The Role of Dysbiosis and Chronic Viral Infection in Autoimmune Rheumatic Diseases

Liz Sutherland, ND

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Overview

Autoimmune diseases are a diverse group of approximately 100 disorders that are characterized by abnormal reactivity of B and T cells against self-antigens.[1] Clinical manifestations can vary greatly, from organ-specific to systemic, and from life-threatening to subclinical. Autoimmune conditions affect about 5-9% of the world's population,[2] and occur more frequently in women than men.[3,4] A 2020 study of the prevalence of antinuclear antibodies (ANAs) found a 50% overall increase in this biomarker of autoimmunity over the course of 25 years, suggesting that autoimmunity is on the rise in the United States.[5] Interestingly, the increase in ANA prevalence was notable among adolescents (ages 12-19), lending some credence to the hygiene hypothesis, which posits that improved hygiene practices and cleaner environments in childhood reduce exposure to immune challenges, and may result in aberrant immune responses when exposed to infections later in life.

Causes of Autoimmune Disease

The current understanding of autoimmune pathogenesis and pathophysiology recognizes multifactorial etiologies, possibly involving a combination of[6]

- Genetic susceptibility
- Hormonal influences
- Epigenetics
- Environmental triggers such as toxic chemicals, adverse life events, diet, and infections

A combination of genetic, epigenetic, and environmental factors is thought to contribute to the development of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) phenotypes.[7] These autoimmune rheumatic disorders are defined by the expression of antinuclear antibodies that target[8]

- Cell proteins
- Nucleic acids (both DNA and RNA)
- DNA-RNA-protein complexes

Autoantibodies and autoreactive T-lymphocytes can interact with autoantigens in a multitude of ways, leading to the wide spectrum of clinical manifestations seen in autoimmune diseases.

Loss of Self-Tolerance

Autoreactivity indicates the loss of self-tolerance, which is the cornerstone of immune regulation. SLE exhibits an extensive array of autoantibodies, indicating a wide-spread derangement of tolerance pathways. Susceptibility to SLE or RA is multigenic, and over 100 potential genetic loci have been identified so far.[9] These genes affect numerous immune system processes including[10]

- B-cell and T-cell signaling
- antigen presentation

Gene variants linked to autoimmune diseases appear to regulate gene *expression* rather than coding for protein sequences.[11] Epigenetic mechanisms, therefore, may modify genes that increase susceptibility to autoimmunity,[12,13,14] and contribute to dysregulated innate and adaptive immune responses with downstream effects on, for example, cytokine balance and the magnitude of the inflammatory response.

The Influence of the Microbiome

Increasing evidence emphasizes the crucial role the gut microbiome plays in maintaining immune system homeostasis, both local innate immune function[15] and adaptive immunity.[16] The gut microbiome performs innumerable functions including[17,18]

- Regulating immune cell proliferation, differentiation, and activation
- Maintaining intestinal mucosal barrier integrity
- Activating epithelial cells that produce antimicrobial peptides
- Supporting neutrophil recruitment

Impact of Dysbiosis

The commensal bacteria, viruses, and fungi that comprise our microbiota may become a source of foreign antigens.[19,20] Microbiome dysbiosis can adversely affect homeostatic mechanisms of immune function, by inducing both specific and nonspecific immune responses that result in autoreactivity.[21] It is notable that dysbiosis is associated with the pathogenesis of SLE and RA, as well as with other autoimmune diseases.[22]

The microbiome composition of patients in the early stages of RA is considerably different from that of healthy individuals. There is a significant decrease in the *Bifidobacterium* and *Bacteroides* genera along with an increase in *Prevotella* species.[23] Proliferation of *Prevotella copri* in the gut is associated with greater disease expression, possibly resulting from the induction of autoantigen-mimicking cross-reactivity. [24,25] *Bifidobacterium infantis* and *Bacteroides fragilis* induce the production of anti-inflammatory Treg cells through several different pathways.[26] In SLE, proliferation of *Ruminococcus gnavus* in the gut is associated with greater disease activity. [27]

Gut Barrier Permeability

Increased gut permeability resulting from compromised barrier function can allow bacteria from the microbiome to translocate into systemic circulation, where they may trigger the production of autoantibodies.[28] For example, *Prevotella copri* is known to disrupt intestinal epithelial tight junctions.[29] In addition to diet,[26] psychological stress is a major disruptor of gut barrier function[30] and may prove to be a contributing environmental factor to autoimmune pathogenesis in susceptible individuals. Microbiome metabolic by-products, such as short-chain fatty acids (SCFAs), influence gut-associated lymphoid tissue (GALT) through epigenetic mechanisms to support immune defensive function and tolerance.SCFAs significantly influence the production of cytokines and immunoglobulins and modulate the activity of immune cells by interacting with

their G protein-coupled receptors, all of which may affect the pathophysiology and progression of autoimmune conditions.[31] Dysbiosis influences the pathogenesis of RA, SLE, and other autoimmune conditions via multiple mechanisms, which likely include[26,27]

- Epitope cross-reactivity
- Activation of antigen-presenting cells
- Induction of Th-17 cell-mediated inflammation
- Increasing intestinal mucosal permeability

The Role of Viral Infection

Chronic viral infections may be one of the main environmental drivers of autoimmunity.[32,33] Viral infections are thought to trigger autoreactivity in susceptible individuals through both specific and nonspecific immune responses via the mechanisms of[34,35]

- Bystander activation
- Molecular mimicry
- Epitope spreading

The onset or recurrence of several autoimmune disorders, including RA and SLE, may be attributable to bystander activation, whereby the local proinflammatory milieu that results from antiviral immune activity can trigger autoreactive bystander T or B cells, which then secrete additional proinflammatory factors in a vicious cycle of escalation.[36] Infection with Epstein–Barr virus (EBV) is associated with the development of RA in both humans and animal models.[37] People with RA have been shown to have higher levels of antibodies against EBV antigens compared with controls.[38] EBV DNA has also been found in the synovial fluid and bone marrow of RA patients.[39]

Molecular mimicry is a significant factor in loss of tolerance. Molecular mimicry refers to the idea that an immune response directed against viral or bacterial antigens may target host molecules that share homologous DNA, RNA, or protein sequences with, or are structurally similar to, microbial epitopes. Molecular mimicry followed by epitope spreading are thought to be the primary mechanisms by which EBV induces RA pathogenesis.[40,41]

EBV, retroviruses, parvovirus B19, and cytomegalovirus may be implicated in the etiology of SLE, likely through molecular mimicry.[42]However, it is not known whether these infections precede, are concomitant with, or develop after SLE pathogenesis. SLE has also developed following severe viral infections like Dengue fever.[43]

Age-Associated B Cells and Latent Viral Infection

Expansion and activation of a subset of B lymphocytes known as age-associated B cells (ABCs), has been linked to SLE.[44]ABCs are an important aspect of the immune system’s response to viruses, but they accumulate as a result of immune senescence and may be responsible in part for the buildup of autoantibodies and increased risk of autoimmunity that is associated with aging.

Latent viral infections where the virus is dormant within cells may contribute to the development of autoimmune disease later in life. This is postulated to be the case with EBV infection, which often occurs in early childhood. In an animal model of RA, mice latently infected with EBV had more severe pathology, a Th1 response profile, and higher levels of ABCs, suggesting that viral latency not active virus was exacerbating the disease.[45]

The Impact of COVID-19

During the COVID-19 pandemic, a substantial number of cases of new-onset autoimmune diseases were reported.[46] Several autoantibodies were discovered in patients infected with SARS-CoV-2, and SARS-CoV-2 infection was also associated with diminished and dysfunctional T-regulatory cells.[47]

A retrospective study accessed the TriNetX database, which contains the largest worldwide dataset for COVID-19 cases, to determine the incidence of autoimmune disorders. They compared two cohorts: COVID-19 patients with a positive PCR test, and a PCR-negative cohort. Each cohort had 887,455 subjects. The study found a

- Significantly higher risk of developing autoimmune diseases, including RA and SLE, within the first six months after COVID-19.[48]

Another study examined a cohort of 640,701 unvaccinated individuals who had COVID-19 confirmed by PCR, with a non-COVID-19 cohort of 1,560,357 individuals. Cohorts were matched for age, sex, and whether they had a preexisting autoimmune condition. The study found

- A 42.6% higher likelihood of developing an autoimmune condition 3–15 months following SARS-CoV-2 infection.
- For individuals with preexisting autoimmune conditions, COVID-19 increased the risk of developing another autoimmune disease by 23%.[49]

Retrospective cohort studies cannot prove a causal link between SARS-CoV-2 infection and development of autoimmune disease, but the evidence suggests that SARS-CoV-2 infection is associated with a considerable increased risk of new-onset autoimmune disease following the acute infection phase.

The increase in overall incidence, and the sheer range of autoimmune diseases identified after infection, have led to numerous theories to explain the molecular mechanisms behind the unique immune dysregulation induced by COVID-19.[50,51] Characteristics of COVID-19 that are similar to immune phenotypes that result in autoimmune reactivity, include[52,53]

- Over-activation of NK cells
- Overactivation of $CD8^+$ T cells
- Dysregulation of B cells, T cells, and inflammatory cytokines

Bystander activation of autoreactive B cells was also noted in a small study of 23 COVID-19 patients.[54]

Association with Long COVID

A recent study has found that antinuclear autoantibodies (ANAs) are present up to 12 months following acute infection in some patients with Long COVID,[55] suggesting a possible causal relationship between autoantibodies and Long COVID pathogenesis and pathophysiology. Factors such as age, comorbidities, and genetic susceptibility likely also play a role in the link between SARS-CoV-2 infection and autoimmune disease.[56]

Key Takeaways

- The pathogenesis of autoimmune conditions likely involves the interplay between a multitude of causes, spanning

    - Genetic predisposition
    - Immunological factors
    - Hormonal factors
    - Diet
    - Environmental triggers, particularly infections

- Chronic viral infections are known to sustain inflammation for a long time, which can become a pivotal contributor to and reactivator of autoreactivity.

- The health of the gut and the gut microbiome is clearly central to overall health, with tangible implications for immunity both within and external to the gastrointestinal system.

- The COVID-19 pandemic afforded the chance for population-based epidemiological studies of autoimmune disease before and following onset, which provided a significant resource for understanding the link between SARS-CoV-2 infection and autoimmunity. The study of large datasets that include worldwide patient cohorts will, hopefully, continue to expand and clarify understanding of autoimmune disease etiology.

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27 State Street, Suite 5 | Montpelier, VT 05602 | 866-962-2276