Gut flora and mucosal function

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The mucosal lining of the gastrointestinal tract is the route through which ingested nutrients are absorbed. It also serves to separate potentially toxic luminal contents and flora. These functions appear to be mutually incompatible, but are achieved by regional specialisations in epithelial structure and organ function. Enteric bacteria interact with enterocytes by influencing cellular electrolyte transport and tight junction permeability in the colon. The products of bacterial metabolism are essential for colonocyte nutrition.

Introduction

The human body and its organs are contained within a continuous epithelial sheet. The most visible portion of this is the skin, but the mucosal epithelium of the gastrointestinal tract is by far the largest in terms of its surface area. The function of the mucosa lining the gastrointestinal tract is also inherently more complex.

The gastrointestinal mucosa provides two basic, but opposed functions. It is a route for transport of nutrients, but also a barrier to its potentially toxic luminal contents and flora. Motility within the tract is closely integrated with these functions to optimise exposure of luminal contents with the mucosa.

Barrier function

The degree of barrier function offered by the gastrointestinal mucosa varies markedly from oropharynx and oesophagus, to stomach, small and large intestine. A thickened, stratified squamous surface to the oropharynx and oesophagus, together with limited contact time, provide a very effective barrier to penetration by luminal antigen, toxin or microbial agent. Wetting by swallowed saliva also appears to be important in reinforcing the squamous epithelial barrier function. Gastric acid secretion appears to be an important mechanism which reduces the viable bacterial load of any contaminated food, although it is partially redundant in the typical Western diet, which is relatively sterile.

Gastric mucosa in the adult is regarded as a "tight" epithelium, highly impermeant to large molecules and also to electrolytes. This may be age-dependent, as there is evidence that, prior to weaning, the stomach is permeable to immunologically significant quantities of macromolecules[1]. This is relevant in food-allergic individuals, in whom gastric mucosal absorption of antigen can stimulate vomiting, which acts to remove the offending antigen. Antigen challenge stimulates gastric acid secretion in sensitised animals and delays gastric emptying[2,3]. These mechanisms denature potential antigen, delaying contact with the small intestinal mucosa, but also have relevance for an understanding of the role of the stomach in limiting microbial access to the small intestine. The stomach's defences do, however, fail to prevent colonisation with *Helicobacter pylori*, which is now recognised to survive effectively in gastric mucosa and induce chronic active gastritis[4]. Attachment occurs to epithelial cells and to mucus. Recent evidence suggests that in childhood infection the failure to eliminate *H. pylori*, with resulting atrophic gastritis and impaired gastric acid secretion, may lead to bacterial overgrowth of the small bowel or colonisation with enteric pathogens[5]. *H. pylori* has also been shown to be a risk factor for subsequent development of adenocarcinoma of the stomach[6].

The small intestinal mucosa is modified to maximise its surface area through mucosal folds, villi and microvilli. Barrier function has been best studied in this region. Simplistically, the small intestinal epithelium may be regarded as consisting of a continuous sheet of enterocytes joined around their circumferences by a specialised structure termed the junctional complex. Transepithelial penetration of this layer occurs by either active or passive mechanisms. The transcellular route involves a passage across apical and basolateral biomembranes and an intervening cytosolic gel. This route is well-adapted for active transport of selected electrolytes and nutrients, but provides an effective barrier to bacteria, and to passive movement of ions and hydrophilic solutes.

Pathogenic bacteria influence mucosal function, either by adherence to the apical surface, invasion of enterocytes, through the effects of toxins which alter cellular electrolyte secretion or absorption or through a combination of these mechanisms. Bacterial invasion with intracellular replication leading to necrosis and shedding of sheets of cells is best characterised by the dysentery associated with

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Shigella and enteroinvasive *E. coli* infection in the colon[7]. Enteric invasion also results in the local release of inflammatory mediators which act as intestinal secretagogues.

The apical brush border is also a target for injury by pathogenic organisms. Infections with enteropathogenic *E. coli*, *Giardia lamblia* and *Yersinia enterocolitica* are all associated with loss of overlying glycocalyx and shortening of microvilli[8]. The mechanism by which this occurs is uncertain, but may involve shortening of central actin filaments. Associated reduction in disaccharidase activity may contribute to malabsorption[9].

Absorption and Secretion

The sodium pump (Na^+ K^+-ATPase) on the basolateral membrane of the enterocyte is the prime moving force for both intestinal absorption and secretion. It does this by creating a low intracellular sodium content and thus a sodium concentration gradient across the cell membrane.

Fluid absorption in the small intestine and ascending colon is achieved by active transport of sodium. Fluid secretion is associated with the active transport of chloride. Absorption and secretion are regulated by four separate mechanisms - neural, hormonal, immune and through interaction with luminal bacteria. Intestinal cells have surface receptors on both basolateral and apical surfaces. The apical receptors are unique in that their purpose appears to be to provide targets for bacterial enterotoxins. Intracellular control is achieved through receptor-mediated effects on intracellular messengers: cAMP, cGMP and ionised Ca^{++}.

Bacterial enterotoxins that influence cAMP include *V. cholera* toxin (LT) and heat labile *E. coli* enterotoxin. Levels of cGMP are affected by heat stable *E. coli* enterotoxin (ST), and *Yersinia enterocolitica* enterotoxin. The interaction of these pathogens with the intestinal mucosa is more complex than previously thought. Cholera toxin (LT) induces active chloride secretion, but the target site of the more recently described *V. cholera* "ZO toxin" is the junctional complex[10]. ZO toxin appears to mimic physiological modulators of epithelial barrier function by causing cytoskeletal rearrangement. In contrast, heat stable *E. coli* toxin (ST) has mixed effects, inhibiting Na^+Cl^- absorption as well as inducing chloride secretion. Local release of inflammatory mediators following mucosal penetration by enteroinvasive bacteria such as *Salmonella*, also leads to increased chloride secretion.

Recent evidence increasingly links infectious enteritis with disturbances in intestinal motor activity, as well as in mucosal electrolyte transport[11]. Contraction and relaxation of small and large bowel are linked to bursts of electrolyte secretion.

The junctional complex between cells represents the major site for passive penetration of hydrophilic solutes. The rate-limiting barrier in this paracellular pathway is the tight junction. There is now evidence that the tight junction has a major regulatory role in epithelial permeability. Regional variations exist which make for instance, the stomach a "tight" epithelium and the jejunum "leaky". This is achieved by alteration in the number of its component strands, which form an obstructing meshwork, of ZO,1 protein which is linked to the cytoskeleton. Contraction of the intracellular cytoskeleton results in increased paracellular permeability. Individual epithelial cells, in response to intracellular signals, are thus able to modulate the structure and function of the junctional complex and epithelial permeability. Intracellular mediators which have been shown to be effective in altering junctional permeability include Ca^{++}, cAMP, G proteins, protein kinase C, inositol triphosphase, calmodulin and nitric oxide[12].

Inflammatory cells such as neutrophils cross into the lumen via tight junctions. Enteropathogenic *E. coli*, *Clostridium difficile*, *Vibrio cholera* and the inflammatory mediatory gamma-interferon have all been shown to disrupt epithelial barrier function by altering tight junction permeability. The net effect of this is to increase intestinal losses of fluid. One rationale advanced for this is that it may aid "flushing out" of pathogens.

The mechanism by which enteropathogenic viruses interact with gastrointestinal mucosa to cause diarrhoea is poorly understood. Rotavirus, for instance, targets villus enterocytes, where it replicates and is associated with villus injury and crypt hyperplasia. Intestinal villus cells are primarily absorptive and crypt cells secretory. It had previously been thought that rotavirus-associated diarrhoea was due to the relative preponderance of Cl- secreting crypt cells compared to NaCl absorbing villus cells. Recent evidence in animal models, however, has shown that diarrhoea can be induced by killed rotavirus and also by component glycoproteins[13].

In contrast to the relatively sterile and "leaky" small intestine, the colon is a "tight" epithelium which has a rich bacterial flora. Substantial quantities of carbohydrate and fibre escape absorption in the small intestine. These are then available for metabolism by colonic bacteria into short chain fatty acids which appear to be important in stimulating colonic fluid absorption and as an energy source for the colonocyte[14]. Broad spectrum antibiotics lead to diarrhoea in part because of the reduction in bacteria producing short chain fatty acids. Recent interest has focused on the role of short chain fatty acids in inflammatory bowel disease[15]. It has been established that rectal irrigation with solutions of short chain fatty acids is an effective treatment of mucosal inflammation.

Conclusion

The mucosal function of the gastrointestinal tract is closely linked to its component microbial flora and entero-pathogens. Regional specialisations are present which serve to separate the more vulnerable small intestine from bacterial overgrowth, but favour bacterial proliferation in the colon where a beneficial association occurs between flora and mucosa.

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腸道菌群和粘膜功能

摘要

胃腸道的粘膜皺是攝入被吸收的營養物的途徑。它也幫助分離潛在有毒的腸腔内容物及菌群，這些功能似乎相互不相配，其是通過上皮結構和器官功能的區域特殊化而達到。腸道細菌通過影響結腸的細胞電解質運轉和緊密連接體的滲透性而與腸細胞互相作用。細菌的代謝產物是結腸細胞的必需營養。

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