Potential Role of Infections in Chronic Inflammatory Diseases

Host immune and inflammatory responses to infections that are poorly controlled may underlie various chronic diseases

Seth Pincus

Autoimmune and chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, diabetes mellitus, and multiple sclerosis, cause considerable morbidity and early mortality. Although much about the pathology underlying these diseases is understood, the factors that initiate disease are not. Hence, therapies typically are directed at consequences of these pathological processes, rather than the root causes.

During the past few decades, several diseases that were thought to have very different origins were found to result from infections. For example, we now know that many peptic ulcers result from Helicobacter pylori infections, several forms of cancer result from either viral (human T lymphotropic virus I and human herpes virus 8) or bacterial (H. pylori) infections, and Lyme arthritis stems from Borrelia burgdorferi infections. Moreover, several inflammatory diseases are postinfectious disorders, including the poststreptococcal syndromes, rheumatic fever and acute glomerulonephritis, and the HLA-B27-associated arthritides that follow infections by various bacteria. With such examples in mind, it is fair to speculate that poorly controlled host immune and inflammatory responses to infections may underlie other inflammatory diseases.

Bacterial, Viral, and Parasitic Post-Infectious Inflammatory Syndromes Are Well Documented

Bacterial infections may be benign, difficult but treatable, overwhelming and deadly, or chronic and persistent. Observations from the preantibiotic era are useful in understanding the relationship between ongoing bacterial infections and inflammatory and immune processes. Consider three different bacteria: Staphylococcus aureus, Mycobacterium tuberculosis, and Treponema pallidum. Each causes a very different host response and disease pattern, the result of unique facets of the organism’s biology (Fig. 1). For example, syphilis arising because of T. pallidum infection is sometimes called “the great pretender” because of its protean manifestations. An initial lesion, the chancre, is highly localized and swarms with bacteria. The bacteria may spread systemically during “secondary” syphilis to cause widespread and polymorphic rashes. Later stages of syphilis may attack different systems, causing cardiovascular or neurologic symptoms, such as tabes dorsalis, or disrupting other tissues such as skin and bone. Some of these later manifestations may reflect autoimmune re-

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sponses resulting from antigenic mimicry. Hence, antibiotic treatments during the late stages of syphilis often do not alter the clinical course.

The postinfectious syndrome of rheumatic fever typically begins following a group A *Streptococcus pyogenes* infection of the oropharynx (“strep throat”). Rheumatic fever is often cited as an example of antigenic mimicry, involving a cross-reaction between the streptococcal M protein and varying “cardiac” antigens. Yet definitive proof of antigenic mimicry is lacking. In acute poststreptococcal glomerulonephritis, immune complexes deposit in the kidney following infection with certain strains of group A streptococci. Thus, depending upon host factors, site of infection, and strain of bacteria, strep A infections can lead to different outcomes mediated by different mechanisms.

The major histocompatibility complex (MHC) Class I antigen, HLA-B27, carries a 30-fold increased risk of several postinfectious inflammatory syndromes, including reactive arthritis and Reiter’s syndrome, which includes arthritis, iritis, and urethritis. Infection with distinct organisms, including *Campylobacter, Chlamydia, Shigella,* and *Salmonella,* can initiate these syndromes, which may persist for months or can be life-long. The association with a Class I MHC antigen suggests that the mechanism of susceptibility involves host CD8 T cells.

Several of the first patients with Lyme arthritis were originally diagnosed as having classical juvenile rheumatoid arthritis. It was only the odd clustering of this rare diagnosis that suggested a distinct syndrome and an infectious source for the disease, *Borrelia burgdorferi,* which is transmitted through tick bites. In some ways, Lyme disease is similar to syphilis, another spirochetal infection. Lyme disease often presents with a spreading bull’s-eye rash with a tick bite at the center, followed by fever and other flu-like systemic symptoms. Months to years later, arthritis, neurological disorders, and cardiac disease may occur. *B. burgdorferi* may be most easily cultured from the leading edge of the early-stage rash and less often during the systemic stage of the disease. Although culture during the late stages is rarely successful, some report detecting this microbe by PCR or the presence of antigen. Treatment of infection during early stages of infection can prevent the late manifestations, but the role of antibiotics after systemic symptoms appear is controversial.

Antigenic mimicry between the *Borrelia* outer surface protein A and the light chain of the human leukocyte antigen LFA-1 occurs at the T cell level. *B. burgdorferi*-infected patients with the class II MHC alleles HLA-DRB1* 0401, 0101, and 0404 are more likely to develop chronic arthritis. These three alleles are structurally similar and are also associated with severe disease in rheumatoid arthritis patients, suggesting that helper T cell responses are involved in the development of prolonged joint inflammation. Although Lyme disease is associated with *B. burgdorferi* infection, the mechanisms of dis-
ease are not fully understood and may involve both infectious and postinfectious processes.

Viral infections also elicit immune and inflammatory responses. Although many viral infections are short-term, others persist for life—sometimes in a chronic active state, other times latent with subsequent reactivation. Clinical manifestations of chronic viral infections may reflect pathology caused by the virus or by the host response to eliminate cells harboring a virus. HTLV-I infections provide an example. The first disease to be associated with this virus was T-cell leukemia, which is driven, in part, by autocrine stimulation by the host factor interleukin-2 (IL-2). Another distinct syndrome, known as tropical spastic paraparesis-HTLV-I associated myelopathy (TSP-HAM), is characterized by tissue damage likely resulting from T cell responses to viral antigens.

Helminthic infections induce TH2 host responses and may cause other ongoing immune responses to veer in that direction. TH2 responses are implicated in allergy and some forms of antibody-mediated autoimmunity. The TH2 bias may also influence efficacy and outcome of vaccines. Fungal infections too may be chronic and induce organism-specific immune and inflammatory responses.

**Infections May Induce Chronic Inflammation or Autoimmunity**

Interactions between microbes and hosts can have different outcomes, ranging from elimina-
Do Microbes Trigger Rheumatoid Arthritis?

Rheumatoid arthritis (RA) is a widespread, progressive, chronic inflammatory condition of the joints that may afflict as many as 6 million Americans. The preponderance of patients are female, and the onset of disease is usually during young adulthood.

Even though RA is usually referred to as a single disease and arthritis is its primary manifestation, it may instead be a collection of similar syndromes. Although the cause of the underlying inflammation in RA is unknown, it often is accompanied by other abnormalities affecting other tissues and organs, particularly blood vessels. The arthritis itself is symmetrical, polyarticular, and frequently involves the small joints.

RA is associated with the HLA-DR4 family of molecules, suggesting that CD4 T cells are involved in pathogenesis. RA is said to be autoimmune because of rheumatoid factor, an anti-IgG antibody, but its role is poorly understood. Higher levels of rheumatoid factor correlate with disease severity and removing it can ease symptoms. But it is not known whether rheumatoid factor acts directly in pathogenesis, is a homeostatic regulator of immune and inflammatory responses, or is an epiphenomenon.

The synovium lining the joints of individuals with RA contains lymphoid follicles and excess numbers of both B and T cells, as well as monocytes and some neutrophils, indicating chronic immune stimulation and inflammation. Because the T cell pool expands in oligoclonal fashion, antigenic stimulation rather than diffuse hyperreactivity seems to be taking place.

Although no specific stimulatory antigen has been identified as the instigator of RA, anti-type II collagen antibodies are found in some but not all RA patients, and a portion of such patients also mount T cell immune responses to collagen. Some experts argue that other events, perhaps infections, elicit these anticollagen antibodies in RA patients and that these antibodies subsequently stimulate chronic inflammatory responses (i.e., antigenic mimicry). In animals, the induction of such antibodies can cause symptoms of arthritis that are similar to RA.

Several types of viral infections have been suggested as a trigger for RA. For example, persistent arthritis occurs as a late manifestation in some patients with rubella and parvovirus B19 infections. Moreover, newly diagnosed RA patients show higher rates of parvovirus B19 infections than do comparable individuals without such infections. In separate studies, some RA patients show abnormal immune responses to Epstein Barr virus and cytomegalovirus. Human endogenous retroviruses have also been implicated in RA, in some cases because of signs of aberrant virus expression or because individuals with RA develop abnormal immune responses to retroviral antigens.

Meanwhile, Lyme disease provides a concrete example of how one type of bacteria, namely *Borrelia burgdorferi*, can cause a form of chronic arthritis that resembles RA. Despite considerable efforts, including the use of highly sensitive PCR, researchers consistently fail to find microbial DNA, in the joints of RA patients. However, other investigators have found bacterial peptidoglycans and peptides through mass spectroscopy analysis. But these materials also can be found in the joints of individuals without RA. Thus, despite plausible mechanisms for how infectious agents could be involved in initiating and maintaining the inflammation responsible for RA (Fig. 3), we still have no firm idea of what causes this disease.
Alternatively, microbes may directly subvert the immune system. For instance, *Bordetella pertussis*, which causes whooping cough, secretes cytotoxins that prevent cilia from clearing this microorganism from host mucosal surfaces. Vaccinia virus interferes with Toll-like receptor signaling. Various herpes viruses encode cytokines and cytokine receptors, alter antigen processing and presentation, and interfere with T cell responses. Both bacterial and viral Fc and complement receptors may interfere with opsonization, as can specific proteases that cleave immunoglobulin and complement. HIV directly attacks the immune system.

Microbial biofilms that form, such as on implants, often prove resistant to both host defenses and antibiotics. Chronic infections such as sinusitis, otitis media, and osteomyelitis are likely to involve biofilms. It is possible that microbial overgrowth syndromes, such as bacterial vaginosis, periodontal disease, and some inflammatory bowel disorders, reflect biofilm formation by the native flora.

Retroviruses may be agents of disease in several ways besides exogenous infection by HIV or HTLV-I. For instance, endogenous retroviruses, or retrovirus gene products, may become activated developmentally. If an intact virus is involved, reintegration may occur. Consequences include oncogenesis, immune and inflammatory responses to viral proteins, and insertional mutagenesis, which may be heritable. In strains of
mice with autoimmune “lupus,” the gp70 protein of the murine leukemia virus acts as a major antigen in renal immune complexes. My colleagues and I are investigating the role of retroviruses in the origins of the autoimmune response in mice carrying the lpr mutation.

**Host Immune Systems Respond Differently to Signals Initiated by Different Microbes**

Host immune systems confront many different types of microbes—eliminating most threats to the system, while not overreacting to signals from innocuous or useful microbes. A failure of the immune response can result in the development of opportunistic infections from otherwise commensal microbes, as in AIDS. More subtle failures may lead to persistence of specific microbial agents following infection or the reactivation of latent infections, such as herpes viruses or tuberculosis. Overactivity of the immune system may lead to allergy, hypersensitivity reactions, or development of autoimmune or inflammatory disorders. Microbial targets of hypersensitivity may be exogenous or part of the normal flora.

Some researchers consider disordered interactions between intestinal flora and host innate pattern recognition molecules a cause of inflammatory bowel disease. The pattern recognition molecules of the innate immune system provide an interface between the host and the microbial world. When these entities identify structural motifs common to pathogenic microbes, they may induce inflammation and enhance adaptive immune responses. These pattern recognition receptors distinguish between pathogens and commensals. Changes could lead to inappropriate inflammation.

Immune responses, both adaptive and innate, can lead to the development of inflammation. These responses may result in the production of antimicrobial antibodies of specific isotype, immune complex deposition, antibodies against cellular targets, or T cell-mediated responses. Inflammatory responses typically help to eliminate offending microbes. But those same inflammatory responses may also damage surrounding healthy tissues. If the microbe persists or if the normal signaling pathways that down-regulate the inflammatory response are disordered, then an ongoing inflammatory response may develop. The tissue damage resulting from this response may be the dominant portion of the clinical disease.

**Mechanisms To Explain How Persistent Inflammatory Responses Lead to Disease**

There are several ways to explain microbe-initiated prolonged inflammatory responses in the absence of persistent infections. One, molecular mimicry, posits close structural similarities between specific microbial antigens and specific host molecules. An attack on the microbial antigen presumably leads to an autoimmune response. While this idea is enormously appealing, there are few, if any, conclusive examples where molecular mimicry is the prime initiator of human disease. Another hypothesis is that a specific infection alters self-antigens to make them frankly immunogenic, enabling the immune response to the altered antigen to persist. A third hypothesis suggests that damage to host tissue during the infection releases previously hidden self antigens, leading to an ongoing response through low-level exposure during the postinfection period.

The role of MHC alleles further complicates the analysis of autoimmune diseases. Such alleles are involved in presenting both endogenous and exogenous antigens to T cells, play a role in forming the T cell repertoire, and also help to determine an individual’s susceptibility to many autoimmune

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**Author, Institute Recovering from Storm’s Effects**

Though Seth Pincus has devoted his career to studies that have direct implications for vaccine development (and in fact is chair of the NIH AIDS Vaccine Study Section), he was bemused to find that in the wake of Hurricane Katrina he was administering the first immunizations of his medical career at a refugee center in Baton Rouge, La. His experiences during and immediately after the storm have been described elsewhere (Science, September 9, 2005, page 1657). Pincus is Director of the Research Institute for Children at Children’s Hospital of New Orleans, which reopened on 1 October, and scientists there have been working to put their research back together, assessing the losses from freezers that were turned off for over 3 weeks, and struggling to regain their research competitiveness.
and inflammatory diseases. The MHC may influence the outcome of a particular infection by causing an overreaction to an otherwise innocuous antigen or may allow persistence of certain pathogens. This can lead to greater microbe-induced pathology, prolonged antigen exposure, or other effects that induce tissue damage.

Invading microbial pathogens or commensal organisms may regulate immune system responses. For instance, modern hygiene practices might reduce the exposure of developing immune systems to antigens—perhaps inducing immune hyperactivity later in life, contributing to allergic and autoimmune diseases. Some epidemiological data support this hygiene hypothesis, but mechanistic explanations are incomplete. Helminthic infections can induce a Th2 bias in ongoing immune responses. Therapeutic uses of this phenomenon are being tested; patients with inflammatory bowel disease are being exposed to antigens from parasites to determine whether pathological Th1 responses can be redirected to more benign Th2 responses. Regulatory T cells (Treg), elicited in response to infection, secrete TGF-beta and can dampen immune responses to other agents.

In summary, infections can initiate chronic inflammation. A single microbe need not be responsible for a particular disease, and different microbes may initiate events that lead down a common pathway. HLA-disease associations suggest that antigen processing and presentation to T cells play a role initiating such inflammatory processes. Inflammation is maintained either by ongoing infection, persistence of antigen, induction of crossreactive immune responses, or through disordered immune regulation or pattern recognition. These ongoing inflammatory responses result in tissue damage. Although autoimmunity may play a role in initiating and maintaining inflammation, or may be an epiphenomenon resulting from the infection or the inflammatory response, the inflammation-induced tissue damage is what we define as the “disease.” Current therapies typically suppress inflammation or underlying immunity. Because these therapies do not attack the cause of the inflammation, such therapies are only palliative and do not eliminate disease. By understanding the initiating events, we may hope to cure or prevent these conditions.

SUGGESTED READING