

January 2, 2012

- [Home](#)
- [Contact](#)
- [Help](#)
- [Author Services](#)
- [Author Log In](#)
- [Subscriber Services](#)
- [Subscriber Log In](#)
- [Johns Hopkins CME](#)
- [About](#)
- [About the Author](#)



- [Medical Specialties](#)
- [Life Sciences](#)
- [Species and Cell Types](#)
- [Research Technology](#)
- [Therapeutic Technology and Methodology](#)
- [Pharmaceutical and Healthcare Industry](#)
-
-
-

Article Published in the Author Account of

Thomas Kamradt

Can Infections Prevent or Cure Allergy and Autoimmunity?

Published on July 25, 2009

Author: [Thomas Kamradt](#)

Institution: Institut für Immunologie, Klinikum der Friedrich Schiller Universität Jena
Address: Jena, 7743, Germany

Abstract: Empirical and scientific data support the phenomenon that infections can prevent and alleviate certain allergy and autoimmune diseases. The author discusses the mechanism behind it and how to maximize the benefits without revoking the deadly consequences of infections.

In western countries the prevalence and incidence of allergic and autoimmune diseases have been increasing dramatically over the last 50 years. In the last two decades, significant progress has been made towards understanding the genetic basis for susceptibility to [autoimmunity](#) or [allergy](#). Genetic factors, however, cannot explain abrupt changes in disease incidence. It is therefore likely that environmental factors, specifically environmental factors that have changed over the last two generations, are critical for the increasing incidence of allergies and autoimmune diseases.

Traditionally, autoimmune diseases such as [multiple sclerosis](#) (MS), type I [diabetes](#), or [rheumatoid arthritis](#) (RA) are believed to have resulted from aberrant immune response to pathogens. In contrast, the “[hygiene hypothesis](#),” first postulated some 20 years ago, proposes that a lack of infections, especially during early childhood, predisposes one to the aberrant immune responses against harmless foreign antigens that cause allergic diseases such as rhinitis, [atopic dermatitis](#), and [allergic asthma](#). Several lines of epidemiological, clinical and experimental research point to more complex connections, either protective or pathogenic, between infection, allergy and [autoimmunity](#).

Infections Can Exacerbate Autoimmune and Allergic Diseases

Autoimmune diseases sometimes occur shortly after suffering from [infectious diseases](#). Classical examples include post-infectious encephalitis disseminata and rheumatic fever. Exacerbation of multiple sclerosis is 2-3 times more likely to occur during or shortly after common infections, and similar findings have been reported for other autoimmune diseases. Many different viruses or microbes have been implicated in the pathogenesis of autoimmune diseases. There is literally no [autoimmune disease](#) for which an infectious origin has not been proposed.

To explain the connection between infection and autoimmunity, both antigen-specific and antigen-nonspecific mechanisms have been suggested. The “[molecular mimicry](#)” hypothesis is based on the finding that lymphocytes can recognize both microbial and self antigens. It suggests that crossreactive lymphocytes, activated by recognition of a microbial epitope (the specific site in a protein to which immune response is generated), subsequently attack self-antigens with similar amino acid sequences and induce autoimmune disease.

Recently, several laboratories have demonstrated that [T cell](#) recognition of multiple different peptides occurs much more frequently than previously assumed and that sequence similarity is not a prerequisite for such crossrecognition. Clearly then, cross-reactivity between a particular microbial antigen and a particular self-antigen does not suffice to induce autoimmune disease. Despite decades of intense effort, no casual link has been proven between a particular infection and a particular autoimmune disease.

The antigen-nonspecific set of ideas holds costimulatory molecules and inflammatory cytokines as major culprits. Pathogens possess molecules such as [lipopolysaccharide](#) (LPS, [bacterial cell wall](#)) or [dsRNA](#) (double stranded RNA) that do not normally occur in the host. Such molecules are dubbed Pathogen Associated Molecular Patterns (PAMPs). PAMPs are recognized by a set of non-clonal receptors, Toll like receptors (TLRs), which are expressed by cells of the innate immune system including dendritic cells or macrophages, which have the capacity to present peptide antigens to T-lymphocytes. Signaling through TLRs activates antigen-presenting cells, which thereupon mature and express a range of proinflammatory cytokines and costimulatory molecules necessary for the full activation of T cells.

Some effector/memory T cells can be activated in a [T cell receptor](#) (TCR)-independent manner to proliferate and produce cytokines, if exposed to mixtures of proinflammatory cytokines or strong costimulatory signals provided by innate immune cells, which are activated via TLR ligands. This TCR-independent activation has been called “bystander activation.” Bystander activation of T cells is suspected to play a role in the pathogenesis of rheumatoid arthritis and in murine models of [autoimmune encephalitis](#). The TCR-independent bystander-activation of autoreactive T helper (Th) cells fits better with the clinical and epidemiological data on the connection between infection and autoimmunity than antigen-specific mechanisms. If the frequency of autoreactive T cells is beyond a certain threshold, bystander activation can trigger sufficient numbers of autoreactive effector T cells to cause autoimmune damage. Thus, a variety of different pathogens could deliver that “final hit” as long as they are sufficiently capable of activating

[Access This PDF as a
Subscriber](#)

[Purchase/Download This Article](#)

[Related Articles](#)

[Email This Article](#)

[Share This Article](#)

innate immune cells by providing TLR ligands.

Allergies. Respiratory viruses such as [respiratory syncytial virus \(RSV\)](#), [rhinovirus](#), or [influenza A](#) can exacerbate [asthma](#). Furthermore, RSV infections in the first year of life might be a risk factor for the development of childhood asthma. Chronic [helminth](#) (parasitic worm) infections have been linked to urticaria (skin allergy), and [Staphylococcus aureus](#) can trigger the exacerbation of atopic dermatitis (itchy skin rash).

Can Infections Protect From Autoimmune or Allergic Diseases?

Within less than 50 years, the incidence of [inflammatory bowel disease](#) (IBD) has tripled in Northern Europe. Between 1989 and 1994 the annual increase in the incidence of [type 1 diabetes](#) in European children less than five years old was 6.3%. Although the incidence of some diseases such as rheumatoid arthritis seems to be remarkably stable, it is clear that the overall incidence of both autoimmune diseases and allergies (atopy) has been increasing over the past several decades.

That improved hygiene standards might carry an increased risk for the development of multiple sclerosis was suggested almost 40 years ago. A number of studies have indicated that infections within the first year(s) of life decrease the risk of developing type 1 diabetes. Similar observations have lately been reported for asthma and allergy. The incidence of some infectious diseases, most notably perhaps hepatitis A and mycobacterial and helminthic infections, is a mirror image of the incidence of both atopic and autoimmune diseases. Helminthic infections, particularly infections with *Schistosomes* or hook worms, seem to be associated with a lower incidence of atopic diseases.

Further support comes from studies that have shown that anti-helminthic [chemotherapy](#) resulted in increased levels of skin test reactivity against common allergens such as house dust mites. Finally, various pathogens can modulate experimental models of both allergic and autoimmune diseases. Helminths and mycobacteria seem to be particularly good at protection and the time point (infections before the onset of atopy or autoimmunity have the greatest impact), age at infection, route, localization and dose of the infections all play a role. For example: low-level helminthic infections can exacerbate rather than downmodulate allergic diseases. The mechanisms by which infections protect from immunopathology are only recently being examined.

Mechanisms

Cytokines

Helminths and other chronic infections strongly induce immunosuppressive cytokines such as interleukin (IL)-10. Functional evidence for a protective role of infection-induced [IL-10](#) and/or TGF- β was provided in murine models where allergen-induced airway inflammation could be inhibited by mycobacterial lipoglycan and the application of antibodies against IL-10 and/or TGF- β blocked that protective effect. Similarly, in a clinical study, the production of parasite-specific [interleukin-10](#) was associated with the suppression of atopic reactivity in *Schistosoma hematobium*-infected children. IL-10 is certainly not the only infection-induced mediator of protection. Colonization of IL-10 deficient mice with *Lactobacilli*, *Heligmosomoides polygyrus*, or *Trichuris muris* (worms) attenuated the colitis that usually develops spontaneously in these mice indicating that other immunological mechanisms in addition to IL-10 must be involved in protection. Taken together, there is accumulating experimental and clinical evidence for IL-10 and TGF- β as important but not exclusive mediators of protection from [chronic inflammation](#) in helminth-infected hosts.

Regulatory T Cells

The question of which cell populations are important for infection-mediated protection has not been extensively addressed thus far. Current opinion favors the induction of regulatory T cells ([Treg](#)) as a result of chronic infection. Data from several different models demonstrate that infections induce CD4⁺CD25⁺Tregs and that the lack of such infection-induced Tregs can have detrimental consequences for the host. Functionally, many but not all Tregs are characterized by IL-10 production. The IL-10-producing CD4⁺ T cells in infected mice express selected ligands that enable them to migrate to sites of inflammation. Therefore, it has been postulated that a decreasing exposure to pathogens prevents the induction of Tregs by infections and thus contributes to the rising incidence of allergy and autoimmune diseases in western countries. This attractive and plausible hypothesis is currently largely speculative but experimental evidence for the induction of Tregs by infections is accumulating.

Innate Immune Cells and Molecules Involved

The differentiation of T cells into different functional phenotypes largely depends on the instructive signals that the T cells receive from dendritic cells (DC). Recent evidence has shown that pathogens can modulate DC differentiation resulting in the induction of Tregs. IL-10 seems to be crucial for dendritic cells' ability to induce Tregs in many experimental settings. Infection with *Mycobacterium vaccae* confers protection from allergen-induced airway hyper-reactivity in mice via the induction of CD11c⁺ cells that produce IL-10 and TGF- β . IL-10 production is not the only mechanism by which dendritic cells from infected animals induce protection against allergy. "Alternatively activated macrophages" have been described that exert their immunosuppressive function independently of IL-10 or TGF- β .

Natural Killer T (NKT) cells also have regulatory capacities. Soluble extracts from *Schistosoma mansoni* eggs increase the percentage of NKT cells and prevent diabetes in non-obese diabetic ([NOD](#)) mice. The microbial molecules and their receptors on innate immune cells that mediate the immunosuppressive effects of pathogens are currently being elucidated.

Memory Pool

The number of lymphocytes as well as their subsets (e.g., naive vs. effector/memory cells) is tightly regulated. During acute antiviral immune responses, up to 50% of all [CD8⁺](#) T cells in the peripheral blood can be directed against one particular viral epitope and it has been shown that such massive responses can impair the memory responses to foreign (heterologous) antigens. It is likely that constant exposure to microbes and viruses maintains a certain pressure on the memory T-cell pool, thus avoiding the uninhibited homeostatic proliferation of autoreactive clones that might occur otherwise.

Clinical Applications

The knowledge about how immune responses develop during infections, autoimmunity and allergies has led to the development of novel therapeutic intervention strategies aimed at reducing both autoimmune and allergic responses in humans utilizing live or dead pathogens or products derived from them.

Intradermal application of killed *Mycobacteria vaccae* suspension resulted in some improvement in children with atopic dermatitis. The same treatment had no significant effects on the severity of asthma in adults. Subcutaneous injection of live *Bacillus Calmette-Guerin* ([BCG](#), used for [immunization](#) against [tuberculosis](#)) significantly improved the clinical symptoms of asthma in adults.

[Lactobacillus rhamnosus](#) given prenatally to mothers, in a double blind, randomized placebo-controlled trial, decreased the incidence of atopic dermatitis children at high risk. Formulas containing *L. rhamnosus* or *Bifidobacterium lactis* improved atopic dermatitis in infants. In contrast, oral administration of *Lactobacilli* was ineffective in adult patients with asthma or [food allergy](#).

A small study found reduced [MRI](#)-activity in [BCG](#)-immunized multiple sclerosis patients. The study was too small to demonstrate any clinical effects of BCG treatment and no follow-up has been published to date. In contrast, therapeutic BCG-[vaccination](#) was ineffective in patients with type 1 diabetes; perhaps the duration of the treatment was too short to mimic chronic infection, but no positive results have been published to date. Interestingly, a small clinical trial found the oral administration of the [Trichuris suis](#) worm's ova safe and possibly effective in patients with inflammatory bowel disease. Further trials are underway.

Infection-induced Immune-suppression Is Not Harmless

The pathogen-induced immune suppression that may be valuable to prevent atopy and autoimmunity also diminishes the protective immune responses against pathogens. BCG and other vaccines are less immunogenic in Africa compared with Europe or North America and the success of BCG immunization is enhanced after anti-helminthic therapy. Several parasitic infections, including schistosomiasis and intestinal helminthiasis have been associated with higher [HIV](#) plasma viral loads and accelerated progression from asymptomatic [HIV](#)-infection to [AIDS](#) and deworming resulted in decreased HIV plasma concentrations. T cells from chronically helminth-infected people express high levels of the inhibitory molecule [CTLA-4](#) (cytotoxic T lymphocyte associated protein 4) and have defects in TCR-induced signaling. These abnormalities are restored and the [immunosuppression](#) is cured after deworming. Therefore, the therapeutic application of helminths could be burdened with clinically relevant immunosuppression.

Future Directions and Concluding Remarks

The number and quality of published clinical studies using pathogens or defined molecules thereof is insufficient for definitive conclusions. Some of the obvious questions are: which microbe should be administered? Obviously the "therapeutic microbe" must be innocuous. It seems that *M. vaccae*, *Lactobacilli* and *T. suis* fit this bill although there are anecdotal

reports of pathogenicity and, clearly, microbes must not be administered to immunosuppressed patients. Route, dose and duration of treatment are important issues and so is the timing. One may suspect that prevention will be easier to attain than cure. A better understanding of the cells and molecules involved in [immunoregulation](#) by microbes and viruses is certainly needed. Could defined molecules substitute for complete microbes as therapeutic agents? Currently it is questionable if the complicated parasite-host interaction can be mimicked by single molecules, and host factors also contribute to the treatment outcome. Considering the morbidity and mortality associated with infectious diseases, including some of those that seem to have a positive influence on allergy and autoimmunity, one certainly does not want to go back to the not-too-distant past when children frequently died of infectious diseases and the average [life expectancy](#) was less than fifty years.

One might be willing, however, to have a somewhat less hawkish view of the immune system's function. Total avoidance or destruction of non-self cannot be accomplished without damaging self. Instead, the immune system seems to benefit from regular encounters with some microbes possibly opening a new window for the therapeutic intervention in autoimmunity and atopy.

References and Further Readings

Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *New England Journal of Medicine* 347:911-920, 2002.

Dunne DW, and Cooke A. A worm's eye of the immune system: consequences for evolution of human autoimmune disease. *Nature Reviews Immunology* 5:420-426, 2005.

Kamradt T, Mitchison NA. Tolerance and autoimmunity. *New England Journal of Medicine* 344:655-664, 2001.

Kamradt T, Göggel R, Erb K. Induction, exacerbation and inhibition of allergic and autoimmune diseases by infection. *Trends in Immunology* 26:260-267, 2005.

Maizels RM, Yazdanbakhsh M. [Immune regulation](#) by helminth parasites: cellular and molecular mechanisms. *Nature Reviews Immunology* 3:733-744, 2003.

Yazdanbakhsh M, Kreamsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 296:490-494, 2002.

[Discovery Medicine, 5(27):283-287, 2005]

Related Articles

- Jul 26, 2009 [Crypticity of Self Antigenic Determinants Is the Cornerstone of a Theory of Autoimmunity](#)
 - Jul 27, 2009 [Genetic Progress Towards the Molecular Basis of Common Autoimmunity](#)
 - Aug 19, 2011 [T Cell Costimulation and Coinhibition: Genetics and Disease](#)
 - Nov 21, 2011 [The Role of Microbial Byproducts in Protection Against Immunological Disorders and the Hygiene Hypothesis](#)
 - May 24, 2009 [Getting a Grip on Antigen-Specific CD4 T Cells: Tracking Autoimmune T Cells In Vivo](#)
 - Sep 10, 2009 [Inflammation, Autoimmunity, and Atherosclerosis](#)
 - Jul 12, 2009 [Treatment of Disease Through Oral Tolerance](#)
 - Dec 26, 2011 [Environmental Triggers and Epigenetic Deregulation in Autoimmune Disease](#)
 - May 12, 2011 [The Potential Role of Th17 in Mediating the Transition from Acute to Chronic Autoimmune Inflammation: Rheumatoid Arthritis as a Model](#)
 - Apr 07, 2011 [Autoantigen Based Vaccines for Type 1 Diabetes](#)
- [More Related Articles](#)

[Access This PDF as a Subscriber](#) | [Purchase/Download This Article](#)

Categories: [Allergy](#), [Autoimmune Disease](#), [Inflammatory Bowel Disease](#), [Microbial Infection](#), [Multiple Sclerosis](#), [Rheumatoid Arthritis](#), [T Cell](#), [Type 1 Diabetes](#), [Type 1 T Helper Cell](#)

Tags: [autoimmunity](#), [dsRNA](#), [molecular mimicry](#), [TCR](#)

Search

[Search Tips/Help](#)

Journal Issues - Current & Archive (Part)

Current Issue, No 067, Dec. 2011 | [No 066, Nov. 2011](#) | [No 065, Oct. 2011](#) | [No 064, Sep. 2011](#) | [No 063, Aug. 2011](#) | [No 062, Jul. 2011](#) | [No 061, Jun. 2011](#) | [No 060, May 2011](#) | [No 059, Apr. 2011](#) | [No 058, Mar. 2011](#) | [No 057, Feb. 2011](#) | [No 056, Jan. 2011](#) | [No 055, Dec. 2010](#) | [No 054, Nov. 2010](#) | [No 053, Oct. 2010](#) | [No 052, Sep. 2010](#) | [No 051, Aug. 2010](#) | [No 050, Jul. 2010](#) | [No 049, Jun. 2010](#) | [No 048, May 2010](#) | [No 047, Apr. 2010](#) | [No 046, Mar. 2010](#) | [No 045, Feb. 2010](#) | [No 044, Jan. 2010](#) |

Global Categories

Medical Specialties

[Addiction Medicine](#) [Aging](#) [Anesthesiology](#) [Bacteriology](#) [Cardiology](#) [Cardiology and Circulation](#) [Dermatology](#) [Drug Discovery](#) [Endocrinology](#) [Epidemiology](#) [Gastroenterology](#) [Genomic Medicine](#) [Geriatrics](#) [Gerontology](#) [Gynecology](#) [Hematology](#) [Hepatology](#) [Immunology](#) [Infectious Diseases](#) [Medical Genetics](#) [Microbiology](#) [Mycology](#) [Nephrology](#) [Neurology](#) [Neurosurgery](#) [Nutrition](#) [Oncology](#) [Ophthalmology](#) [Orthopedics](#) [Otolaryngology](#) [Pathology](#) [Pediatrics](#) [Personalized Medicine](#) [Pharmacogenetics](#) [Pharmacogenomics](#) [Pharmacology](#) [Plastic and Reconstructive Medicine](#) [Preventive Medicine](#) [Psychiatry](#) [Psychology](#) [Pulmonology](#) [Radiology](#) [Regenerative Medicine](#) [Reproductive Medicine](#) [Rheumatology](#) [Surgery](#) [Toxicology](#) [Traditional Chinese Medicine](#) [Translational Research](#) [Transplantation](#) [Urology](#) [Virology](#)

Life Sciences

[Anatomy](#) [Anthropology](#) [Biochemistry](#) [Bioinformatics](#) [Biology](#) [Biophysics](#) [Cell Biology](#) [Chemistry](#) [Developmental Biology](#) [Ecology](#) [Embryology](#) [Environmental Science](#) [Epigenetics](#) [Genetics](#) [Genomics](#) [Glycomics](#) [Molecular Biology](#) [Neuroscience](#) [Physiology](#) [Plant Biology](#) [Proteomics](#)

Species and Cell Types

[Bacterium](#) [Fungus](#) [Human](#) [Other Species](#) [Parasite](#) [Rodent](#) [Streptococcus gordonii](#) [Virus](#)

Research Technology

[Antibody Production](#) [Biotin-Avidin Technology](#) [Bispecific Antibody](#) [Carbohydrate](#) [Cell Culture](#) [Cell Fusion](#) [Cell Tracking In Vivo](#) [Cellular Electrophysiology](#) [Chemiluminescence](#) [Combinatorial Chemistry](#) [Disease Gene](#) [Discovery Drug](#) [Delivery Flow Cytometry](#) [Gene Knockout](#) [Gene Targeting](#) [Gene Transfer](#) [Genetic Engineering](#) [High Throughput Screening](#) [Imaging](#) [Immunotechnology](#) [Microscopy](#) [Molecular Engineering](#) [Molecular Profiling](#) [Nanotechnology](#) [Nuclear Magnetic Resonance](#) [Nuclear Transfer](#) [Nucleic Acid](#) [Organism](#) [Cloning Protein](#) [RNA Interference](#) [Stem Cell Technology](#) [Tissue Engineering](#) [Transgenic Technology](#) [X-Ray Crystallography](#)

Therapeutic Technology and Methodology

[Diagnosis](#) [Experimental Therapy](#) [Therapy](#)

Pharmaceutical and Healthcare Industry

[Biotechnology](#) [Commercialization of Discoveries](#) [FDA Drug Regulation](#) [Pharmaceutical Industry](#)

Global Tags

List of 100 Random Tags: (or [View All Tags](#))

[advanced breast cancer](#) [alpha-galactosidase](#) [antidepressant](#) [APOBEC3F](#) [APOE e4](#) [APP](#) [autoimmunity](#) [axonal remodeling](#) [bcl-2](#) [beclin-1](#) [blood clotting](#) [c-Myb](#) [CA-125](#) [caloric restriction](#) [carbon monoxide](#) [carcinogenesis](#) [caspase](#) [CD28](#) [chemokine receptor](#) [circadian rhythm](#) [computational biology](#) [defensin](#) [degradomics](#) [developmental plasticity](#) [drug target](#) [elite suppressor](#) [erythropoietin](#) [estriol](#) [estrogen receptor](#) [Flt3L](#) [fluorodeoxyglucose](#) [fMRI](#) [fosamprenavir](#) [fusion protein](#) [gene signature](#) [genetic reprogramming](#) [glycosaminoglycan](#) [gp41](#) [H-Ras](#) [hearing loss](#) [heterozygosity](#) [histone acetylation](#) [histone modification](#) [HIV viral load](#) [HLA-B27](#) [homologous recombination](#) [hydrogel](#) [IGF-1](#) [IGF-1R](#) [IL-1](#) [inducible nitric oxide synthase](#) [leukotriene](#) [major histocompatibility complex](#) [matrix metalloproteinase](#) [medicinal herb](#) [metabolic programming](#) [metabolic rate](#) [MICA](#) [miR-122](#) [MLN341](#) [molecular mimicry](#) [monoclonal antibody](#) [mouse genome](#) [MRSA](#) [neurokinin-1 receptor](#) [neuroprotection](#) [Novartis](#) [oligonucleotides](#) [decoy patch](#) [clamping](#) [pemetrexed](#) [peripheral adiposity](#) [PET](#) [pluripotent embryonic-like state](#) [postmenopausal osteoporosis](#) [prostaglandin](#) [Proteasome](#) [protein quality control](#) [proteinuria](#) [proteolipid](#) [peptide](#) [pyruvate kinase](#) [quinoxaline](#) [renin-angiotensin aldosterone system](#) [reproductive cloning](#) [RPE65](#) [RSV](#) [SGLT2 inhibitor](#) [single nucleotide polymorphism](#) [SLE](#) [small interfering RNA](#) [sphingosine 1-phosphate](#) [STI571](#) [stress response](#) [substance P](#) [telomere](#) [tics](#) [tissue-specific gene delivery](#) [TP53](#) [ubiquilin](#) [vif](#) [X-linked](#)

Copyright 2012, [Discovery Medicine](#). All Rights Reserved.