DR. HYMAN+

Understanding Autoimmunity

Elroy Vojdani, MD

Objectives

1. To understand what an autoimmune is.
2. To see how malfunctions in the defense and repair mechanisms caused by environmental factors are responsible for the induction of autoimmune disease.
3. To understand that, like many complex disorders, autoimmune disease takes years to fully develop

What is Autoimmunity?

Autoimmunity is the failure of an organism to recognize its own constituent parts as ***self***, which results in an immune response against its own cells and tissues.

Any disease that results from such an aberrant immune response is termed an

autoimmune disease.

THE STAGES OF AUTOIMMUNITY

Stage 1
Silent Autoimmunity

– Elevated antibodies but no symptoms or loss of function

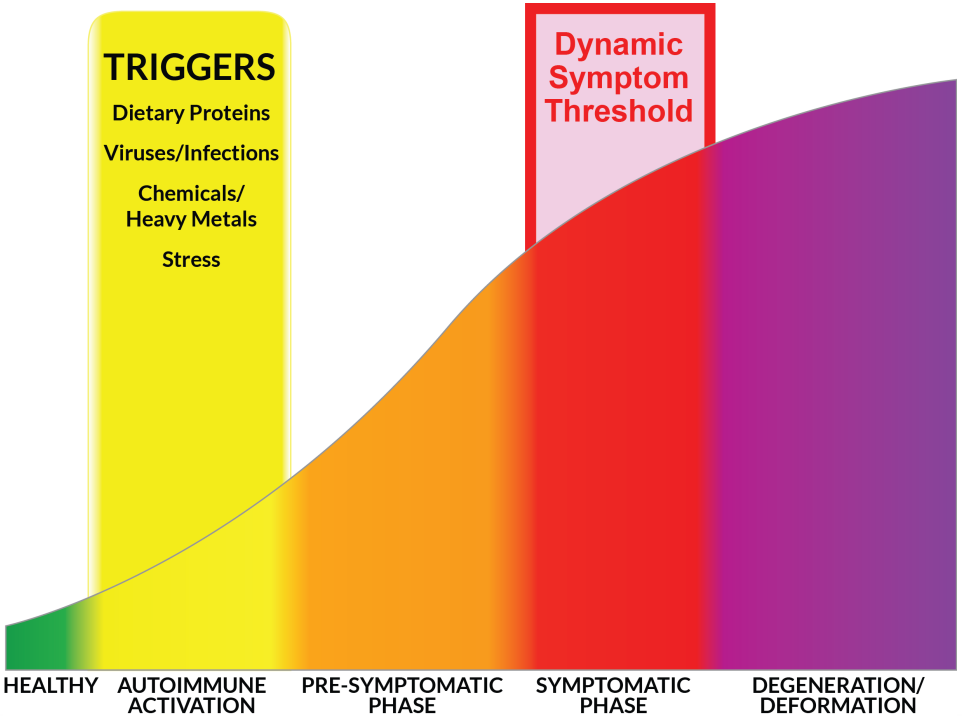
Stage 2
Autoimmune Reactivity

– Elevated antibodies with symptoms and loss of function, but no severe destruction of the tissue associated with disease

Stage 3
Autoimmune Disease

– Elevated antibodies and significant symptoms, signs, labs, imaging, and special studies associated with significant loss of function

Identify the state of disease



Autoantibodies Precede Clinical Manifestation of Autoimmune Diseases

Autoimmune Disease	Detected antibodies	Years preceding clinical disease
Rheumatoid Arthritis	IgM Anti-IgG, Anti-Citrunillated Peptide, Anti-Carbamylated Peptide	13.8 Years
Systemic Lupus Erythematosus	ANA, dsDNA, Ribonucleoprotein, Phospholipid, Type VII Collagen	8.1 Years
Multiple Sclerosis	Anti-Proteosome, Anti-MBP, Anti-MOG	3 Years
Type 1 Diabetes	Anti-Insulin, GAD-65, Thyrosine Phosphatase, ZNT8	10 Years
Autoimmune Thyroiditis	Anti-Thyroglobulin, Anti-Thyroid Peroxidase, Anti-TSHR	7 Years
Adrenal Autoimmunity	Anti-21-Hydroxylase, Anti-17-Hydroxylase	10 Years
Primary Billiary Cirrhosis	Anti-Mitochondrial Antibody	19 Years
Systemic Sclerosis	Anti-Topoisomerase-1, Anti-Centromere, Anti-RNA Polymerase-3	NR
Sjogren's Syndrome	ANA, RF, Anti-SSA, Anti-SSB	7 Years
Celiac Disease	Anti-Tissue Transglutaminases IgA, Anti-Gliadin IgA	NR
Crohn's Disease	ASCA, Outer Membrane-Porin C, Bacterial Flagellin	4.5 Years
Ulcerative Colitis	ANCA, Tropomyosin	4.5 Years

From Ma et al. J Autoimmun 2017; 83: 95-112

DR. HYMAN+

THE IMPORTANCE OF IDENTIFYING EARLY EVENTS

Dissecting the immunologic response specific to inciting agents is critical for identifying the early events that are necessary for the induction of autoimmunities and other diseases

We believe that elucidation of the exposome-induced antibody response will provide insights into the early events necessary for the creation and expansion of autoreactive T and B cells, a cardinal feature of the autoimmune response.

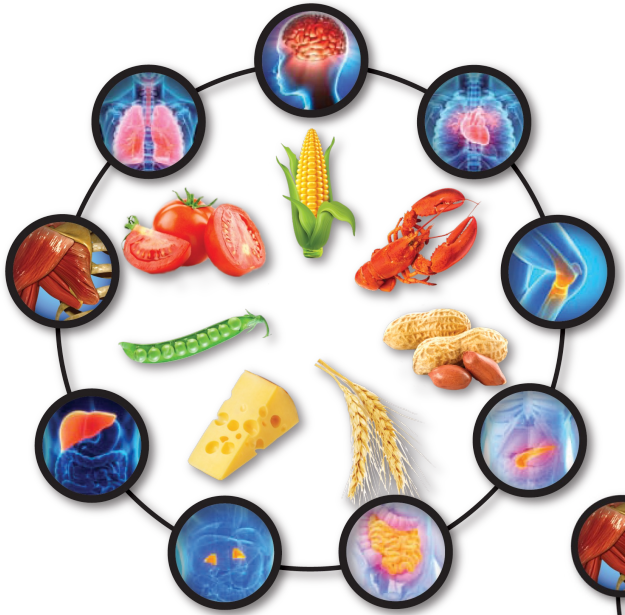
IN CONCLUSION, THE IDENTIFICATION OF EARLY EVENTS IN THE COURSE OF DISEASE DEVELOPMENT IS THE CORE PRINCIPLE OF FUNCTIONAL MEDICINE AND PERSONALIZED LIFESTYLE MEDICINE.

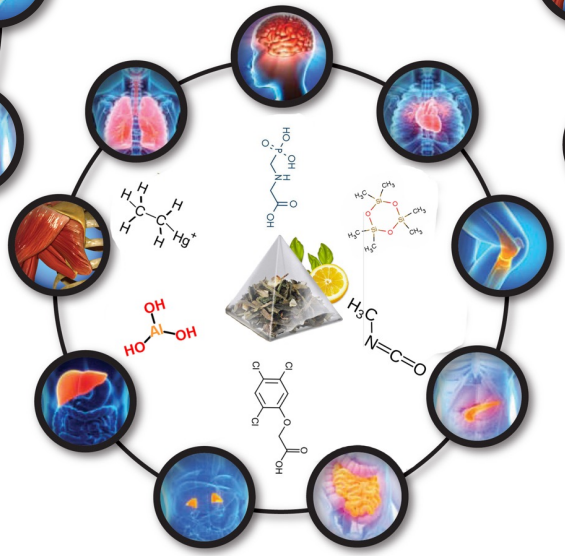
Concordance of Autoimmune Diseases among Monozygotic and Dizygotic Twins

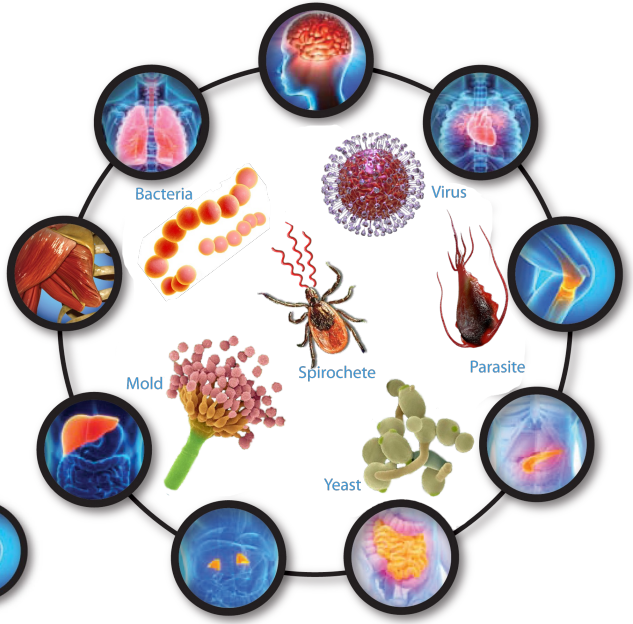
Disease	Monozygotic twins	Dizygotic twins
Rheumatoid Arthritis	26.7%	7%
Systemic Lupus Erythematosus	39.3%	3.2%
Multiple Schlerosis	15.4%	1.7%
Type-1 Diabetes	50%	10%
Autoimmune Thyroiditis	35%	3%
Celiac Disease	49%	10%
Systemic Schlerosis	8%	10.5%
Crohn's Disease	58.3%	3.9%
Ulcerative Colitis	6.3%	0%
Total	32%	5.5%

From Ma et al. J Autoimmun 2017; 83: 95-112

Triggers of Autoimmunity







frontiers in Immunology

REVIEW
published: 10 January 2020
doi: 10.3389/fimmu.2019.03094

Environmental Exposures and Autoimmune Diseases: Contribution of Gut Microbiome

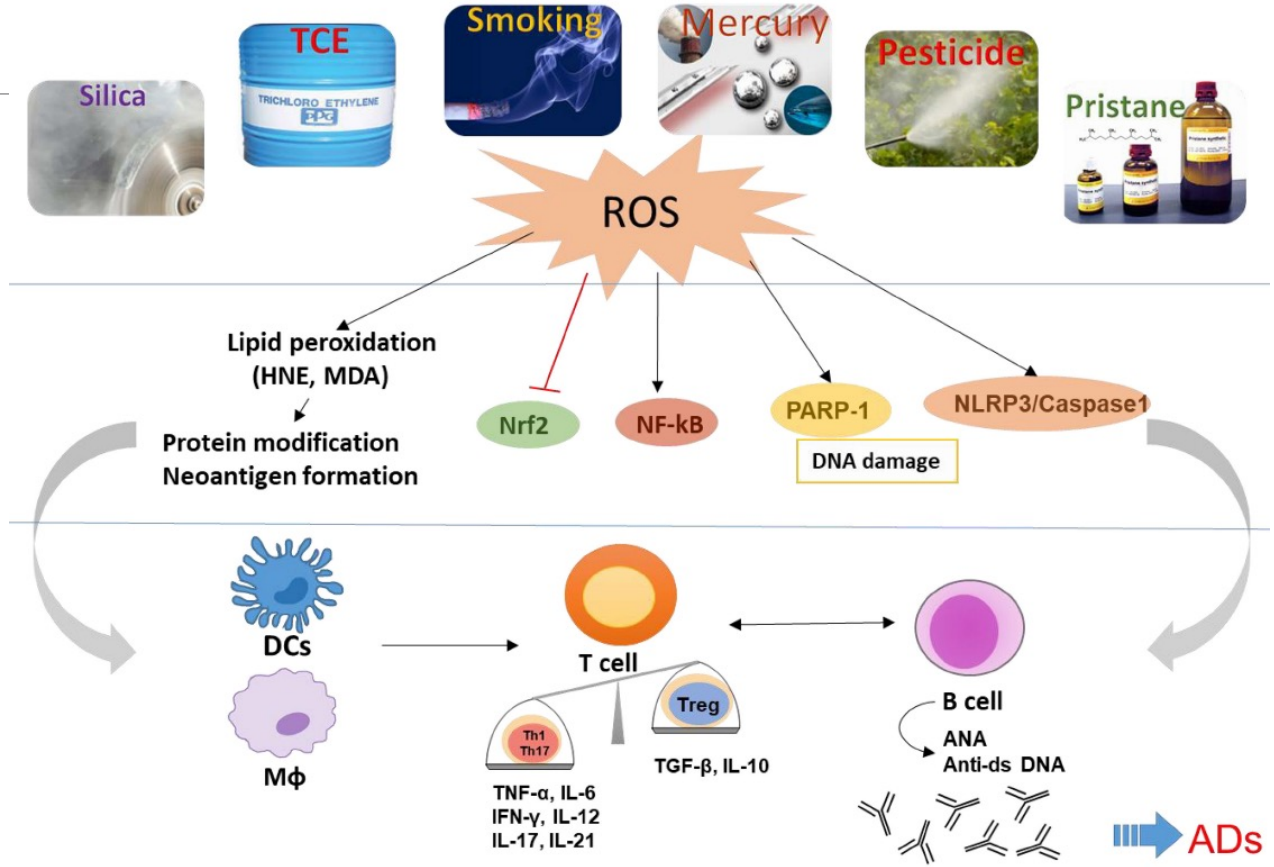
M. Firoze Khan and Hui Wang*

Dysbiosis of the gut microbiome is another important environmental factor that has been linked to the onset of different ADs. Altered microbiota composition is associated with impaired intestinal barrier function and dysregulation of mucosal immune system.

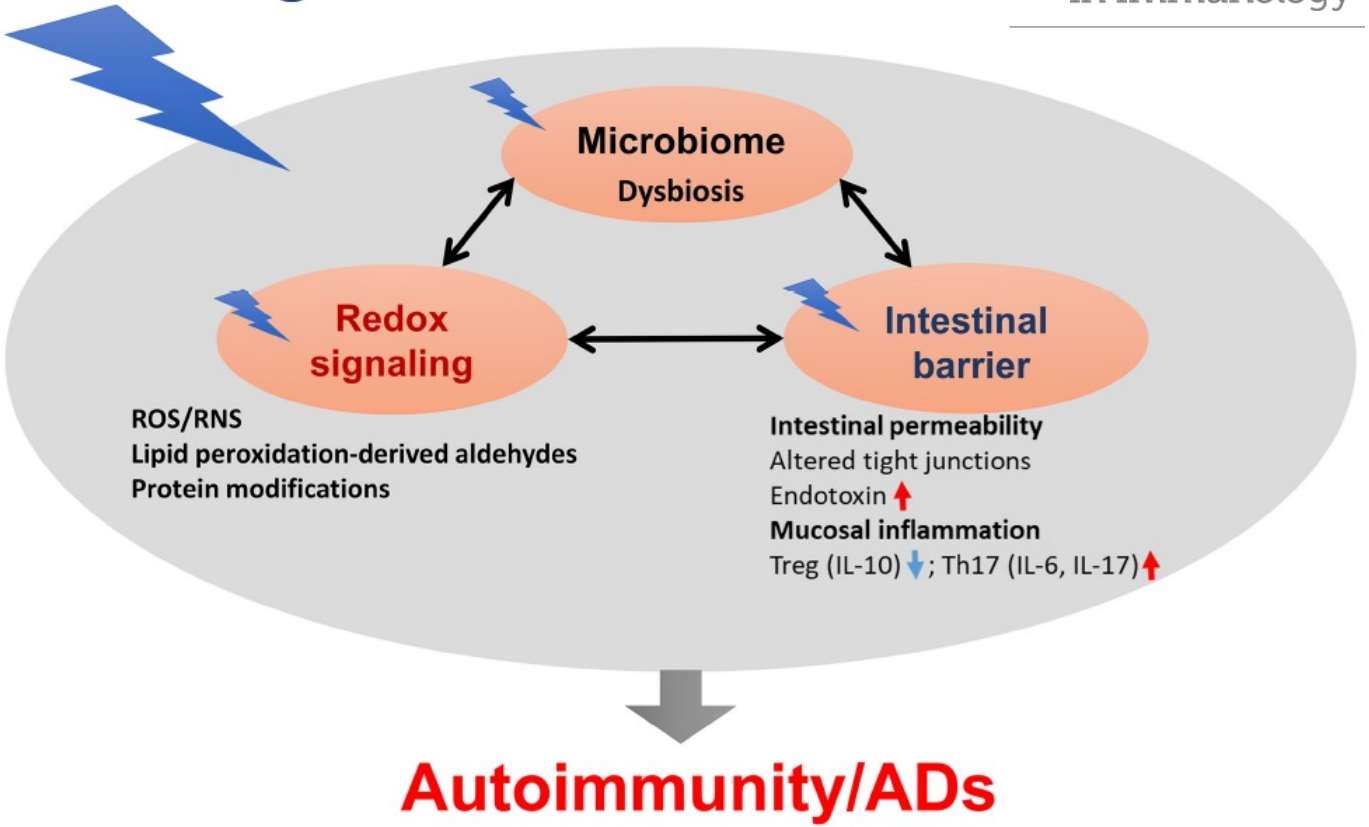
which these environmental agents contribute to the disease pathogenesis remains largely

The most challenging aspect of autoimmunity is to identify the early events that trigger immune dysregulation and autoimmunity.

Proposed mechanistic pathways linking environmental agents to the development of **autoimmune diseases.**



Environmental Agents



Proposed link between gut dysbiosis and autoimmune diseases.

National Institutes of Health

THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

"Approximately one-third of the risk of developing an autoimmune disease can be attributed to heritable factors; the remainder is thought to be associated with non-inherited events."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

March 2005

Journal of Autoimmunity 39 (2012) 249–252

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review

Heritability versus the role of the environment in autoimmunity

Carlo Selmi [a,b,*], Qianjin Lu [c,**], Michael C. Humble [d,***]

More recently, the National Institute of Environmental Health Sciences (NIEHS) convened an expert panel workshop to review the body of literature examining the role of the environment in the development of autoimmune disease.

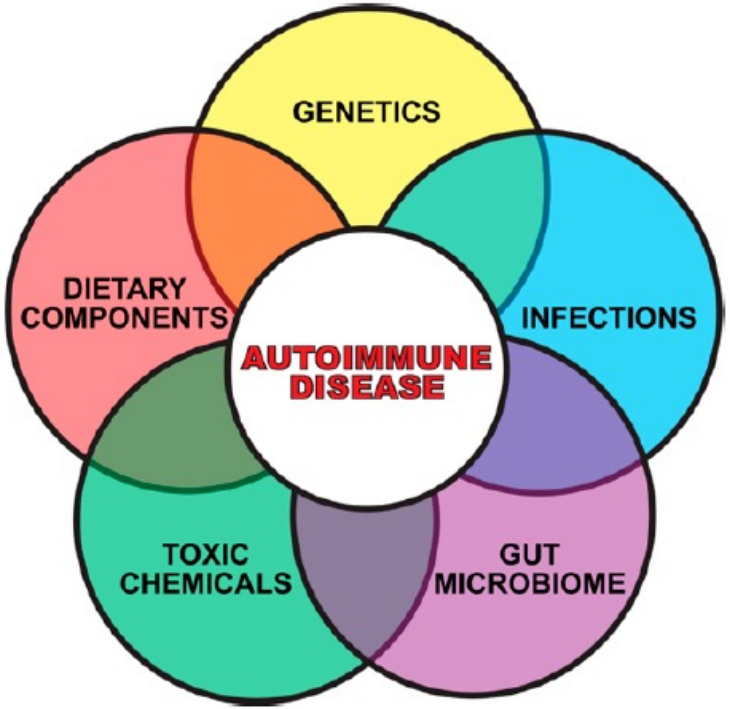
On the whole, the workshop's findings concluded that genetics and heritability can only account for a portion of the incidence of autoimmune disease, supporting the hypothesis that the etiology of autoimmune disease involves both genetic and environmental factors. **More emphasis therefore should be placed on the role of epigenetics and environmental components in the manifestations of autoimmune disease.**

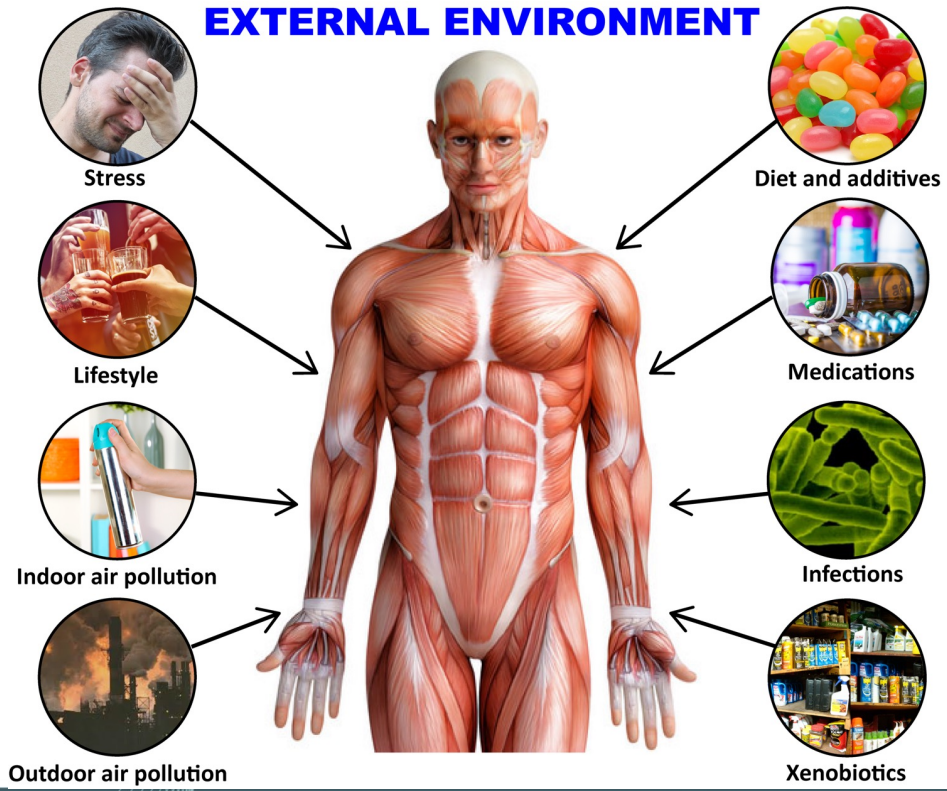
ISP pathophysiology

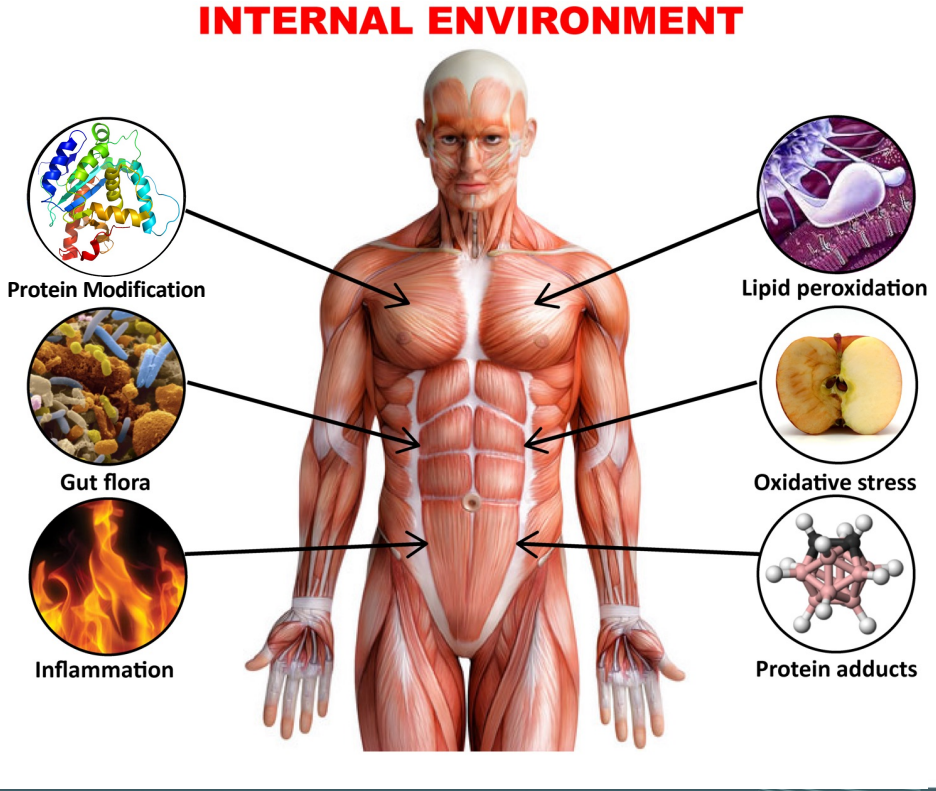
Pathophysiology **2021**, *28*, 513-543

MDPI

Gene plus exposome factors that contribute to autoimmune diseases




EXTERNAL ENVIRONMENT
Stress
Lifestyle
Indoor air pollution
Outdoor air pollution
Diet and additives
Medications
Infections
Xenobiotics


INTERNAL ENVIRONMENT
Protein Modification
Gut flora
Inflammation
Lipid peroxidation
Oxidative stress
Protein adducts

REVIEWS

Nature Reviews Immunology **volume 21**, pages 739–751 (2021)

Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?

Cezmi A. Akdis [1,2]

Abstract | There has been a steep increase in allergic and autoimmune diseases, reaching epidemic proportions and now affecting more than one billion people worldwide. These diseases are more

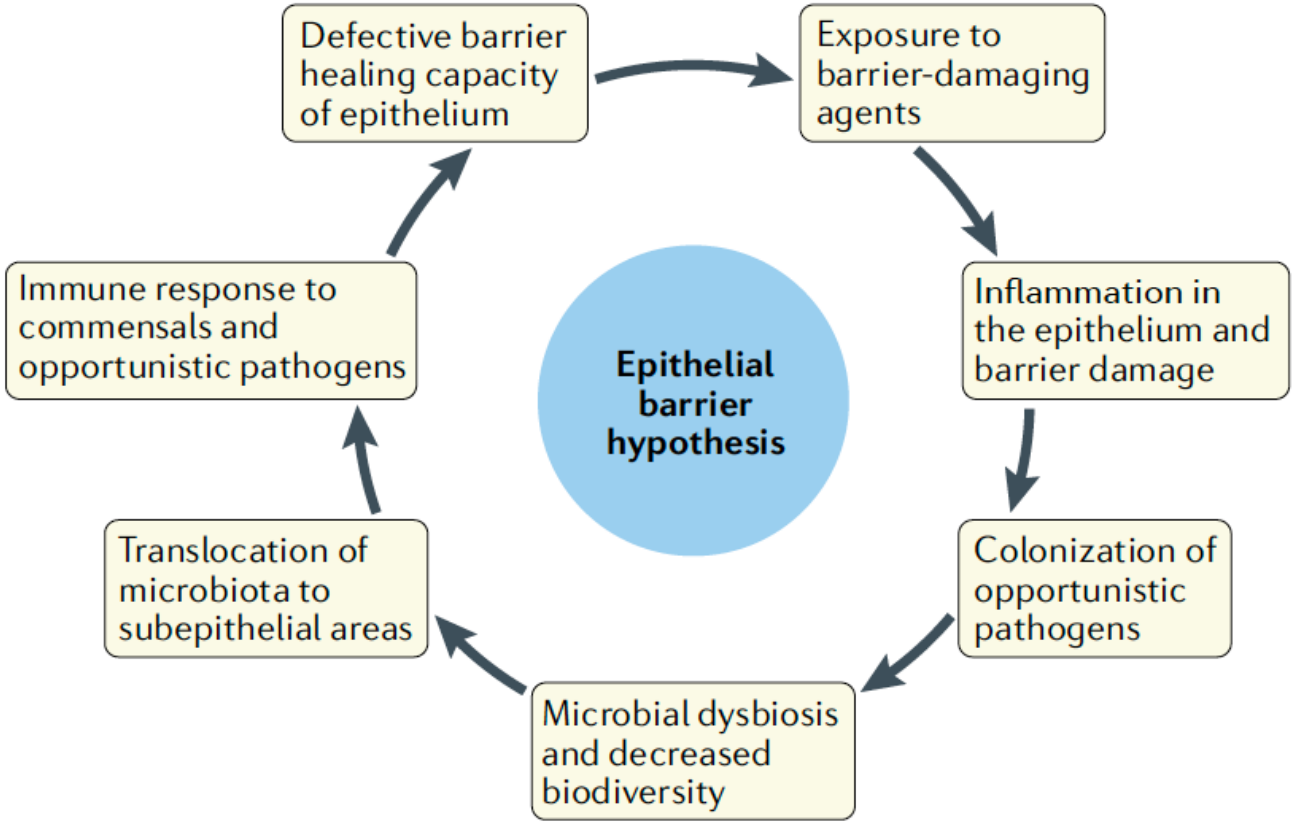
There has been a steep increase in allergic and autoimmune diseases, reaching epidemic proportions and now affecting more than one billion people worldwide. These diseases are more common in industrialized countries, and their prevalence continues to rise in developing countries in parallel to urbanization and industrialization.

and autoimmune conditions such as asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, coeliac disease and inflammatory bowel disease. In addition, leakiness of the gut epithelium is also implicated in systemic autoimmune and metabolic conditions such

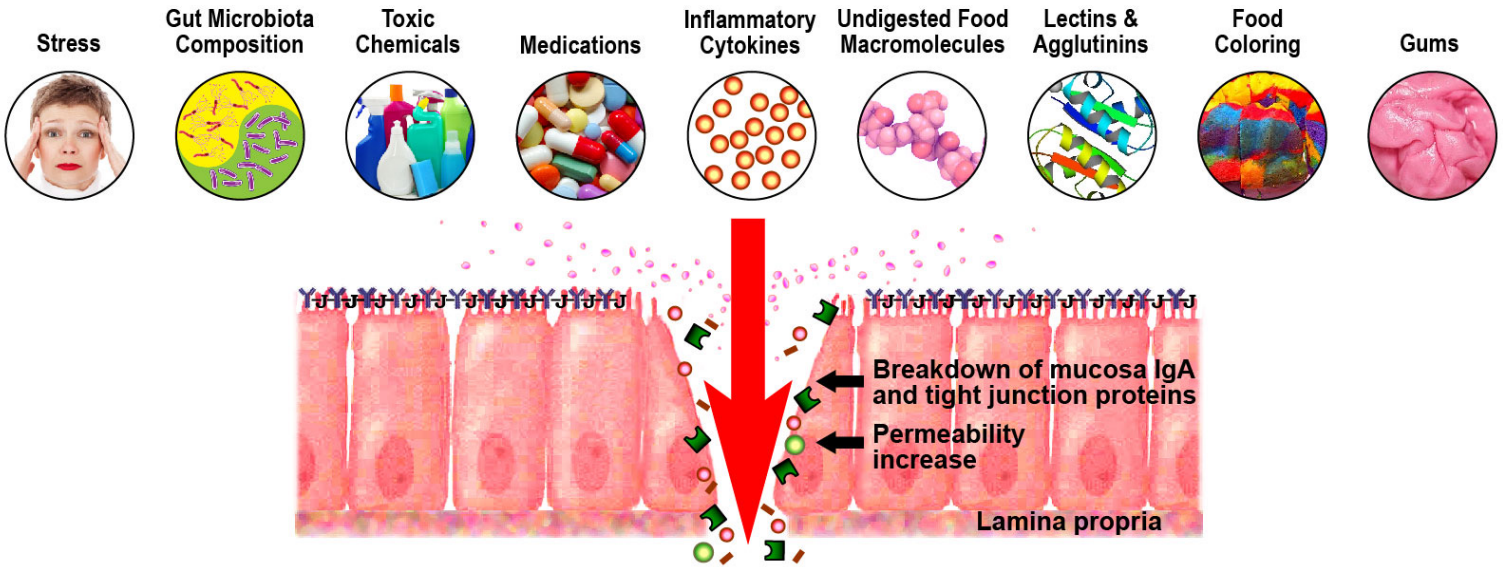
Five major barriers in the human body

- Skin barrier
- Lung barrier
- Intestinal barrier
- Blood-brain barrier
- Immune barrier

Nature Reviews Immunology **volume 21**, pages 739–751 (2021)



The epithelium cannot fully repair and close the barrier, instigating a vicious circle of leaky barriers, microbial dysbiosis and chronic inflammation.

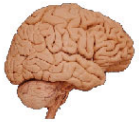


INTESTINAL BARRIER DYSFUNCTION

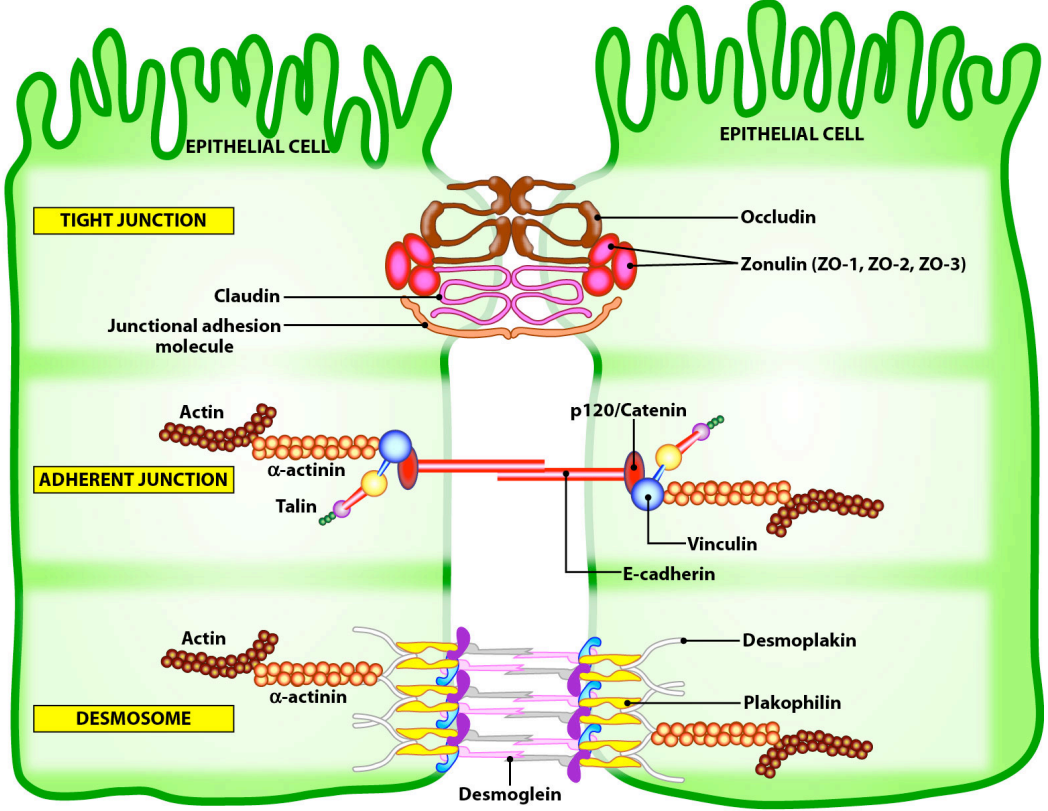
FOOD ALLERGY & INTOLERANCE

IMMUNE SYSTEM ABNORMALITIES

AUTOIMMUNITY



INFLUENCE ON THE BLOOD-BRAIN BARRIER AND NEUROAUTOIMMUNITY



Tight junction complexes regulate epithelial cell interaction

Review

The intestinal epithelial barrier in the control of homeostasis and immunity

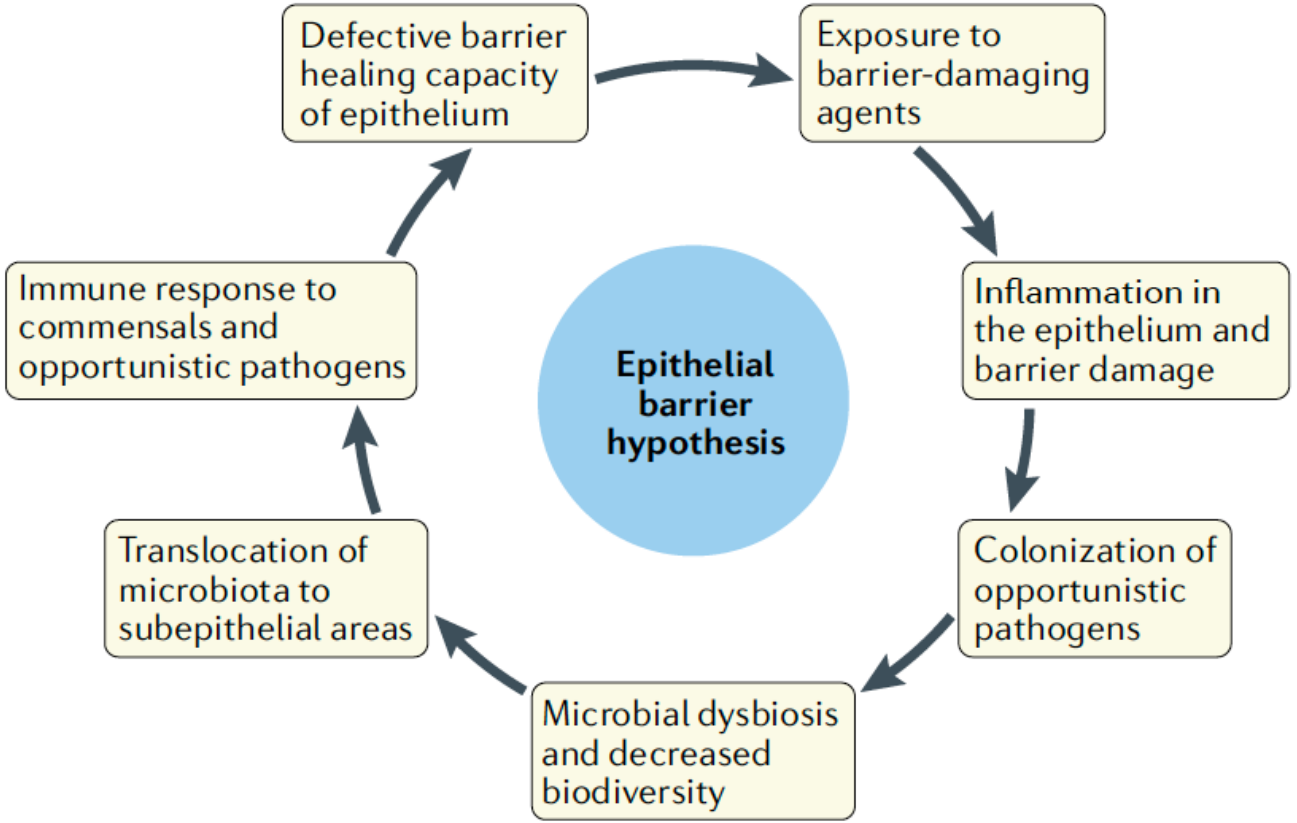
Maria Rescigno

European Institute of Oncology, Department of Experimental Oncology, Milan, Italy

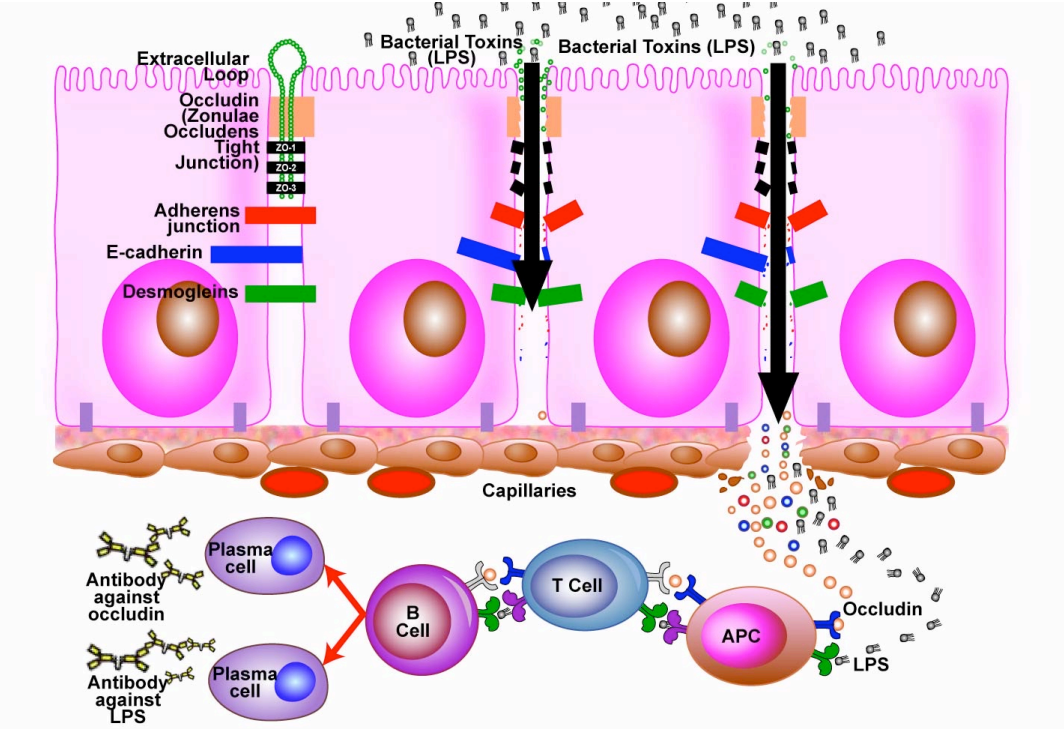
- In the intestine, multiple interactions occur with the external world. Thus, the intestinal mucosal barrier has to tolerate millions of microorganisms that commonly inhabit the gut, degrade and absorb food, and establish tolerance or immunity, depending on the nature of the encountered antigens.
- Recent findings have highlighted that intestinal epithelial cells are not simply a barrier, but also are crucial for integrating these external and internal signals and for coordinating the ensuing immune response.

Trends Immunol, 2011, 32(6): 256-264

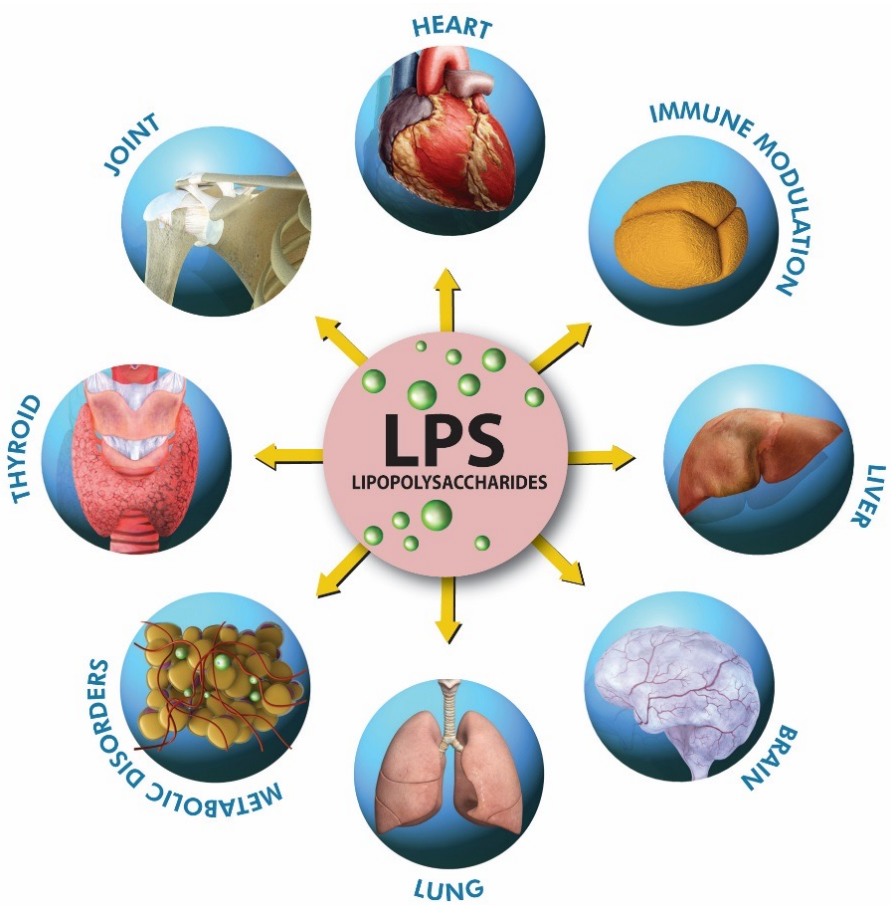
Nature Reviews Immunology **volume 21**, pages 739–751 (2021)



The epithelium cannot fully repair and close the barrier, instigating a vicious circle of leaky barriers, microbial dysbiosis and chronic inflammation.

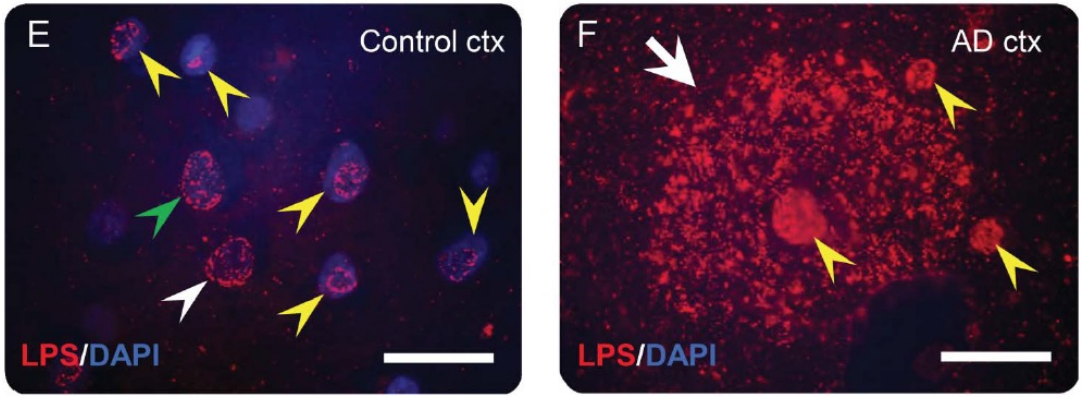


Proposed role of abnormal intestinal permeability in the pathogenesis of autoimmune disease.

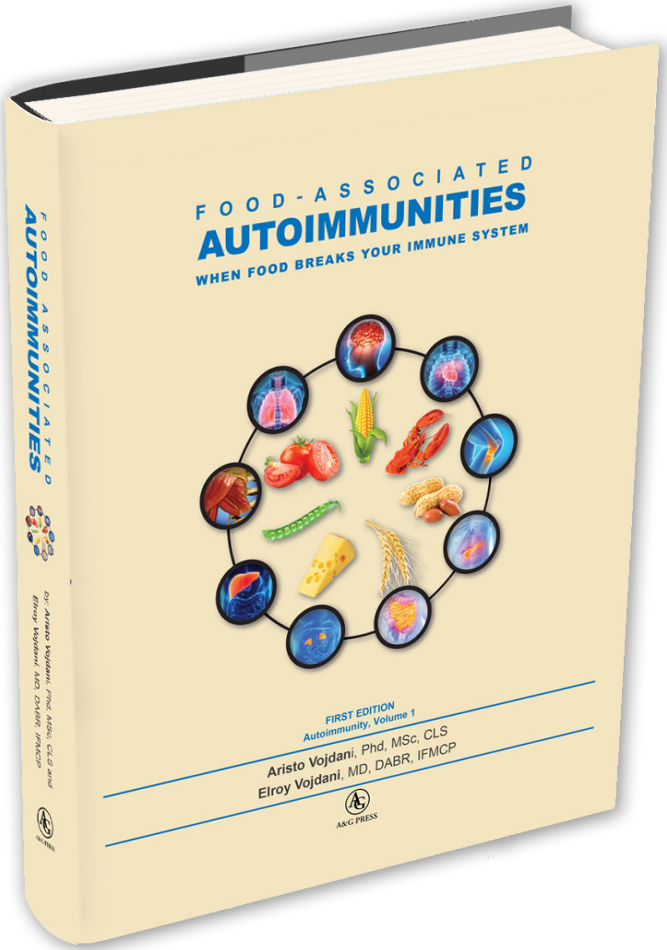

HEART
IMMUNE MODULATION
LIVER
BRAIN
LUNG
METABOLIC DISORDERS
THYROID
JOINT
LPS
LIPOPOLYSACCHARIDES

Neurology 2016;87:2324-2332

Gram-negative bacterial molecules associate with Alzheimer disease pathology



Immunocytochemistry for LPS showed staining in both control and Alzheimer disease (AD) brains. Control "E" shows LPS staining in the DAPI-stained gray matter (yellow, green, and white arrows). AD "F" shows large foci of LPS (yellow and white arrows)



FOOD-ASSOCIATED AUTOIMMUNITIES

WHEN FOOD BREAKS YOUR IMMUNE SYSTEM

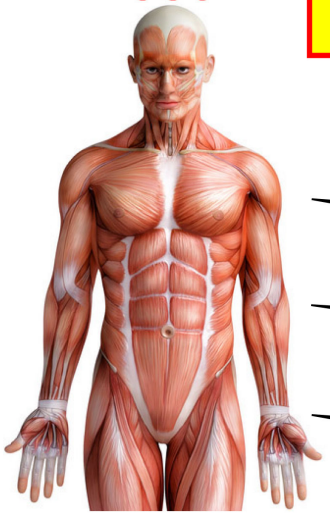
Aristo Vojdani and Elroy Vojdani, 2019

Chapter 11: Immune System Under Fire: Why Food Immune Reactivity and Autoimmunity Are On the Rise

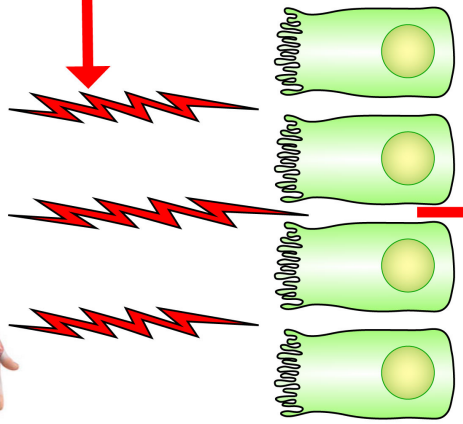
Modern day food has been drastically altered and mutated to maximize flavor, quantity, shelf life and visual appeal. Food is also being subjected to a host of additives for the same reasons. The human digestive system is being asked to process foods and chemicals to which it was never meant to be exposed.

EXPOSOME

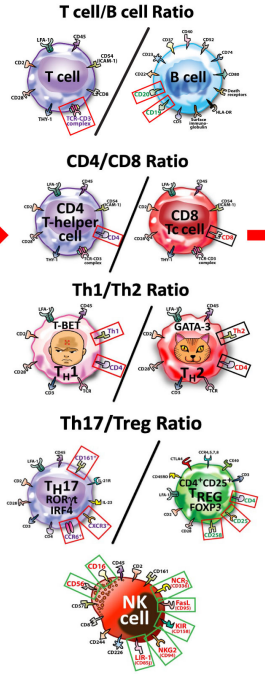
EARLY EVENTS → BREACH IN THE BARRIERS → BREACH IN IMMUNE DEFENSES → INFLAMMATORY AND AUTOIMMUNE DISORDERS, ALLERGIES AND HYPERSENSITIVITIES



UNHEALTHY LIFESTYLE
Food additives, preservatives, toxic chemicals, pollutants, bacteria, fungi



Breakdown in gut barrier and entry of macromolecules into the circulation, immune response, and antibody production



Abnormal Lymphocyte Map

Exposome factors, early events that are involved in the breach of barriers and immune defenses that are associated with inflammatory, autoimmune and neurodegenerative disorders, allergies and hypersensitivities.

Journal of Neuroimmunology 260 (2013) 92–98

Contents lists available at SciVerse ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Aquaporin 4 molecular mimicry and implications for neuromyelitis optica

Radhika A. Vaishnav [a,b], Ruolan Liu [a], Joab Chapman [f], Andrew M. Roberts [b], Hong Ye [c], Jovan D. Rebolledo-Mendez [d], Takeshi Tabira [g], Alicia H. Fitzpatrick [e], Anat Achiron [h], Mark P. Running [e], Robert P. Friedland [a,*]

A B S T R A C T

Neuromyelitis optica (NMO) is associated with antibodies to aquaporin 4 (AQP4). We hypothesized that an-

Neuromyelitis optica (NMO) is associated with antibodies to aquaporin 4 (AQP4). The article hypothesizes that antibodies to AQP4 can be triggered by exposure to environmental proteins. High similarities in peptide sequences were detected with those of corn, soy, spinach and tomato.

Similarity between human aquaporin-4 and different plant AQP-4

Hindawi Publishing Corporation
Autoimmune Diseases
Volume 2015, Article ID 905208, 10 pages
http://dx.doi.org/10.1155/2015/905208

Research Article

Detection of Antibodies against Human and Plant Aquaporins in Patients with Multiple Sclerosis

Aristo Vojdani,[1,2] Partha Sarathi Mukherjee,[3] Joshua Berookhim,[1] and Datis Kharrazian[2,4]

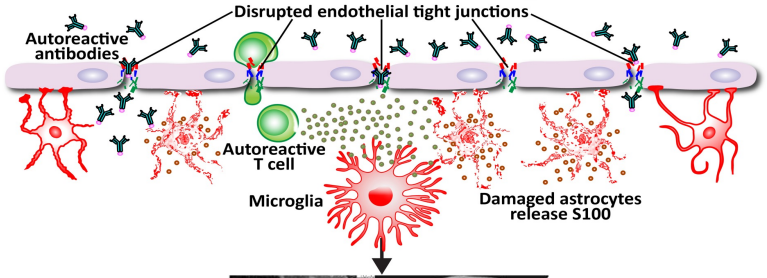
[1]*Immunosciences Lab., Inc., 822 S. Robertson Boulevard, Suite 312, Los Angeles, CA 90035, USA*
[2]*Department of Preventive Medicine, Loma Linda University, 24785 Stewart Street, Loma Linda, CA 92354, USA*
[3]*Department of Mathematics, Boise State University, 1910 University Drive, Boise, ID 83725, USA*
[4]*Department of Clinical Sciences, Bastyr University California, 4106 Sorrento Valley Boulevard, San Diego, CA 92121, USA*

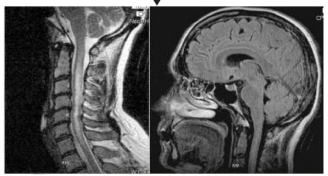
Around 90% of MS sufferers are diagnosed with relapsing-remitting MS (RRMS). We conclude that a subclass of patients with RRMS reacts to both plant and human AQP4 peptides. This immune reaction against different plant aquaporins may help in the development of dietary modifications for patients with MS and other neuroimmune disorders.

Antibody against Aquaporin-4 in

Cross-reaction with Human Aquaporin-4

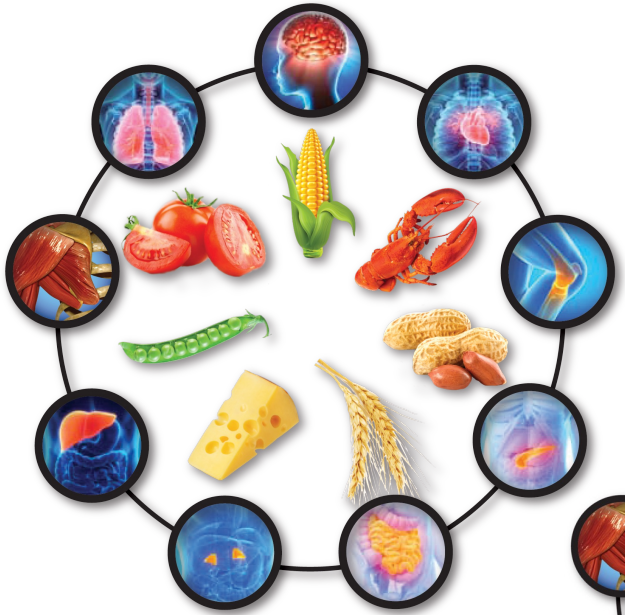
BBB Permeability

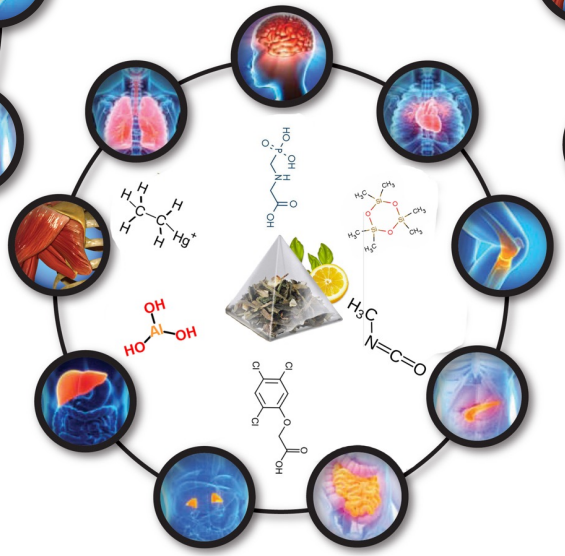


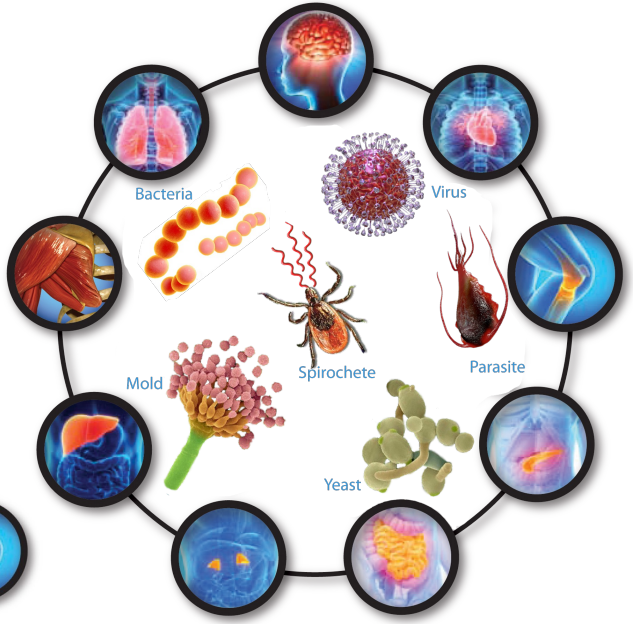


Neuromyelitis Optica

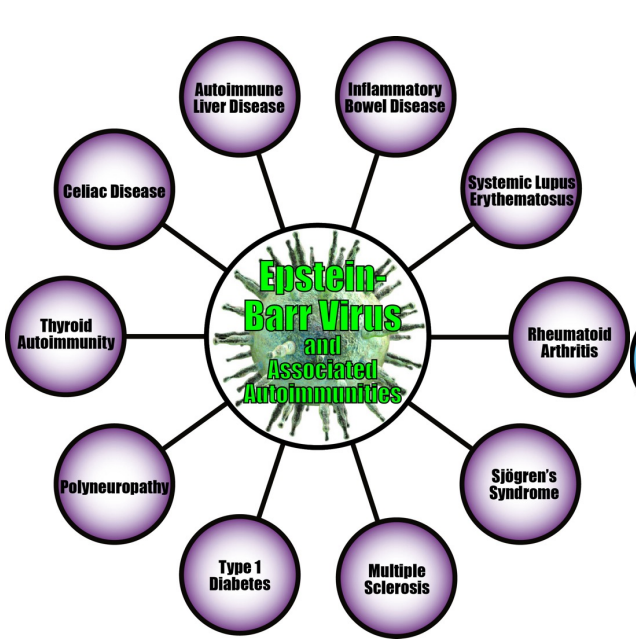
Triggers of Autoimmunity

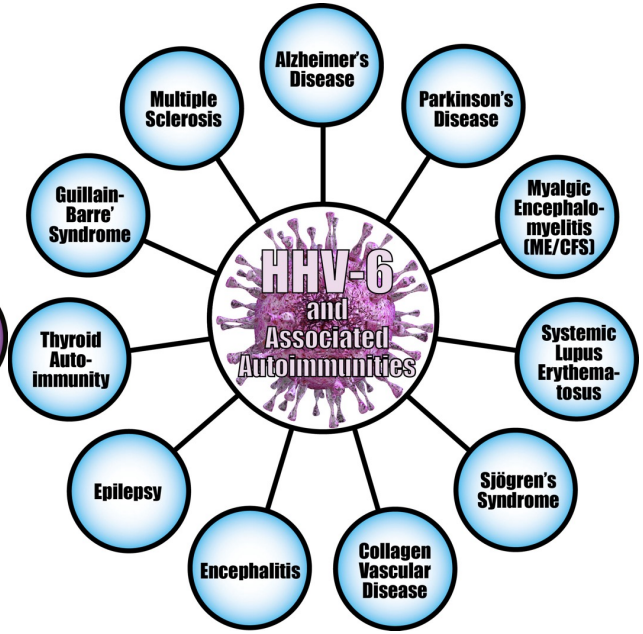






Infection & Autoimmunity





The Autoimmune Viral Trio