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- professor of pediatrics at HarvardMedical School
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- Director, Mucosal Immunology Center, Harvard
- Director, Center for Celiac Research and Treatment
- Director, Mucosal Immunology and Biology Research Center;
- Associate Chief for Basic, Clinical and Translational Research
- 213 publications on pubmed.gov
- Identified zonulin as the protein activated in intestinal permeability





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REVIEW

All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases [version 1; peer review: 3 approved]

Alessio Fasano [1,2]

[1]Mucosal Immunology and Biology Research Center, Center for Celiac Research and Treatment and Division of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, Massachusetts, USA
[2]European Biomedical Research Institute of Salerno, Salerno, Italy

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Abstract

Improved hygiene leading to reduced exposure to microorganisms has been implicated as one possible cause for the recent "epidemic" of chronic inflammatory diseases (CIDs) in industrialized countries. That is the essence of the hygiene hypothesis that argues that rising incidence of CIDs may be, at least in part, the result of lifestyle and environmental changes that have made us too "clean" for our own good, so causing changes in our microbiota. Apart from genetic makeup and exposure to environmental triggers, inappropriate increase in intestinal permeability (which may be influenced by the composition of the gut microbiota), a "hyper-belligerent" immune system responsible for the tolerance–immune response balance, and the composition of gut microbiome and its epigenetic influence on the host genomic expression have been identified as three additional elements in causing CIDs. During the past decade, a growing number of publications have focused on human genetics, the gut microbiome, and proteomics, suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

Keywords

Chronic inflammatory diseases, Gut permeability, microbiome, zonulin

Open Peer Review

Reviewer Status ✔ ✔ ✔

	Invited Reviewers		
	1	**2**	**3**
version 1 31 Jan 2020	✔	✔	✔

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2 **Michael Maes**, Chulalongkorn University, Bangkok, Thailand
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There is growing evidence that the elements of gut permeability, immune system response, and gut microbiome—together with genetic predisposition and exposure to environmental triggers— make the *"perfect storm"* for Chronic Inflammatory Disease development.

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the *"perfect storm"* for Chronic Inflammatory Disease development.

- Genetic Vulnerability
- Environmental triggers
- Altered Microbiome (Dysbiosis)
- Intestial Permeability
- Systemic Immune Response (Inflammation)

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If there is 1 concept, that becomes the paradigm you look through for all chronic disease, this is it.





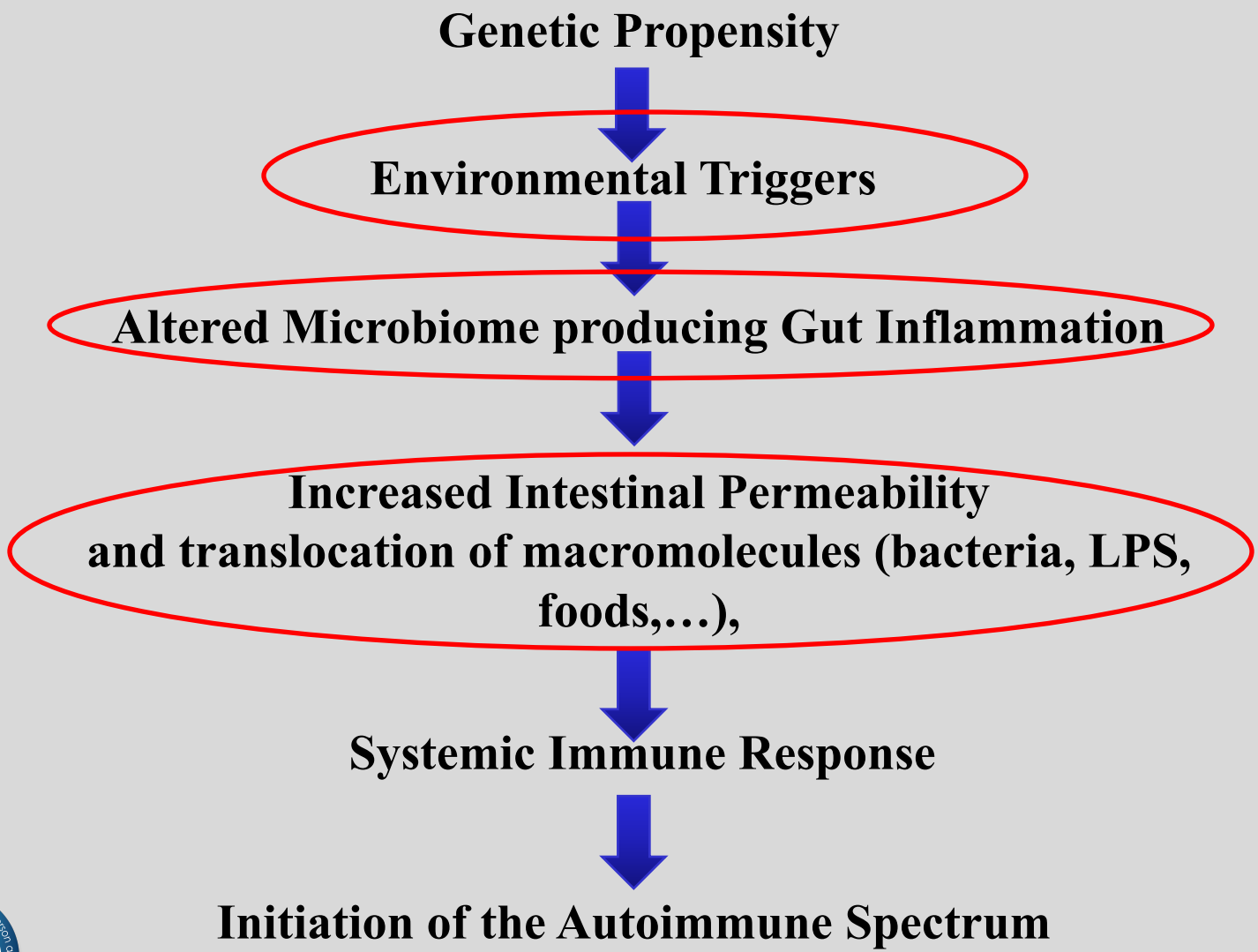
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The Autoimmune Tautology



Valitutti F, Fasano A, Breaking Down Barriers: How Understanding Celiac Disease Pathogenesis Informed the Development of Novel Treatments. Dig Dis Sci. 2019 Jul;64(7):1748-1758

frontiers in Immunology

REVIEW
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The Autoimmune Ecology

Juan-Manuel Anaya, Carolina Ramirez-Santana, Maria A. Alzate, Nicolas Molano-Gonzalez and Adriana Rojas-Villarraga*

Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

Autoimmune diseases (ADs) represent a heterogeneous group of disorders that affect specific target organs or multiple organ systems. These conditions share common immunopathogenic mechanisms (i.e., the autoimmune tautology), which explain the clinical similarities they have among them as well as their familial clustering (i.e., coaggregation). As part of the autoimmune tautology, the influence of environmental exposure on the risk of developing ADs is paramount (i.e., the autoimmune ecology). In fact, environment, more than genetics,

As part of the autoimmune tautology, the influence of environmental exposure on the risk of developing ADs is paramount (i.e., the autoimmune ecology). In fact, environment, more than genetics, shapes immune system function.

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autoimmune/inflammatory syndrome induced by adjuvants; BAFF, B-cell activating factor; CD, celiac disease; CFA, complete Freund's adjuvant; CIA, collagen-induced arthritis; CMV, cytomegalovirus; CrD, Crohn's disease; CREB, cAMP response element-binding protein; CVD, cardiovascular disease; DAMPs, damage-associated molecular patterns; DAS 28, disease activity score-28; DCs, dendritic cells; DEPAP, 1,2-di-oleyl ester; DMARDs, disease-modifying antirheumatic drugs; dmC, deoxymethylcytosine; DNMT1, DNA methyltransferase 1; dsDNA, double-strain DNA; EAE, experimental autoimmune encephalomyelitis; EBV, Epstein–Barr virus; EPW, expert panel workshop; ERK, extracellular signal-regulated kinase; EULAR, European league against rheumatism; FICZ, 6-formylindolo (3.2-b) carbazole; GC, germinal center; GD, Graves' disease; GO, Graves opthalmopathy; GSE, gluten-sensitive enteropathy; GST, glutathione S-transferase; HMGB1, high mobility group box 1; hnRNP, heterogeneous nuclear ribonucleoprotein; HR, hazard ratio; HRT, hormonal replacement therapy; HT, Hashimoto's thyroiditis; IFN, interferon; Igg, immunoglobulin; IRAK1, interleukin 1 receptor associated kinase 1; IRF, interferon regulatory factor; LN, lupus nephritis; LPS, lipopolysaccharide; MAPKs, mitogen-activated protein kinases; MD, mean difference; MDHAQ, multi-dimensional health assessment questionnaire; MHC, major histocompatibility complexes; MS, multiple sclerosis; MTX, methotrexate; MYD88, myeloid differentiation primary response protein 88; NCV, new cluster variables; NF-κB, nuclear factor-κB; NLRs, nod-like receptors; OC, oral contraceptive; OR, odds ratio; OSs, organic solvents; PAD, peptidylarginine deiminase; PAMPs, pathogen-associated molecular patterns; pAPS, primary antiphospholipid syndrome; PBC, primary biliary cirrhosis; PBMC, peripheral blood mononuclear cells; PolyA, polyautoimmunity; PRR, pattern recognition receptors; PSC, primary sclerosing cholangitis; PTMs, post-translational modifications; RA, rheumatoid arthritis; RCTs, randomized controlled trials; RF, rheumatoid factor; RPL, recurrent pregnancy loss; RR, relative risk; SE, shared epitope; SES, socioeconomic status; SHM, somatic hypermutation; SIR, standardized incidence ratios; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology; SMD, standardized mean difference; snRNA, small nuclear RNA; snRNP, small nuclear ribonucleoprotein; SPD, secondary progressive disease; SS, Sjögren's syndrome; SSc, systemic sclerosis; T1DM, type 1 diabetes mellitus; TAK1, TGFβ-activated kinase 1; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; Th17, T helper 17 cells; TIRAP, TIR domain-containing adaptor protein; TLR, toll-like receptor; TNF, tumor necrosis factor; TRAF6, TNF receptor associated factor 6; TRAM, TRIF-related adaptor molecule; Treg, T regulatory cells; Tresp, T-responder cells; TRIF, TIR domain-containing adaptor protein inducing IFNβ; UC, ulcerative colitis; UV, ultraviolet.

Front Immunol. 2016 Apr 26;7:139



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Among the several potential intestinal luminal stimuli that can stimulate zonulin release, small exposure to large amounts of bacteria (and its exhaust LPS) and gluten, have been identified as the two most powerful triggers

in causing CIDs. During the past decade, a growing number of publications have focused on human genetics, the gut microbiome, and proteomics, suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

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Gluten is misinterpreted by the zonulin pathway as a potential harmful component of a microorganism.

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Reviewer Status ✓ ✓ ✓

	Invited Reviewers		
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JAMA | Review

Celiac Disease and Nonceliac Gluten Sensitivity
A Review

Maureen M. Leonard, MD, MMSc; Anna Sapone, MD, PhD; Carlo Catassi, MD, MPH; Alessio Fasano, MD

IMPORTANCE The prevalence of gluten-related disorders is rising, and increasing numbers of individuals are empirically trying a gluten-free diet for a variety of signs and symptoms. This review aims to present current evidence regarding screening, diagnosis, and treatment for celiac disease and nonceliac gluten sensitivity.

OBSERVATIONS Celiac disease is a gluten-induced immune-mediated enteropathy characterized by a specific genetic genotype (*HLA-DQ2* and *HLA-DQ8* genes) and autoantibodies (antitissue transglutaminase and antiendomysial). Although the inflammatory process specifically targets the intestinal mucosa, patients may present with gastrointestinal signs or symptoms, extraintestinal signs or symptoms, or both, suggesting that celiac disease is a systemic disease. Nonceliac gluten sensitivity is diagnosed in individuals who do not have celiac disease or wheat allergy but who have intestinal symptoms, extraintestinal symptoms, or both, related to ingestion of gluten-containing grains, with symptomatic improvement on their withdrawal. The clinical variability and the lack of validated biomarkers for nonceliac gluten sensitivity make

Although both conditions are treated with a gluten-free diet, distinguishing between celiac disease and nonceliac gluten sensitivity is important for long-term therapy. Patients with celiac disease should be followed up closely for dietary adherence, nutritional deficiencies, and the development of possible comorbidities.

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Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

an immediate and transient increase in gut permeability takes place in all individuals who ingest gluten.

Celiac disease is a chronic, small-intestinal immune-mediated enteropathy initiated by exposure to dietary gluten in genetically predisposed individuals and characterized by specific autoantibodies against tissue transglutaminase 2 (anti-tTG2), endomysium, and/or deamidated gliadin peptide.[1] Although up to 40% of the population carries the genotype *HLA-DQ2* or *HLA-DQ8*, which is required for the development of celiac disease, only 2% to 3% of *HLA-DQ2* or *HLA-DQ8* carriers subsequently develop celiac disease.[2] Celiac disease, once considered a relatively rare gastrointestinal condition affecting almost exclusively young white children, can develop at any age and can affect almost any race. Celiac disease was first described by Samuel Gee in 1887. Wheat was hypothesized as the possible offending agent by William Dicke in 1941.[3]

The epidemiology, clinical presentation, pathophysiology, and management of the disease have changed since its initial description. There is strong evidence that celiac disease is an autoimmune disease triggered by the ingestion of gluten present in wheat, barley, and rye in genetically predisposed individuals. The prevalence of celiac disease in the general population is 1%, with regional differences (**Table 1**).[4] Celiac disease can affect any human organ or tissue (Table 1 and **Table 2**).[6]

Nonceliac gluten sensitivity is a term used to describe individuals who have intestinal signs or symptoms, extraintestinal signs or symptoms, or both, related to ingestion of gluten-containing grains (Table 2), with improvement when these are removed from a patient's diet. The frequency of nonceliac gluten sensitivity is unknown owing to the lack of validated biomarkers, but it is thought to be more common than celiac disease. Wheat allergy, the third gluten-related disorder, which will not be addressed in this review, is defined as an adverse type-2 helper T-cell immunologic reaction to wheat proteins and typically presents soon after wheat

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