Probiotics and stabilisation of the gut mucosal barrier

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Probiotic bacteria are used to treat disturbed intestinal microflora and altered gut permeability which are characteristic to many intestinal disorders. Examples include children with acute rotavirus diarrhoea, subjects with food allergy and patients undergoing pelvic radiotherapy. Altered intestinal microflora has been treated by oral intake of probiotic bacteria which are able to survive gastric conditions, colonise the intestine, at least temporarily, by adhering to the intestinal epithelium. Such probiotic microorganisms appear to be promising candidates for the treatment of clinical conditions with abnormal gut microflora and altered gut mucosal barrier functions.

Introduction

The intestinal epithelium and the normal intestinal microflora represent a barrier to the movement of pathogenic bacteria, antigens and other noxious substances from the gut lumen. Under normal circumstances this barrier is intact and provides normal intestinal function. When either the epithelial cells or the normal microflora are disturbed altered permeability facilitates the invasion of pathogens, foreign antigens and other harmful substances. For future clinical applications and the development of new probiotic bacteria understanding of the mechanisms of this barrier system are essential.

Mucosal and microflora defects and disease

Intestinal barrier

The intestinal mucosa is an important organ of defence providing a barrier against the antigens encountered by the enteric route, and most foreign antigens are excluded by the intestine's mucosal barrier.[1] Apart from the barrier function, the intestinal mucosa is efficient in assimilating antigens. For this purpose, there are specialised antigen transport mechanisms in the villous epithelium and particularly in Peyer's patches, essential for evoking specific immune responses.[2]

Even in physiological conditions, a quantitatively nonimportant but immunologically important fraction of antigens bypasses the defence barrier. They are absorbed across the epithelial layer by transcytosis along two functional pathways.[2] The main degradative pathway entails lysosomal processing of the protein to smaller peptide fragments which reduces immunogenicity of the protein and is important in host-defence in diminishing the antigen load. More than 90% of the protein internalised passes in this way. A minor pathway allows the transport of intact proteins which results in antigen-specific immune responses. In health paracellular leakage of macromolecules is not allowed due to intact intercellular tight junctions maintaining the macromolecular barrier. The integrity of the defence barrier is necessary to prevent inappropriate and uncontrolled antigen transport.

Intestinal antigen handling determines subsequent immune response to the antigen. These include immune exclusion of antigens encountered by the enteric route by interfering with the adherence of antigens, immune elimination of substances that have penetrated the mucosa, and immune regulation of the systemic immune response to antigen-specific systemic hyporesponsiveness.[3] There is evidence that during the absorption process across the intestinal mucosa, antigens are altered into tolerogenic form.[4]

Immature gut defence barrier

The barrier functions are incompletely developed in early infancy. Intestinal permeability can be transiently increased postnatally, particularly in premature infants.[5,6] The binding of antigens to immature gut microvillus membrane is increased compared to the mature mucosa, which has been shown to correlate with the increased uptake of intact macromolecules.[7] An increased antigen load may evoke aberrant immune responses and lead to sensitisation.[8]

Intestinal inflammation

As a result of local intestinal inflammation, a greater amount of antigens may traverse the mucosal barrier and

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the routes of transport are altered.[9] Aberrant antigen transport results in overriding the normal tolerogenic signal into an immunogenic stimulus favouring allergic reactions.[10,11] Foreign antigens such as viruses, bacteria or dietary antigens can induce local inflammation in the intestinal mucosa.

Acute gastroenteritis

Rotavirus is the most common cause of acute childhood diarrhoea worldwide.[12] Rotaviruses invade the highly differentiated absorptive columnar cells of the small intestinal epithelium, where they replicate. Partial disruption of the intestinal mucosa ensues with loss of microvilli and decrease in the villus/crypt ratio. Rotavirus infection has been shown to be associated with increased intestinal permeability.[13] Moreover, the levels of immune complexes containing dietary β-lactoglobulin in sera were significantly higher in patients with rotavirus diarrhoea than in nondiarrhoeal patients. Macromolecular absorption has also been shown to be increased in rotavirus gastoenteritis.[13-16] The intestinal microflora affects gut permeability, so that in the absence of intestinal microflora, disturbance in intestinal absorption of macromolecules is more severe than in its presence.

Food allergy

Food allergy is defined as an immunologically mediated adverse reaction against dietary antigens. The immaturity of the immune system and the gastrointestinal barrier may explain the peak prevalence of food allergies in infancy.[17] In food allergy, intestinal inflammation[18] and disturbances in intestinal permeability[19] and antigen transfer[20] occur when an allergen comes into contact with the intestinal mucosa. During dietary elimination of the antigen, the barrier and transfer functions of the mucosa are normal.[18-20] It has therefore been concluded that impairment of the intestine's function is secondary to an abnormal intestinal immune response to the offending antigens.

Atopic dermatitis

Atopic dermatitis is a common and complex, chronically relapsing skin disorder of infancy and childhood. Hereditary predisposition is an important denominator of atopic dermatitis, and hypersensitivity reactions contribute the expression of this predisposition.[21] The relationship between environmental allergens and exacerbation of atopic dermatitis is particularly apparent in infancy so that dietary antigens predominate and allergic reactions to foods are common.[17]

In a recent study,[22] macromolecular absorption across the intestinal mucosa was assessed *in vitro* in children (aged 0.5-8 years) with atopic dermatitis. In these patients, the offending foods were identified and eliminated, and the intestinal mucosa was not challenged *in vitro* nor *in vivo*. Significantly increased absorption of protein, in intact and degraded form, was found in the atopic dermatitis patients compared to controls. The result may reflect a primarily altered antigen transfer in atopic dermatitis. Aberrant antigen absorption could partly explain why patients with atopic dermatitis frequently show heightened immune responses to common environmental antigens, including dietary antigens.

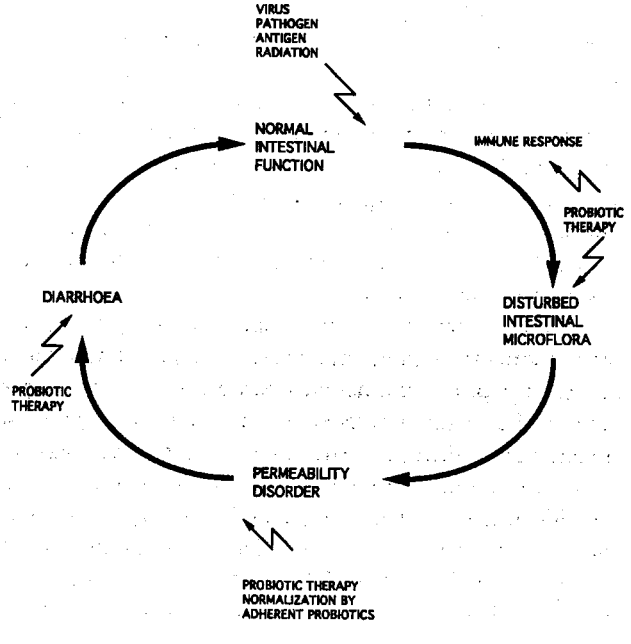
Crohn's disease

Crohn's disease is a chronic and idiopathic inflammation of the gastrointestinal tract with characteristic patchy transmural lesions containing granulomas. The outbreak of Crohn's disease is thought to require genetic predisposition, immunologic disturbance and the influence of intraluminal triggering agent(s), for example bacteria or viruses. Crohn's disease is associated with impairment of the barrier function. In a recent *in vitro* study,[23] a rise in macromolecular absorption in uninvolved parts of the intestine was detected in patients with clinically moderate or severe Crohn's disease. An interplay between the immune effector cells and the intestinal vascular endothelium has been suggested to result in disrupted vasculature, cell-mediated immunity with lymphokine production and a vigorous IgG response and finally dysfunction of the mucosa.[24,25]

Pelvic radiotherapy

Radiotherapy has a profound effect on the intestinal mucosa and the highly proliferative tissue. Radiation creates changes in bacterial flora, vascular permeability of the mucosa and intestinal motility.[26,27] The villi retract and shorten within a few days from the beginning of the treatment and total disappearance may result.[26,27] The result is a flat surface covered by thin columnar epithelial cells which may also be lost leading to ulcerated surface. Within three to ten days the intestinal epithelium may be completely denuded and the villous surface is replaced by a layer of exudate in which masses of bacteria are present. Bacteria can penetrate the damaged villi leading to bacteraemia in extreme cases.[26,27] The reasons for radiation enteropathy in man include both damage to intestinal mucosa, changes in the intestinal microflora and impaired immune response (Figure 1).

Figure 1. Changes during intestinal disorders and potential targets of treatment and prevention.



Clinically, the primary reactions start during early weeks of treatment giving such symptoms as nausea, vomiting and diarrhoea. The late secondary reaction, eg, fibrosis and obstruction of the intestine, may give clinical symptoms years after. The relationship between early and late reactions is not clear, although some studies have indicated that the severe early reactions precede serious late effects.[27,28] *Lactobacillus* supplementation in lethally irradiated mice has been reported to prolong their survival.[29]

Future developments

Probiotic bacteria (eg, *Bifidobacterium bifidum* and *Lactobacillus* GG) have beneficial effects on the clinical course of rotavirus diarrhoea.[30-32] In a similar manner, *Lactobacillus acidophilus* preparations and *Lactobacillus casei* preparations have been beneficial in the prevention of radiation enteropathy.[33-35] Among the possible mechanisms responsible for the favourable clinical response is promotion of the immunologic and nonimmunologic defence barrier in the gut.

Oral introduction of *Lactobacillus* GG has been associated with alleviation of intestinal inflammation and normalisation of increased intestinal permeability[36] and gut microflora.[37] Another explanation for the gut-stabilising effect of *Lactobacillus* GG could be improvement of the intestine's immunologic barrier, particularly intestinal IgA responses.[36]

Important properties for probiotic bacteria

The most important properties for future probiotics include the acid and bile tolerance, adherence to human intestinal mucosa, temporary colonisation of the human gastrointestinal tract, production of antimicrobial substances and inhibition of pathogen growth.[38] It is also important that the strains used are of human origin since many of the properties may be species dependent. Probiotic bacteria with these properties and documented clinical effects include *Lactobacillus acidophilus* NCFB 1748, *Lactobacillus casei* Shirota strain, *Lactobacillus* GG and *Lactobacillus acidophilus* LA1.[38] All of these are also currently further tested for difference intestinal problems and offer alternatives for dietary treatment of intestinal disorders. In the future, it is likely that we shall see more specific clinical targets for probiotic therapy and then the above mentioned strains are likely to play an important role in new products.

Conclusion

These results taken together indicate that probiotic bacteria appear promising candidates for the treatment of clinical conditions with altered gut mucosal barrier functions. Probiotic bacteria may stabilise the intestinal microflora and they can be used for immunotherapy to counteract immunological dysfunction and to stabilise the gut mucosal barrier to strengthen endogenous defence mechanisms.

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原生菌（Probiotic）和腸道粘膜屏障的穩定

摘要

原生菌（Probiotic）被用於治療腸道菌群紊亂和腸道滲透性變更。後者是很多腸道疾病的特徵，例如：兒童急性輪狀病毒腹瀉、食物過敏者和接受骨盆放射治療的病人。腸道菌群失調可通過口服原生菌治療。該細菌能在胃的環境中生存，並粘附到腸上皮，至少暫時地移植腸道。這些原生菌似乎給那些以腸道菌群紊亂和腸道粘膜屏障功能失調為主要機理的疾病的治療帶來希望。

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