LEAKY GUT SYNDROME

UNSUSPECTED DAMAGE FROM INCREASED INTESTINAL PERMEABILITY

The intestine is an extremely complex living system that participates in the protection of the host against aggressions from the external environment. This defensive task is based on 3 constituents that are in permanent contact and dialog with each other: the microflora, mucosal barrier, and local immune system [1]. The intestinal epithelium is the largest mucosal surface in the human body, and provides an interface between the external environment and the host [2]. The intestinal mucosa surface reaches several hundreds of square meters, probably between 500 and 600 [Biology Web, State University of New York] due to three successive levels of anatomical folding respectively called *plica*, *villi* and *microvilli*. Besides, the human intestinal ecosystem is remarkably dynamic. The host organ is lined with a perpetually and rapidly renewing epithelium: approximately 20-50 million cells are shed per minute in the small intestine and 2-5 million per minute in the colon [3].

The intestinal epithelium conducts several functions required for intestinal homeostasis, among which the ability to form a **barrier** to oppose the permeation of solutes [4]. The small intestine epithelial cells are sealed by tight junctions made of a large, stable multiprotein complex maintained by numerous protein-protein interactions [5]. This intercellular gate formed by tight junctions is size- and ion-selective and, hence, represents a semi-permeable diffusion barrier [6]. Another fundamental function performed by small intestine enterocytes consists in the **transport** (absorption) of micronutrients, which results from the multiple enzymatic transporters present in the microvilli representing what is called the *brush border*.

The ***leaky gut syndrome*** implies not only an alteration of the tight junctions - loss of **barrier** function - but also a damaged brush border - loss of **absorption** function [4]. This condition leads to a massive entrance of antigens, pathogens, toxins and undigested foods, with multiple negative consequences on human health. A leaky intestinal barrier allows the antigens to penetrate the *lamina propria* and disrupt the immune system, leading to autoimmunity, inflammation and allergy [7]. Such dramatic consequences have also been acknowledged for pediatric patients: "*This review provides an overview of evidence for the role of tight junction breakdown in diseases such as systemic inflammatory response syndrome (SIRS), inflammatory bowel disease, type 1 diabetes, allergies, asthma, and autism*" [8]. The entrance of pathogens can be called translocation and leads to different forms of sepsis. The entrance of toxins clearly overloads the liver, and the entrance of undigested foods provides the roots for food allergy as dietary proteins haven't necessarily been digested yet before their entry.

Crohn's disease represents a perfect example of the ***leaky gut syndrome***, as all the patients suffering from this intestinal autoimmune and inflammatory disease present a higher intestinal permeability compared with healthy control subjects [9]. Not surprisingly, the association between gut leakiness and Crohn's is so strong that increases in intestinal permeability precede clinical relapses in Crohn's disease and consequently are good indicators of subclinical disease [10]. ***Cœliac disease*** provides another model for altered intestinal permeability, characteristically elevated in untreated cœliac disease [11]. Besides, most pathological issues accompanying cœliac disease reflect either the consequences of lost **barrier** function (up to ten times more autoimmune diseases, increased risks of rheumatoid arthritis and far more frequent digestive lymphomas) or the consequences of lost **transport** function (anemia, osteoporosis, fatigue, depression, short stature, infertility…).

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