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The immunological balancing act of the intestinal epithelium between defence and tolerance

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The intestinal and digestive system – an overview

Our digestive system is extremely adaptable and efficient. This high level of efficiency is associated with the interplay between different organs: the mouth, the salivary glands, the oesophagus, the stomach, the intestines and the rectum, but also the liver and the pancreas are involved in the digestive processes (Figure 1). The digestive system is responsible for the intake and transport of food, for the mechanical and enzymatic breakdown of its different components and for the uptake of substances such as proteins, carbohydrates, mineral salts, trace elements, fats and vitamins, for example, which it makes available to the organism.

The transfer of nutrients and fluids from the lumen of the intestine into the circulation and the lymph system takes place, however, through a thin, permeable barrier, the intestinal mucous membrane (mucosa), which represents the human organism's greatest surface area of contact with the outside world (i.e. with the contents of the intestine).

The single-layer intestinal epithelium covers the whole gastrointestinal tract, whereby the surface of the mucosa is enlarged to about 400 m² by the formation of intestinal villi.

The epithelial cells of the small intestine also form so-called micro-villi on their surface, so that the area of the active surface is again considerably increased. Because of its microscopic appearance, this layer of micro-villi is called brush border (Figure 2).

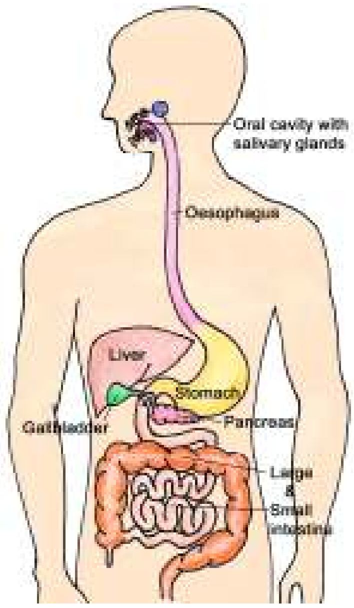

Fig 1 the gastrointestinal tract

The intestinal mucosa - a fragile but active barrier

In the upper portions of the intestine the intake of food leads to constant exposure of the mucous membrane to foodstuff antigens and microorganisms. In addition, the symbiotic microflora in the ileum and in the colon creates additional antigen stress. These demands placed on it require a well developed immune defence in the intestinal mucosa.

The intestinal mucosa is not only a passive barrier between the organism and the outside world. The uptake of nutrients is guaranteed by active mechanisms of absorption. The opposing demands on this barrier, namely the absorption of nutrients and protection against external factors, constitute a difficult dilemma, especially for the body's defence functions.

On first impression, tight junctions between the individual epithelial cells and a well pronounced, flexibly functioning immune system seem to be sufficient for defence against pathogenic factors.

However, in order to "train" the immune system, the epithelium should not provide complete protection against the penetration of antigens into the tissue. Therefore, intact components of the food, as well as sporadic intestinal bacteria, may be found in the mesenteric lymph nodes. Antigens can, for example, pass through the epithelium at the site of permeable cellular connections, such as where the cells exfoliate at the tips of the villi, or they are actively taken up through specialised cells.

Through these mechanisms the intestinal mucosa is constantly exposed to contact with a large number of antigens, which have to be tolerated by the immune system, without any immune reaction taking place.

This also means that the contents of the intestine are under constant active surveillance of the mucosal immune system, which has to differentiate between pathogenic agents and the beneficial microorganisms of the intestinal flora. The extremely complex microorganism community of the intestinal flora exists alongside the mammalian organism in so-called mutualism, defined as "living together with mutual benefits".

Results of recent research into the role of this commensal microflora lead scientists to look upon the human organism as an ecosystem of its own.

The ecosystem, Human

The human intestine is colonised by an immense number of micro-organisms, most of them in the distal portion, the colon. Their number, which can be up to 100 trillion, is about ten times greater than the number of cells in the human body. The microflora consists of an astonishingly large number of gram-positive and gram-negative, either facultative aerobic or anaerobic, microorganisms. Under normal conditions the enormous biotic mass helps to keep the colonisation of the intestine with pathogenic germs at bay and for its part does not trigger any inflammatory response of the immune system – this is apparently tolerant of these antigens.

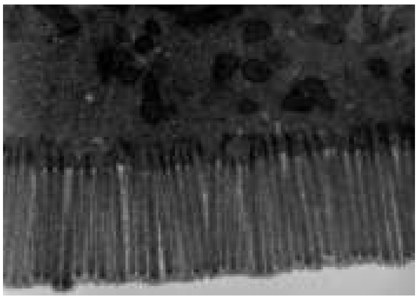

Fig 2: Brush-border membrane of the jejunum (Transmission-selectron microscope TEM)

The microorganisms of the intestinal flora are thus not only tolerated by the body, but have functions that are essential for the organism, so that we in fact live mutualistically, that is, in mutual dependence. This dependence has developed with the creation of species through co-evolution of the microbiome and the host organism. By natural selection these have mutually contributed to each others fitness, adaptability and efficiency.

The microorganism community of the intestinal flora consists of up to 400 different species of bacteria, eukaryotes and archaea. It can be considered as a separate, independent organ and has a metabolic performance comparable to that of the liver. Certain important functions of the intestinal microbiota are connected with the digestion and the uptake of food. For example, the microorganisms represent quasi an anaerobic bioreactor and can break down components of the food enzymatically and make them available to the body, which are not digestible for the human metabolism.

The microbiome includes a large number of metabolic pathways. The nature and the efficiency of the microflora thus crucially influence the processing of the components of the food and therefore on the human metabolism, for example on the carbohydrate and protein metabolism. The functionality of the microbiome can vary considerably from individual to individual; therefore the processing of the food can vary depending on the efficiency of the internal bioreactor, which in turn can have a direct influence on the nutritional status of the whole organism.

Also, the intestinal flora can synthesise substances which the human organism itself cannot produce or cannot produce in sufficient quantities, e.g. vitamin K. A further benefit for the host organism is the metabolisation and detoxification of potentially pathogenic substances from the metabolism or from food, such as carcinogens or drugs.

Another important role is played by the microbiota in the development of the mucosal immune system. The mutualistic microorganisms seem to have an antiinflammatory effect in that they suppress the activation of the immune cascade by antigens of commensal bacteria and nutritional antigens, and thus protect the intestinal mucosa against damage due to inflammation.

The numerical comparison and the role played by the composition of the microbiota in the metabolism of the organism show that the human body is a kind of superior organism from many different species. This opens up a new field of study after the decoding of the human genome, namely the investigation of the genome of our microbiotic partner, the microbiome.

The gastrointestinal immune system: between friend and foe

Healthy individuals have an extensive and highly active gastrointestinal immune system, which is strictly regulated in order to prevent excessive or inadequate immune reactions to components of the food and bacteria of the microflora.

Via the mucosa, the gastrointestinal immune system is confronted with a major risk of infection from pathogens taken up with food. The intestines thus contain most of the body's immune cells. The specific immune system of the gastrointestinal tract is located mainly in the lower portion of the small intestine. Here there are about 200 Peyer's plaques (PPs), accumulations of lymphatic tissue that contain so-called M-cells, which constantly transport intestinal bacteria and antigens into the lymphatic organs. Thousands of additional individual lymphatic follicles are also distributed throughout the intestines. Dendritic cells (DCs) lie under the intestinal epithelium of the mucosa (lamina propria). With their protrusions these reach through the epithelium into the lumen of the intestine and constantly monitor the antigen spectrum of the intestinal bacteria (Figure 3), thus functioning as antigen-presenting cells. In the lamina propria other immune cells are present, such as CD8+ T-cells. CD4+ T-cells, macrophages and IgA-antigen-producing plasma cells.

In contrast to the systemic immune system, the gastrointestinal immune system must not respond to all external stimuli, but has to tolerate a multitude of antigenic stimuli, without activating the immune cascade. In the upper segments of the intestine the majority of such stimuli originate from nutritional antigens and in the lower portions also from bacterial components of the microflora.

Various factors seem to contribute to this suppression of the immune reaction to mutualistic microorganisms. Through pattern-recognition receptors the epithelium is able to recognise symbiotic and pathogenic bacteria directly. Epithelial cells can modulate the mucosal immune system. Through anti-inflammatory cytokines such as interleukin-10 and transforming growth factor β1 (TGFβ1), regulatory T-cells inhibit the potentially tissue-damaging response of immune cells.

A further important factor in the suppression of inadequate immune reaction is the role of specifically differentiated macrophages and dendritic cells in the intestinal mucosa. Although the macrophages resident in the intestinal mucosa are capable of phagocytosis and of killing bacteria, unlike the tissue macrophages they are unable to produce pro-inflammatory cytokines. The mucosal dendritic cells develop, through epithelial factors, into non-inflammatory dendritic cells which are incapable of activating T-cells.

In the overview, a key for the ability of the immune system to react adequately to pathogens, without affecting the mutualistic organisms, seems to be the spatial separation of the triggering of immune reactions in the Peyer's plaques and their execution in the lamina propria of the mucosa. If mutualistic microorganisms penetrate into the mucosa they are phagocytised by macrophages and dendritic cells in the lamina propria, without triggering an immune reaction. Pathogenic invaders are eliminated in the lamina propria either by antigen-mediated defence or by non-inflammatory macrophages.

A laps in this ceasefire agreement leads to inflammatory intestinal diseases.

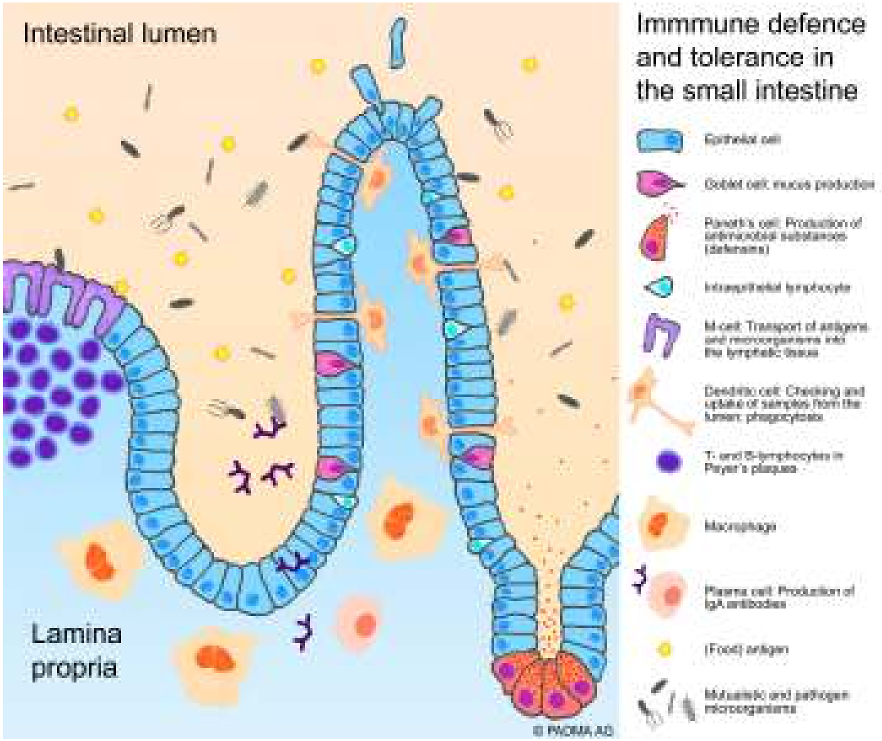

Fig. 3 Cross-section through the intestinal mucosa (blue) with Peyer's plaque (left) and an intestinal villus (right)

The forgotten unspecific immune system

Recent studies have revealed another mechanism by which pathogenic microorganisms are held in check. Specific cells in the mucosal cavities (between the intestinal villi), namely the Paneth cells, secrete a series of antibacterial peptides into the lumen of the intestine, e.g. α-defensins, lysozyme and phospholipase A2. These molecules use very efficient anti-bacterially-acting mechanisms, in that they directly attack the outer bacterial wall, so that the bacteria cannot develop resistance.

Such antimicrobial substances are normally excreted in a basic concentration, and the presence of bacteria leads to an increased production. Because of their antibacterial properties the defensins affect the composition of the microorganisms and play a decisive role in the regulation of the gastrointestinal immune system. The bactericidal substances that are flushed out of the intestinal cavities into the lumen also protect the precursors of the intestinal epithelial cells in the crypts, which guarantee, through division, the continued production of epithelial cells, goblet cells and M-cells.

Reduced production of such anti-bacterial substances has been observed in various intestinal diseases.

This brief summary of the multitude of influencing factors that play a role in the regulation of the highly differentiated gastrointestinal immune system makes it clear what effort the organism has to make in order to maintain the immunological balance between defence and tolerance. If this balance is disturbed, for example by increased pro-inflammatory stimuli or inadequate anti-inflammatory signals, this can lead to the development of inflammatory bowel diseases.

For instance, various studies show that individuals with reduced secretion of α-defensins from the Paneth cells are much more susceptible to intestinal infections. Reduced cellular function of the Paneth cells also leads to increased bacterial growth of the intestinal flora and thus to dysregulation of the relationship between the microbiota and the host organism and thus to disturbance of the mucosal immune response. The healthy microbiota normally also have mucosa-protecting properties, on the one hand through competition with any pathogenic microorganisms and on the other in that they induce the secretion of anti-microbial substances by the intestinal epithelial cells.

Stimulation of unspecific defence

In the Western world the ability of the intestinal immune system to eliminate pathogens and at the same time to stay relatively unsusceptible to nutritional antigens and the microflora seems to be decreasing.

While with the decreasing microbial burden of food and living conditions the exposure of the human organism to pathogens is also decreasing, the spread of food allergies and intolerances as well as chronic intestinal inflammation due to non-infectious causes is constantly on the increase.

At the level of the systemic immune function this has led to the hygiene hypothesis which says that a certain degree of contact with (pathogenic) microorganisms provides protection against the development of allergies. The immune system appears to need a certain stimulation in order to train, so to speak, the anti-inflammatory signal pathways that are set in motion in the course of the inflammation cascade. Such anti-inflammatory and regulatory stimuli are particularly important in the case of the gastrointestinal immune system, with its high level of exposure to microorganisms and antigens. Here, these stimuli come into the body through the food. Probiotics make use of this training effect. The systemic immune system is considered to be also positively stimulated through the gastrointestinal immune system. If there is no periodic stimulation, the anti-inflammatory-signal pathways are inactive. This can result in an excessive reaction of the immune system to stimuli which are in themselves benign, subsequently leading to pathogenic conditions such as allergies or chronic intestinal inflammation.

Additionally, stimulation of the unspecific defence of the intestines should be taken into consideration. The intake of a varied, balanced diet has positive effects on the digestion and the intestinal health. Especially aromatic plants and herbs have various supportive effects. Essential oils have antibacterial effects and thus reduce the inflammatory stimuli. Hot-tasting and bitter substances increase the salivation, and spices e.g. ginger, coriander and pepper support the biliary activity and thus promote the digestive process. Such a diet, rich in secondary plant substances, can increase the secretory capacity of the intestines.

"In the West the ability of the intestinal immune system to eliminate pathogens and at the same time to stay relatively unsusceptible to nutritional antigens and the microflora seems to be decreasing"

In the case of unspecific digestive disorders the question arises whether the immune system can be strengthened through the support of the digestion provided by these seconddary plant substances. E.g. does the increased secretory capacity also lead to the increased excretion of defensins? If this is so, the improvement of the digestion would also be associated with an immune system promoting component.

Such an approach is demonstrated in plant-based preparations from Asian-medicine systems which are traditionally applied to promote a healthy digestion. One such example is the Sendu 5 formula (PADMA DIGESTIN) which is based on pomegranate according to a recipe from Tibetan medicine. This formula contains a mixture of aromatic spices (cardamom, long pepper, lesser galangal, cassia bark) and the astringent pomegranate seeds. The pomegranate is known to have antioxidative, anti-inflammatory, antiproliferative and pro-apoptotic properties and in traditional medicine it is used in inflammatory bowel diseases. To summarise, it can be said that this Tibetan mixture of herbs and spices stimulates the secretory activity in the gastrointestinal tract, with a possible secondary effect on the unspecific immune system of the digestive tract.

Another positive effect of secondary plant substances as are contained in vegetable foodstuffs and in herbs and spices, namely the inhibition of cancer cells, could be demonstrated in many studies. The high cellular turnover of the intestinal mucosa seems to make it susceptible to cancerous changes. The pro-apoptotic effect of herbal substances may counteract such developments. Here, too, a suitably positive milieu can be created through stimulation of the unspecific intestinal immune system and a healthy microbiome.

CONCLUSION FOR MEDICAL PRACTICE

As the largest barrier of the organism against the outside world, the intestinal mucosa is constantly exposed to a great number of antigens, which the immune system tolerates without an inflammatory reaction being triggered. Various factors seem to contribute to the maintenance of this fine balance between defence and inflammation-free normality.

Besides the lymphatic system, the intestine also possesses unspecific defence mechanisms, for example antibacterial peptides secreted by Paneth cells which influence growth and composition of the microorganisms and thus play a decisive role in the regulation of the gastrointestinal immune system.

In the West the ability of the intestinal immune system to provide defence while at the same time tolerating components of the food and microbiota seems to be decreasing. This is shown by the increased incidence of food allergies and intolerances and chronic intestinal inflammatory diseases such as Crohn's disease or irritable bowel syndrome.

One approach could be the strengthening of the unspecific immune system. Here, secondary plant substances such as are contained in the traditional herbal preparations can make a supportive contribution both through their antibacterial properties and by increasing the gastrointestinal secretion.