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Leaky intestine

Leaky intestine: involved in developing illnesses?

Summary

New experiments show that the gut leakage occurs in several different diseases. This leaking seems to have appeared even before the disease has arisen.

FACTS: Intestinal physiology

When we eat something the digestion of the food begins in the oral cavity and thereafter in the acid environment of the stomach, continuing in the small intestine, before the food reaches the large intestine where bacteria aid in digesting the last remains of the food. The intestine is shaped like a long tube that runs from the stomach to the anus. A tight barrier against the "outside" is maintained by the intestinal epithelial cells, the enterocytes, which are linked to each other via so-called tight junctions (Figs. 1 and 2). To increase the absorptive surface the intestine is folded so that long, fingerlike extensions, villi, are formed and each enterocyte has, in turn, a folded upper part called microvilli. The intestinal mucosa is divided into two regions: one villus-region and one crypt-region (Fig. 3). The villus-region is involved in the digestion and absorption of the food, while cells in the crypts secrete antibacterial substances that keep the crypts relatively free of bacteria. Inside the crypts lie the intestinal stem cells, which give rise to new intestinal cells, which then migrate up along the villus-region.

The intestine – an arena for bacteria and immune cells

Our intestine carries out two competing tasks: it must absorb nutrients from the food we eat, but at the same time prevent passage of unwanted substances or microorganisms. In order to accomplish this, the intestine keeps a tight barrier towards the outside and, in addition, the majority of the body's immune cells are located in the intestinal mucosa, where they constantly catch material from both the out- and inside of the intestine, and are ready to trigger the body's defense of

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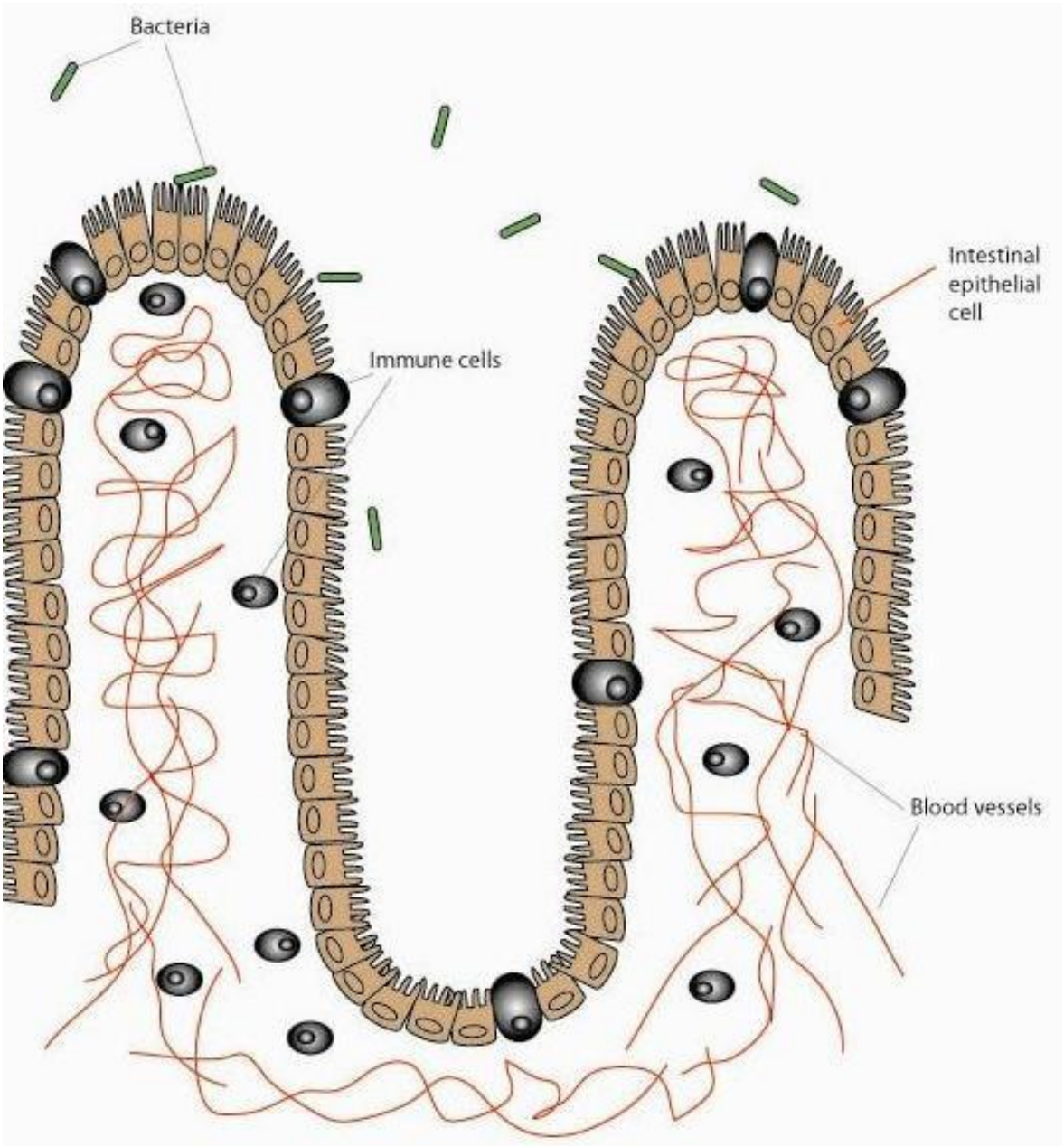

Figure 1. *Intestinal villi. The intestinal surface is folded to increase the absorptive surface, which enables a large uptake of nutrients. Finger-like projections, villi, and the intestinal cells' microvilli further increase the surface area.*

cells and antibodies if an unwanted microbe or toxic substance has got through the intestinal barrier. Inside the intestinal lumen there are more bacteria than there are cells in the entire body and all of these bacteria should preferably keep to the right side of the intestine. Should any bacterium cross over into the blood on the other side of the intestine, it could lead to death, since the bacteria can quickly multiply there. The most recent research shows, however, that the intestine is leaking in a number of different diseases, and that this leakage even appears to have arisen before the disease has begun. Therefore, intensive research is now being conducted to find out the role of the intestinal barrier in the development of different diseases.

The barrier function of the intestine

The intestinal barrier can be affected by a number of factors, such as the diet, bacteria, stress and different disease conditions. If the intestine becomes more "open" than normal, unwanted substances leak through the permeable intestine and into the body. This often leads to an immune response that can irritate the intestine and make it inflamed. In the worst scenario, blood poisoning can occur if a mean bacterium mangages to cross the intestinal barrier and enter the blood stream.

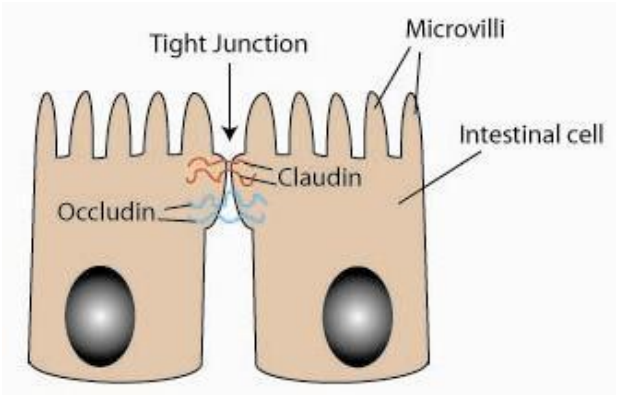

Figure 2. *The intestinal cells are linked to each other via so-called tight junctions. Occludin and claudin are two proteins that build up the connection between the cells; apart from these proteins there are a number of other proteins that are important for the function of the connection.*

Why does the intestinal barrier begin to leak? Some bacteria can influence the enterocytes and affect their tight junctions so that the intestine becomes more permeable – which promotes invasion. In contrast, other bacteria can help seal the intestinal barrier, but exactly how this occurs is, as yet, unknown. What is known is that so-called probiotic bacteria produce substances that kill other, pathogenic, bacteria, and that probiotics can stimulate the intestinal immune cells in a way that is favourable during different inflammatory conditions.

Stress also opens the intestinal barrier and that is why you can experience intestinal problems when you are under a lot of stress. Exactly what mechanism is responsible remains to be clarified, but our central nervous system is in close connection with the intestine's vast nervous system, the enteric nervous system. It is believed that the intestinal immune system is involved in the stress reaction and it has also been observed that the bacterial flora changes during stress, so that the "good" lactobacilli decrease in number. Then "bad" bacteria can multiply, which irritates the intestine.

What we eat greatly influences the permeability of the intestinal barrier. Cayenne pepper and other strong spices open the barrier, while black- and green pepper has the opposite effect. Fibre also appears to have a strengthening effect on the barrier.

Intestinal leakage in many diseases

The latest research shows that the permeability of the intestine is elevated in a number of diseases, such as diabetes typ I, multiple sclerosis, celiac disease and in different inflammatory bowel diseases, and the role of the intestinal barrier in disease development is currently being investigated.

In both animal and human studies it has been observed that the intestinal barrier is more open even before

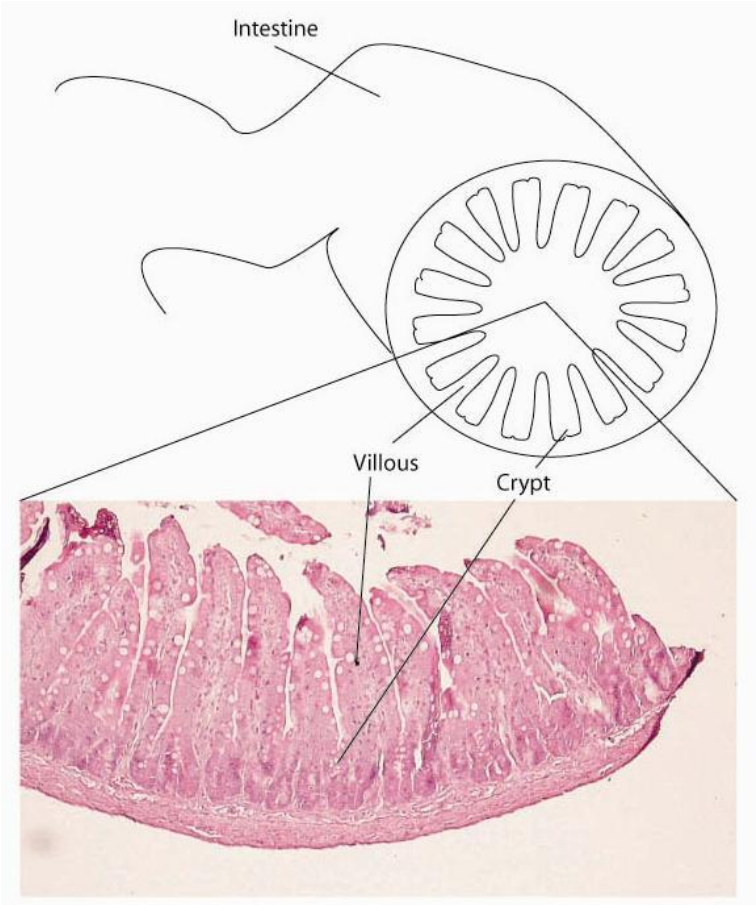

Figure 3. *Cross-section of the intestine, in which its long, finger-like projections, villi, can be seen.*

diabetes symptoms arise. One could imagine that the open barrier lets through substances that either irritate the intestinal immune cells, and in that way start the autoimmune reaction leading to the destruction of the insulin-producing cells, or that substances that are similar to some protein on these cells enter the body, which triggers the immune system to react to the protein and thereby also the insulin-producing cells. When a significant number of cells have been destroyed, the body can no longer regulate the blood sugar level and diabetes symptoms arise.

Also, in different skin disorders, such as atopic dermatitis and psoriasis, a leaky barrier has been observed. It is interesting that in some clinical studies with probiotic bacteria, which often help in tightening the intestinal barrier, atopic dermatitis was prevented. This suggests that the intestinal permeability is of importance for these diseases.

Multiple sclerosis (MS) is an autoimmune disease where the immune system wrongly reacts to parts of the nervous system, leading to a gradually increasing paralysis of the body. Interestingly, there are studies that suggest that MS-patients have a leaky gut. Studies on mice have shown that probiotic bacteria can protect against MS, but it remains to be investigated whether the intestinal barrier was affected by the bacteria.

Why the intestinal barrier is more open in some diseases is not entirely known, but in order for the intestine to maintain a tight barrier it is required that its immune system is intact. Defects in the gut-associated immune system can cause the crypts to be filled with bacteria that otherwise only would have been found on the tops of the intestinal villi. These bacteria can then make the enterocytes' tight junctions open up, which leads to a leaky gut. It is also believed that genetic mutations can affect the proteins that regulate the intestinal barrier.

Future perspectives – the diseases of the western world

Many of the autoimmune diseases have a higher prevalence in northern America and northern Europe. It is speculated that this could be because we in this part of the world have too clean an environment around us, which makes us more prone to allergies and autoimunne diseases. The use of antibiotics during pregnancy and during childbirth is larger in the western part of the world, and research shows that antibiotics disrupt the gastrointestinal tract's natural flora, so that the levels of bad bacteria (e.g., members of the family *Enterobacteriaceae*) increase at the expense of good bacteria (e.g., lactobacilli and bifidobacteria). The early, colonizing microflora has been shown to be of importance for the development of diseases later in life and, since bacteria can affect the intestinal barrier, it is not far-fetched to assume that it could be the bacterial flora that affects the intestinal barrier at an early age. Hence, the development of several diseases could possibly be prevented by affecting the colonizing flora and, by getting rid of bacteria that make the intestine leaky and irritated, diseases might even be cured. A tight intestine simply seems to be essential to our health.

References

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Exercise

1. Find out more about autoimmune diseases.
2. Keep a journal where, for one week/month, you write down how your stomach feels (for example, stomach-ache). Then try to consider whether you have been stressed and, if so, whether that has influenced the stomach in any way. Then eat some probiotic and record whether that makes any differences.

