The Gut Mucosal Firewall and Functional Medicine

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Abstract

The evidence is strong: Protection and restoration of the intestinal firewall is of primary importance in many patients suffering from a wide range of chronic diseases. The functional medicine approach to evaluation and treatment of problems associated with compromised integrity of the intestinal firewall represents a successful application of the systems biology approach to the management of chronic disease.

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In 1979, I had the opportunity to meet Arthur Kaslow, MD, a gastroenterologist practicing in Santa Barbara, California. He was a presenter at a medical meeting I was attending that was focused on the exploration of the origin of chronic diseases. Dr Kaslow had just released his book *Freedom from Chronic Disease*,[1] which described a program to restore health he had developed through years of clinical practice. This program was based on Dr Kaslow's observation that certain foods contributed to a person's chronic disease not only as a result of the nature of the nutrients or antinutrients in the food, but also as a consequence of the influence they had on the gastrointestinal milieu. I was still early in my career in 1979, and Dr Kaslow's presentation made a strong impression on me because this was the first time I had heard a medical professional discuss testing stools for digestive ability and the presence of altered microbial organisms in the gut that contributed to systemic disease.

Several years later, I found myself once again learning about research into the influence of the gut on systemic health. This came about when I received a very special gift—a first edition copy of the 1908 book *The Prolongation of Life* by Elie Metchnikoff,[2] who was awarded the Nobel Prize in Physiology or Medicine that year for his discoveries related to the innate immune system. In his book, Metchnikoff[2] described his views about the important role the gut microbial content has on health and disease. He posed that altered gut microbiota contributes to the chronic diseases of aging, and—like Kaslow—that restoration of healthy microbiota in the gut represents a potential treatment for chronic illness. I find it interesting and very relevant that in 1966 the famous ecologist Rene Dubos wrote, "The states of health or disease are the expressions of the success or failure by the organism in its efforts to respond adaptively to environmental challenges," and he identified one of the important environmental challenges to be the individual's enteric microbiota.[3]

In the 1980s—as I was developing the concept of functional medicine—a number of clinical laboratories started offering stool analysis. This analysis measured the level of digestive enzymes, fat, and undigested protein, and the presence of various microorganisms in the stool, including bacteria and yeast. Doctors using these tests in clinical practice started to recognize the correlation of altered stool analysis variables with chronic health issues.[4] When the lactulose/mannitol challenge test was developed and became available as a routine clinical laboratory test, it allowed for evaluation of the integrity of the mucosal cells lining the gastrointestinal tract.[5] An increase in the ratio in the urine of lactulose-to-mannitol excreted after oral administration of a set amount of 2 nonmetabolizable sugars was shown to be indicative of a breakdown in mucosal integrity of the intestines and the development of a permeable gut.[6-10] This condition was termed *leaky gut* by Bjarnason, who went on to write a series of papers concerning this condition in the course of a decade.[11-15] The stool calprotectin test, which has been commercially available since 2002, has demonstrated the relationship between "leaky gut" and increased inflammation in the gut.[16,17] Calprotectin is a protein secreted into the stool by neutrophil cells associated with an inflammatory response of the intestinal immune system. It has been well established that an increase in stool calprotectin is associated with loss of integrity of the intestinal mucosal cells and "leaky gut," which is in turn associated with many gastroenterological and systemic inflammatory diseases, such as arthritis.[18-20]

The activation of the gut immune system produces a state of chronic inflammation that results from exposure to antigenic insults that can come from either dietary or

enteric microbiological sources. It is well known that the dietary intake of gluten can induce immunological reactions of the gut immune system associated with gluten enteropathy and systemic inflammatory conditions (including increased risk to dementia) in gluten-sensitive individuals.[21,22] It has become more well recognized that altered gut microbiota—termed *dysbiosis*—can also contribute to systemic inflammatory diseases.[23-25]

When I did an online search of the National Library of Medicine database, I found it interesting that the first use of the term *intestinal microbiome* to describe the gut microbiota appeared in 2002.[26] Since that original paper, 2695 National Library of Medicine abstracted papers have been published that discuss the clinical and biological features of the intestinal microbiome in health and disease. In doing the math, one realizes that it has taken more than 100 years from the original discussion by Metchnikoff on the health and disease aspects on the intestinal microbiome for the topic to become a highly regarded clinical research and development area. It is now recognized that the interface of the individual's intestinal immune system with their gut microbiome has a critical effect on metabolism and immunity spanning the function of many organs and diseases including cancer, diabetes, arthritis, obesity, anxiety/depression, and autism.[27-33]

Recent research indicates that the intestinal microbiome also has a role to play in priming the immune system to react to allergic disease, including childhood atopic disorders such as eczema and asthma.[34] The importance of the connection of the central nervous system to the intestinal microbiota has also become much more well understood with the concept that the intestinal microbiome is the "brain's peacekeeper."[35] These studies indicate that the influence of the intestinal microbiome is far reaching, as the gut is in communication with both the nervous and immune systems, and this demonstrates a bidirectional influence on circadian rhythm and a role in epigenetic regulation of neuronal function.

The Gut Mucosal Firewall

Now that there is a greater understanding of gut mucosal barrier function and the effect of the intestinal microbiome and dietary components on the mucosal integrity, what are the clinical takeaways? Studies of systemic diseases that are associated with increased gastrointestinal permeability represent the emergence of the cross-disciplinary era of systems biology in medicine. Discoveries have resulted in collaboration among the fields of gastroenterology, immunology, neurology, endocrinology, oncology, and internal medicine to create a functional approach to complex chronic diseases that result from alteration in the integrity of the gut mucosal barrier function, intestinal microbiome, enteric immune system, and systemic inflammation.

The focus of this collaborative approach to the prevention and management of disease is to establish a personalized assessment and treatment plan for the patient based on restoration of proper intestinal mucosal function. Put another way, the goal is to create a "firewall" to protect against systemic exposure to substances that activate the inflammatory arm of the immune system. To accomplish this objective many variables that are unique to the person need to be evaluated. These include the following:

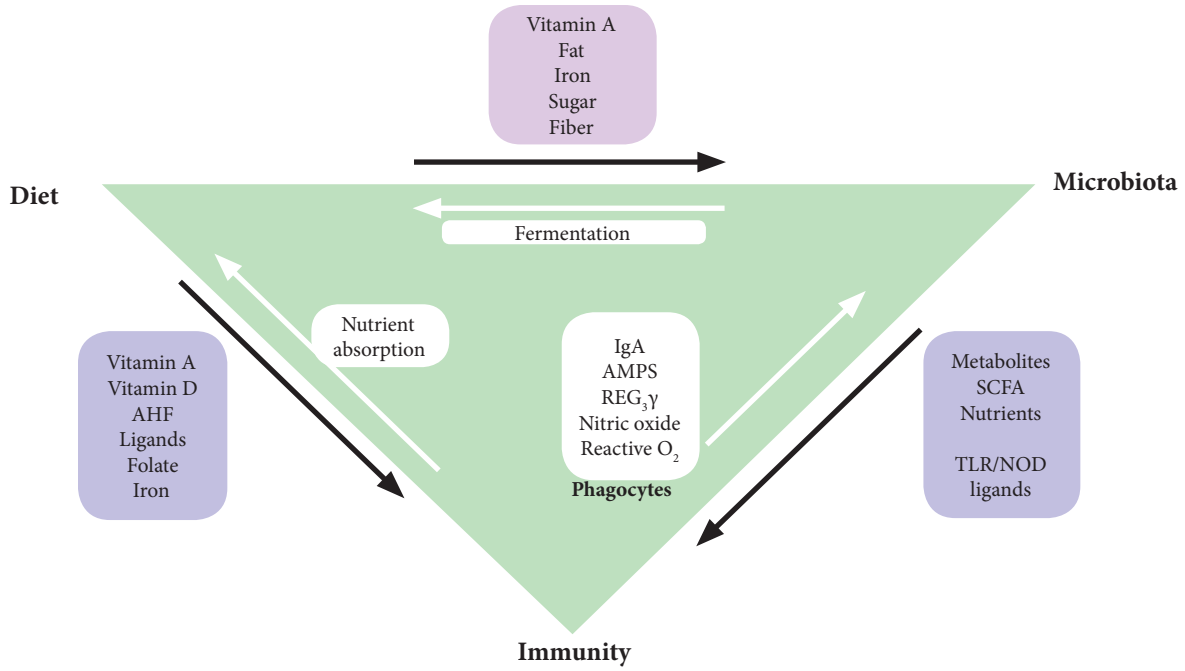
1. The composition of the intestinal microbiome:
   a. Bacteria.
   b. Yeast.
   c. Fungi.
   d. Viruses.
   e. Archaea.
   f. Helminths.
2. Dietary antigens.
3. Drugs or chemicals:
   a. Nonsteroidal inflammatory drugs.
   b. Prescription medications.
   c. Alcohol.
   d. Xenobiotics.
4. Psychosocial stress factors.
5. Diseases of the gastrointestinal tract.
6. Genetics related to immunological sensitivities.

This list represents a systems biology checklist of variables that lead to understanding the origin of alterations in the functional integrity of the "gut mucosal firewall." This concept was described elegantly in a recent article by Belkaid and Hand[36] from the National Institute of Allergy and Infectious Disease, titled "Role of the Microbiota in Immunity and Inflammation." In this article, they describe the interdependence of diet, immunity, and microbiota interactions as illustrated in Figure 1.

The intestinal mucosal firewall provides the functional barrier of defense for the immune and nervous systems from both dietary and microbiota influence on their function. In the functional medicine model, which is based on the application of systems biology to medicine, intestinal function is one of the 7 key physiological processes. The integrity of the mucosal firewall is of critical importance in establishing the communication of the innate and acquired immune systems with the intestinal contents. A breakdown in the intestinal firewall can result in exposure of antigenic components within the intestines to the enteric immune and nervous systems thereby initiating inflammatory immune activation through T regulatory cells, T_h17 cells, and their crosstalk with B cells of the acquired immune system.

The clinical application of this functional medicine model requires an understanding of gut barrier function, the gastrointestinal immune system, food- and microbiome-associated antigens, and the enteric nervous system, as well as how all of these affect organ system function. Here again we see the need for cross-disciplinary understanding, in this case specifically about the role of

Figure 1. Interdependence of Diet, Immunity, and Microbiota Interactions[36]



Abbreviations: AHR, aryl hydrocarbon receptor; IgA, immunoglobulin A; $REG_3\gamma$: regenerating islet-derived protein 3 gamma; SCFA, short-chain fatty acid; TLR, toll-like receptor; NOD, nucleotide-oligomerization domain.

the intestinal firewall in health and disease and the science that underlies recent developments in this field of study.

Consider the historical journey that has been required to gain important insights about the intestinal firewall: from the work of Elie Metchnikoff to that of the ecologist Rene Dubos to the pioneering work of Arthur Kaslow. All were pioneers of systems biology and the personalized functional medicine approach of today. It has come to be well recognized that tight junctions and leaky intestines play important roles in many diseases seen among patient populations that span from the pediatrician to the geriatrician.[37-40] It is now well known that certain pattern recognition receptors that reside on the surface of mucosal and immune cells called toll-like receptors are activated by specific lipopolysaccharides (LPS) that are components of Gram-negative bacteria that reside within the intestinal microbiome. The release of LPS from specific bacteria can trigger increased inflammation, breakdown of the gut firewall, and increased inflammatory mediators and endotoxins in the blood.[41-42] Recent experimental studies indicate that the oral administration of bovine colostrum (containing immune-active peptides and specific species of probiotic organisms as well as certain phytochemicals such as curcumin) can inhibit the release of LPS and block inflammatory signaling at the toll-like receptor, resulting in protection of the intestinal firewall.[43-48]

The evidence is strong: Protection and restoration of the intestinal firewall is of primary importance in many patients suffering from a wide range of chronic diseases. The functional medicine approach to evaluation and treatment of problems associated with compromised integrity of the intestinal firewall represents a successful application of the systems biology approach to the management of chronic disease.[49]

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