Gut Pathology - Part Six

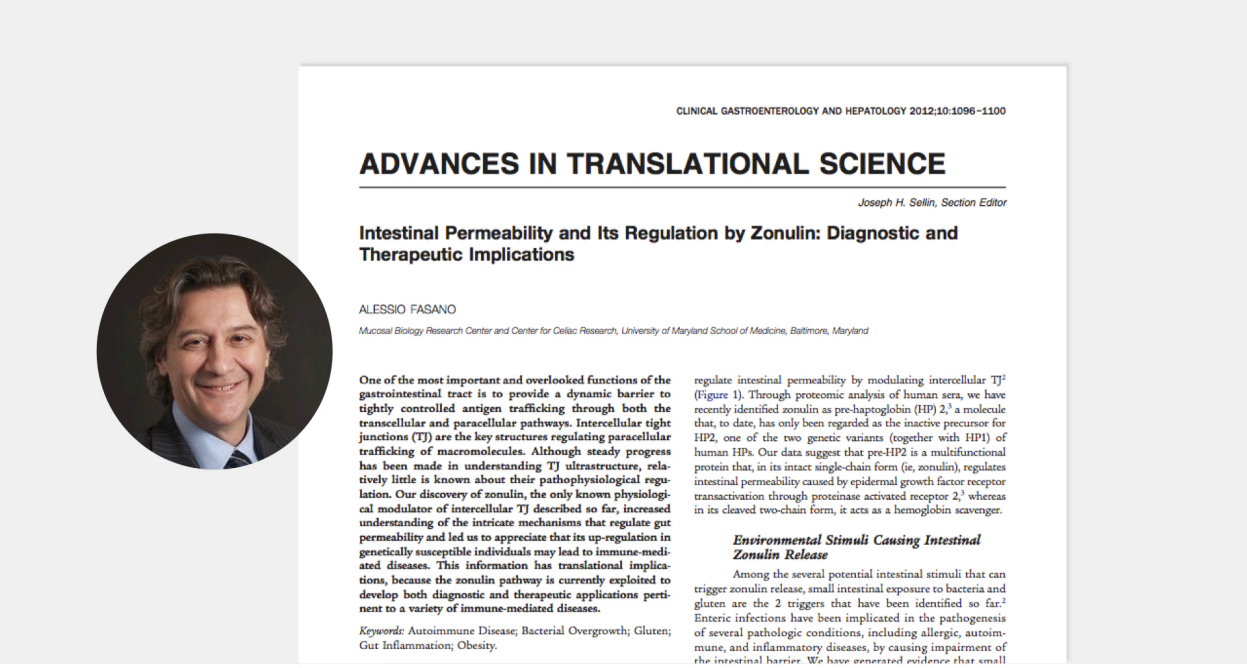
The symptoms of disrupted gut microbiome and fungal overgrowth, which I see as kind of a subcategory of dysbiosis, that's maybe an important distinction because fungi, like candida, are not external exogenous pathogens, they're commensals that can become overgrown when we have dysbiosis. So, the symptoms of this range from obvious things like gastrointestinal discomfort to less obvious symptoms like depression, anxiety, brain fog, ADHD, autism spectrum disorder, skin disease, neurological problems, and more. We've already covered some of the mechanisms that would explain this, but in short, disrupted gut microbiota can lead to production of compounds that have a neurotoxic effect, can lead to inflammatory cytokine production, which can suppress activity of the frontal cortex and cause all kinds of other problems. And we're still learning about the mechanisms that explain these associations.

In terms of diagnosis, fungal overgrowth will turn up on stool tests, and there are also some markers for it on urine organic acids tests, like d-arabinitol. I will say that currently I trust the stool markers for fungal overgrowth more than urine markers, depending on the specific marker and the combination presented. Dysbiosis or disrupted gut microbiome can be detected in stool tests using culture and proteomic stool analysis. It can quantify some species of beneficial bacteria and can be helpful in a rough way. We'll talk more about the pros and cons of stool testing methodologies in Lesson 6.

Next pathology that I want to talk about is food intolerance. In many cases, food intolerances are a consequence of other pathologies, such as disrupted gut microbiome or SIBO or intestinal permeability or things like parasites. But of course, it can also be a cause of some of these things, like intestinal permeability. I've listed them as a specific pathology because once they're present they can cause a lot of problems and often need to be addressed independently of all of these pathologies, or after those pathologies have been addressed, if they still persist. Gluten, of course, is one of the most commonly discussed examples. Celiac disease used to be fatal, before we knew what wheat gluten was, and that it caused celiac, and it was often fatal in kids. In non-celiac gluten sensitivity, even though it's typically looked at as being less serious than celiac disease, you can have very serious complications including ataxia, which is a form of paralysis, and other neurological problems. Other food intolerances, like to dairy products for example, may not be as severe as gluten intolerance, but they can cause chronic low-grade inflammation, intestinal permeability, which can then lead to antibody production to everything from the joints to the myelin sheath in the brain, and certainly over time can lead to some very serious pathologies and disease. So, we're going to talk more about diagnosis and treatment of these in the next section of the presentation.

Next pathology is intestinal permeability, currently and formerly known as *leaky gut*. As we discussed in the physiology section, one of the main functions of the gut is to serve as a barrier system. Most of the time, this works well, but several aspects of the modern lifestyle cause it to malfunction. These factors lead to abnormalities in the GI tract, compromise the integrity of the gut barrier, increase the entry of undigested antigens into the submucosa and circulation, and then they challenge the immune system in that particular way. So reaction to these antigens is what activates immune and inflammatory cascades, and that results in the production of pro-

inflammatory cytokines and a whole array of antibodies, which further contributes to increased intestinal barrier permeability, so again we have another classic vicious cycle.



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ADVANCES IN TRANSLATIONAL SCIENCE

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Intestinal Permeability and Its Regulation by Zonulin: Diagnostic and Therapeutic Implications

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One of the most important and overlooked functions of the gastrointestinal tract is to provide a dynamic barrier to tightly controlled antigen trafficking through both the transcellular and paracellular pathways. Intercellular tight junctions (TJ) are the key structures regulating paracellular trafficking of macromolecules. Although steady progress has been made in understanding TJ ultrastructure, relatively little is known about their pathophysiological regulation. Our discovery of zonulin, the only known physiological modulator of intercellular TJ described so far, increased understanding of the intricate mechanisms that regulate gut permeability and led us to appreciate that its up-regulation in genetically susceptible individuals may lead to immune-mediated diseases. This information has translational implications, because the zonulin pathway is currently exploited to develop both diagnostic and therapeutic applications pertinent to a variety of immune-mediated diseases.

Keywords: Autoimmune Disease; Bacterial Overgrowth; Gluten; Gut Inflammation; Obesity.

regulate intestinal permeability by modulating intercellular TJ[2] (Figure 1). Through proteomic analysis of human sera, we have recently identified zonulin as pre-haptoglobin (HP) 2,[3] a molecule that, to date, has only been regarded as the inactive precursor for HP2, one of the two genetic variants (together with HP1) of human HPs. Our data suggest that pre-HP2 is a multifunctional protein that, in its intact single-chain form (ie, zonulin), regulates intestinal permeability caused by epidermal growth factor receptor transactivation through proteinase activated receptor 2,[3] whereas in its cleaved two-chain form, it acts as a hemoglobin scavenger.

Environmental Stimuli Causing Intestinal Zonulin Release

Among the several potential intestinal stimuli that can trigger zonulin release, small intestinal exposure to bacteria and gluten are the 2 triggers that have been identified so far.[2] Enteric infections have been implicated in the pathogenesis of several pathologic conditions, including allergic, autoimmune, and inflammatory diseases, by causing impairment of the intestinal barrier. We have generated evidence that small

Image source: http://www.amazon.com/Alessio-Fasano/e/B00J7ZIU42/ref=ntt_dp_epwbk_1

Dr. Alessio Fasano is a pioneer in celiac and non-celiac gluten sensitivity research. He was actually the first person to discover zonulin, which is a protein that regulates tight junction permeability in the gut, and he believes that leaky gut is actually a precondition to developing autoimmunity along with genetic vulnerability and environmental triggers. He's argued that increased permeability of the intestinal barrier to macromolecules is associated with a whole range, again, of local and systemic inflammatory conditions, including of course celiac and non-celiac gluten sensitivity, food intolerances, Inflammatory Bowel Disease (IBD), numerous autoimmune diseases, neurological conditions like MS, cognitive dysfunction, behavioral disorders, skin conditions, and new connections that we're discovering, again and again, on a nearly monthly basis.

As a reminder, zonulin is considered to inhibit the entry of bacteria, antigens, toxins, and other pathogens while the absorption of nutrients is left intact. Studies have shown a linkage between zonulin levels, inflammatory markers, and a variety of diseases, so we know that this connection in intestinal permeability is important.