageal barrier function [22]. Studies on barrier function in GERD patients are few, however, increased ion and water flow between the epithelial cells, resulting in dilated intercellular spaces (DIS), have been observed in ERD patients via microscopy, irrespective of endoscopy findings [23] or acid reflux time [24]. Jovov *et al.* [25] showed altered permeability in both erosive and non-erosive areas of patients with ERD. The cell-to-cell adhesion proteins contributing to impaired barrier function in ERD involve upregulation of claudin-1 [21], plakoglobin and desmoglein-1, desmoglein-2 and desmoglein-3 [26]. Although alterations of mucosal integrity (tissue impedance and permeability to fluorescein) in GERD patients are more pronounced in the distal than the proximal esophagus [27•], the proximal is more sensitive to acid exposure, suggesting that increased permeability is not directly involved in GERD symptoms.

Baseline permeability measurements in NERD patients have so far not been reported. However, NERD patients show abnormal responses in transepithelial potential difference to acid perfusion *in vivo* [28] and DIS that are reversible by omeprazole treatment [29].

MCs in FGIDs

It is well established that close connections between immune cells, such as MCs, eosinophils, or plasma cells, and nerve fibers are abundant in the intestinal mucosa [30,31]. As much as 70% of the mucosal MCs are in direct contact with nerves [32] and recently Buhner *et al.* [33••] proved a bidirectional signaling between submucous neurons and MCs in human ileum and colon. Nerve-MC signaling is of great importance in barrier dysfunction in stress [34] and FGIDs [35], and several studies have confirmed the role of MCs in barrier regulation [17••,36–38]. Upon neural stimulation, MCs are activated, directly or via other immune cells [39] and undergo piece-meal degranulation, a process leading to secretion of mediators. The exact mediators that induce barrier dysfunction in humans remain to be elucidated, however, TNF-α, IFN-γ and other cytokines, as well as histamine, chymase and tryptase [40,41] have been implicated.

Although the mechanisms are not fully elucidated, it is evident that bacterial stimulation leads to enhanced transport across the intestinal mucosa with production of pro-inflammatory cytokines by MCs, such as TNF-α, increasing transcytosis, and paracellular permeability by decreasing TER, the number of junctional strands and reducing the depth of the tight junctions [42,43].

IBS

Evidence for mucosal immune activation in IBS has been reported in some, but not all studies. Increased MC numbers have been found in the colon as well as in the small bowel. Guilarte *et al.* [44] demonstrated a pronounced increase in MC numbers and a higher level of luminal tryptase in the jejunum of patients with IBS-D.