Autoimmune Disease 2002: An Overview

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Autoimmune disease includes a large spectrum of clinically distinct entities that share a common etiology, a misguided, self-directed immune response. Collectively, they are major contributors to morbidity and mortality. Normally, the body utilizes a number of strategies to avoid the pathologic consequences of autoimmune reactions, but these defenses may fail for a combination of hereditary and environmental factors. Infection has long been regarded as a common environmental trigger of autoimmune disease. Our laboratory has developed a mouse model of myocarditis induced by Coxsackievirus B3 infection and demonstrated some of the steps involved in the transition from an infection to an autoimmune disease. Such basic studies may suggest improved treatment or preventive measures for this group of diseases. ***Key words: Autoimmunity/B cell/Chemokine/Coxsackievirus/Cytokine/Infection/Myocarditis/T cell. J Investig Dermatol Symp Proc 9:1–4, 2004***

The autoimmune diseases represent a diverse family of disorders with different clinical presentations but with a common etiology that involves an immune response to autologous antigens. It has been estimated that there are at least 80 human diseases in which autoimmune responses participate significantly as the initial cause or as a contributor. The immune-mediated injury may be localized in a single organ system, as occurs in the pancreatic islets in Type I diabetes mellitus and in the central nervous system in multiple sclerosis. Or the diseases may affect a multitude of organs, as seen in systemic lupus erythematosus. Although most of the autoimmune-related diseases disproportionately strike women, persons of both sexes and all ages, races, and ethnic and socio-economic groups are affected.

THE BURDEN OF AUTOIMMUNE DISEASE

Most of the autoimmune diseases individually are rare, but collectively they represent a major medical and public health problem. A recent report by a committee of the U.S. National Institutes of Health suggests that 14 to 22 million persons in the United States suffer from one of these diseases. Because of their chronic nature and their debilitating effects, autoimmune diseases exact high economic costs, estimated at $100 billion annually. Several of the autoimmune diseases affect women in their reproductive years, so the impact on young families is particularly pronounced.

Unfortunately, there is very little accurate information on the incidence and prevalence of the autoimmune diseases. Several years ago, our group undertook a detailed review of the published literature (Jacobson *et al*, 1997). We identified all of the studies published between 1965 and 1995 that provided estimates of the incidence of one of the autoimmune diseases. Reliable figures could be found for only 24 of them. Most of the studies were carried out in North America or Western Europe and provided no insight into the incidence of autoimmune diseases in the developing world. Using data from these reports, we estimated the total number of incident cases of these 24 diseases in 1996 in the United States to be 237,203 new cases, of which 172,695 occurred in women and 64,506 in men. These numbers translate to estimated incidence rates of 1.6 cases per 100,000 females and 0.5 cases per 100,000 males. Put another way, we estimated that every five years 1,186,015 new cases of an autoimmune disease will occur in the United States, assuming that incidence rates remain constant. The highest incidence rates were found for rheumatoid arthritis and the two major autoimmune thyroid diseases, Graves' disease and Hashimoto's thyroiditis. It was clear to us that all of these figures were gross underestimates of the incidence of autoimmune disease in the United States. For example, the autoimmune diseases affecting the skin, such as psoriasis, dermatitis herpetiformis, pemphigus and pemphigoid, were not included because no eligible epidemiologic studies were available.

Estimates of the prevalence of the autoimmune diseases are equally problematic. For many of them, criteria for diagnosis are unsettled and therefore many cases remain unclassified. Often autoimmune diseases undergo periodic exacerbations and remissions, so estimates of the extent of cases of a disease within a population at a specified time may be misleading. In general, most of the autoimmune diseases are chronic; cures are unusual, and survival is generally measured in decades. Prevalence is thus high despite relatively low annual incidence rates. In our study, we estimated that 8.5 million people in the United States, or 3.2% of the population, were living with at least one of the 24 autoimmune diseases in 1996. Prevalence rates for women and men were 5.0% and 1.4%, respectively. Extrapolation from these figures gives the previously cited estimates for the prevalence of all of the autoimmune diseases in the range of 5% to 8% of the U.S. population. To gauge the impact of the autoimmune diseases, one can cite figures from the SEER registries showing that approximately 9 million people in the United States suffered from cancer in 1997 and, according to the NCHS statistics, approximately 22 million

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Abbreviations: HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; SLE, systemic lupus erythematosus; TCR, T-cell receptor; TNF, tumor necrosis factor.

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people were affected by heart disease. Furthermore, the prevalence of heart disease and most forms of cancer has declined in this country whereas the prevalence of most of the autoimmune diseases has steadily risen.

Although most are not considered life threatening, autoimmune diseases are a significant cause of mortality in the United States. A recent study by Walsh and Rau estimated that there were 11,687 U.S. deaths from one of the 24 autoimmune diseases included in our earlier study in 1995 (Walsh and Rau, 2000). These diseases were among the 10 leading causes of death for women in every age group up to 65 years.

As stated above, the majority of autoimmune diseases disproportionately affect women (Whitacre, 2000). This disparity is substantial in the case of the autoimmune thyroid diseases, scleroderma, lupus, and Sjögren's disease, in which about 80% of patients are females. In other diseases, the difference is smaller: Females represent 60% to 75% of patients with multiple sclerosis, myasthenia gravis, and rheumatoid arthritis. In contrast the male-to-female ratio in sarcoidosis, inflammatory bowel disease, and type I diabetes mellitus is approximately one to one. In a few diseases, such as ankylosing spondylitis, there is male predominance.

Many reports suggest marked differences in the distribution of autoimmune diseases among different racial and ethnic groups. For example, in the United States and Great Britain, inhabitants of African origin are believed to have much higher rates of systemic lupus erythematosus than do their European-derived counterparts, but they have a lower risk for type I diabetes and multiple sclerosis. The highest rates for Type I diabetes and multiple sclerosis are found among northern Europeans, especially Finns, but equally high rates have also been described in isolated areas of Sardinia. Some native American tribes have been reported to have a high prevalence of scleroderma; other tribes, of spondylarthropathies. Asian Americans living in Hawaii have one of the lowest rates of Type I diabetes and multiple sclerosis, but these rates are subject to change as the populations move to the continental United States. It is therefore unclear how much these differences are based on genetic factors and how much on environmental influences, such as nutrition, infectious agents, occupational exposures, and social stress.

THE ETIOLOGY OF AUTOIMMUNE DISEASE

A principal function of the immune system is to defend against infection. The problem is that the agents of infection are highly diverse and frequently changing, with new infectious disorders emerging regularly. It is now evident, moreover, that the responsibility of the immune system is to recognize any foreign substance, living or dead, introduced into the body by a parenteral route. The immune system therefore must be capable of recognizing virtually an unlimited range of molecules, many of which will be found in the body of the host itself. When the immune system recognizes self antigens, autoimmune disease can result. Fortunately, the body manages a number of maneuvers to minimize the risk that these autoimmune responses will be harmful. Ehrlich epitomized these measures in his picturesque phrase, "horror autotoxicus," or a fear of self-poisoning.

Measures to ensure tolerance to self may act at the central or peripheral level (Kamradt and Mitchison, 2001). Central tolerance is the process by which autoimmune progenitor cells are eliminated by apoptosis before they enter the peripheral circulation. In the case of T cells, deletion of potentially autoreactive clones occurs in the thymus. Presumably, a similar process of negative selection occurs for autoreactive B cells in the bone marrow. In addition, B cells are given a "second chance" to avoid elimination by receptor editing. Clonal deletion in the bone marrow and thymus, however, is at best an imprecise process. Negative selection requires that the autologous antigens be presented in the thymus or bone marrow during critical steps of lymphocyte maturation. The major blood group antigens and major histocompatibility antigens are well represented, and T cells and B cells reactive to these widely distributed selfantigens are essentially never found (Dighiero and Rose, 1999). Organ-specific antigens of the thyroid gland and brain, on the other hand, are poorly represented in the thymus and bone marrow, and therefore thyroid-reactive and brain-reactive T cells are common in peripheral sites. It is thus relatively easy to initiate autoimmune responses to these tissues.

Peripheral tolerance is the process by which cells that escape deletion in the thymus or bone marrow are controlled so that tissue damage does not occur. A number of processes have been discovered to rein in these dangerous cells in the periphery. They include, first, anergy, the process whereby cells encountering an antigen-specific stimulus in the absence of costimulatory signals become inactive and eventually may die by apoptosis. The necessary costimulatory signals may be provided by tissue inflammation or infection, circumstances in which anergy is terminated and autoimmunity may arise. A second mechanism is immunological ignorance, in which the self-reactive lymphocytes fail to localize in the presence of their corresponding antigen. Generally, chemokines and adhesion molecules determine patterns of lymphocyte migration (Von Andrian and Mackay, 2000). Local injury therefore may be the occasion for breeching the wall of ignorance. Finally, the immune system is subject to important regulatory mechanisms. These include populations of T cells and macrophages that directly or indirectly downregulate immune responses. If these mechanisms have been impaired, immune responses, including autoimmunity, may continue unabated and progress to autoimmune disease.

On the basis of our understanding of normal immune response, it is possible to envision the circumstances that favor development of harmful autoimmunity (Rose, 2002a). First, a genetic predisposition favors the development of autoimmune responses. In addition to many studies on experimental animals, there is compelling evidence of the importance of genetics in the etiology of autoimmune diseases in humans. It includes data showing that identical twins are more likely to suffer from the same autoimmune disease than are fraternal twins. Relatives of patients with autoimmune diseases are at greater risk for developing the same or another autoimmune disease. As a general statement, it seems that about a third of this risk is inherited. For most autoimmune diseases, it is likely that multiple genes are involved. The most prominent genes are members of the major histocompatibility complex, a group of genes known to regulate immune responses. Thus, there are clear associations of HLA with Type I diabetes, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, and Graves' disease. A number of other immune-related genes are under active investigation for their association with autoimmune diseases, especially genes involved in the production of cytokines, cytokine receptors, chemokines, and other regulators of the immune response.

Nonheritable factors make up more than half of the risk of developing an autoimmune disease among humans. A portion of the nonheritable risk is associated with the randomness built into the immune system (Nossal, 2001). As previously explained, in order to accomplish its task of recognizing any foreign intruder, the immune system develops a nearly limitless number of recognition structures, utilizing in part postgermline recombination, reassortment, and hypermutation of variable-region genes. Thus, even identical twins have differing immune responses. Beyond these stochastic differences, however, there is persuasive evidence that external factors participate in the instigation of human autoimmune diseases (Davidson and Diamond, 2001). The best studied external agents are drugs, such as procainamide, that can trigger a lupus–like syndrome in genetically susceptible individuals. The causal role of these drugs is shown by the finding that the disease remits when the drug is discontinued and can be reinitiated by drug re-administration. A number of other drug-related autoimmune illnesses have been described, including hemolytic anemias, thrombocytopenias, and leukopenias. Sunlight

is known to produce exacerbations of lupus in SLE patients, and a great deal of epidemiological evidence suggests that silica increases the incidence of scleroderma.

Infectious agents are the most commonly putative triggers of human autoimmune disease (Davidson and Diamond, 2001). The classic example is streptococcal infection leading to the development of rheumatic heart disease. Guillain–Barré syndrome has been associated with a number of bacterial and viral infections, and reactive arthritis follows a variety of gastrointestinal infections. Epidemiological evidence associates Type I diabetes mellitus with previous rubella and possibly with Coxsackievirus B4. More than a dozen viral agents have been claimed to precipitate the onset of multiple sclerosis, and a similarly long list of putative viral agents can be assembled for lupus. In fact, it seems probable that a number of different infectious agents can give rise to the same autoimmune disorder in genetically predisposed individuals.

The mechanisms by which infectious agents may modulate the autoimmune process is not clear. The most popular explanation suggests molecular mimicry, the sharing of epitopes between the infectious agent and cell tissues. It is true that autoantibody production commonly follows viral infection, but there are very few, if any, firm examples of human diseases attributable to molecular mimicry (Rose and Mackay, 2000). A role for superantigens of bacteria and viruses that activate an entire family of T cells nonspecifically has also been suggested. An alternative explanation for the association of infection with autoimmune disease is the mobilization of endogenous antigens so that they are presented by resident dendritic cells (Rose, 2000b). Dendritic cells efficiently present antigen-presenting cells to naive T cells. Because T cells require a second, nonspecific signal to rescue them from anergy, the second stimulus can be presented by the infectious process. For example, dendritic cells activated by infection express the B.7 family of costimulatory molecules.

In order to develop greater insight into the mechanisms by which infection can initiate a pathogenic autoimmune process, we developed a model of Coxsackievirus B3–induced myocarditis in mice (Rose and Baughman, 1998). We discovered that all of the many strains of mice we infected developed an acute but self-limited viral myocarditis. During the early stage of this disease, infectious virus could be isolated. Although most strains of mice recovered completely, a few strains progressed to a chronic, ongoing myocarditis in the absence of infectious virus. The myocarditis was characterized by the production of heart-reactive autoantibodies. Further investigations showed that these antibodies are specific for the cardiac isoform of myosin. On the basis of this clue, we immunized mice with cardiac myosin, using as controls mice immunized in the same manner with skeletal myosin. We found that all of the mouse strains susceptible to ongoing myocarditis following viral infection developed myocarditis by immunization with cardiac myosin. Mouse strains that failed to develop postviral myocarditis were not affected by the immunization. The development of this autoimmune disease correlated with the production of IgG-1 myosin-specific autoantibodies, and the lesions could be transferred to naive mice with CD4 T cells. Thus, it has been possible to reproduce a postinfection autoimmune disease by immunization with a well-defined antigen. In fact, the actual peptide sequence responsible for inducing myocarditis in several strains of rats and mice has been delineated.

In subsequent experiments, we addressed the question of why only a few strains of mice go on to develop the autoimmune myocarditis following viral infection whereas most mice recover completely from the viral disease. We found that two of the inflammatory cytokines produced early during initial viral infection are key in the progression to autoimmune myocarditis. Administration of IL-1 or TNF-α to unresponsive mice directed them to develop autoimmune myocarditis. Conversely, blocking either IL-1 or TNF-α prevented the development of disease in susceptible strains (Neumann *et al*, 1993). Recently, we found that complement, another key component of the innate immune response, is also required for the development of autoimmune myocarditis and that complement C3d sparks the production of IL-1 and TNF-α (Kaya *et al*, 2001). Unexpectedly, NK cells were found to protect against the development of autoimmune myocarditis, so that depleting them rendered resistant strains susceptible to the disease (Fairweather *et al*, 2001). Following that clue, we examined the role of IFN-γ, a major product of stimulated NK cells, and discovered that administration of anti-IFN-γ or immunization of mice deficient in IFN-γ produces an especially severe form of myocarditis, resulting eventually in dilated cardiomyopathy (Afanasyeva *et al*, 2001a). Many of these mice developed heart failure, functionally similar to the heart failure evident in humans with dilated cardiomyopathy. Administration of recombinant IFN-γ protected against this life-threatening autoimmune disorder.

The prominence of myosin-specific IgG-1 antibodies in this disease was at first quite puzzling because this isotype of IgG is usually correlated with TH2 responses (Afanasyeva *et al*, 2001b). We therefore examined the histologic picture of myocarditis more closely and found that in severe cases eosinophils and giant cells were plentiful. The levels of IgE rose during immunization. The development of myocarditis in susceptible strains was prevented by administration of anti-IL-4. Severe myocarditis in the mouse thus exhibits the phenotype typical of a TH2 response. The findings provide a note of caution regarding the general assumption that organ-specific autoimmune diseases are associated with a TH1 response and that a TH2 response signifies recovery. Clearly, TH1 and TH2 responses are involved in the final pathogenic picture, because the disease is also prevented by depleting IL-12 or using IL-12 receptor knockouts. At the same time, our findings show that IFN-γ downregulates whereas IL-12 promotes the autoimmune disease by an IFN-γ-independent pathway. Finally, we have been able to show that IL-10 plays a role in recovery from autoimmune myocarditis because depleting this interleukin causes extension of the disease with extensive cardiac fibrosis.

These experiments emphasize for the first time the importance of innate immune response in determining the later course of an autoimmune reaction following a viral infection. Although many strains of mice develop myosin-specific autoantibodies following CB3 infection, most of these antibodies are low-affinity IgM and are probably harmless. Moreover, most are not specific for the cardiac isoform of myosin, but cross-react with skeletal and brain myosin. Thus, the presence of a specific autoimmune response to cardiac myosin is a marker of a pathological autoimmune reaction. The role of the virus in producing this antigenic stimulus is debatable. We have found no direct evidence of molecular mimicry in the form of a shared sequence. To the contrary, immunization with inactivated virus failed to induce an autoimmune response. Moreover, strains of virus that failed to infect the heart are ineffective in inducing autoimmune myocarditis, even though the virus replicated profusely in the pancreas (Horwitz *et al*, 1998). For these reasons, we suggest that the role of the virus is to liberate or otherwise expose endogenous cardiac myosin rather than to mimic a self antigen (Rose, 2000). The second, and equally critical, role of virus infection is to foster the production of those cytokines or other modulators of the immune response that drive the autoimmune reaction to a pathological outcome. Some of the factors generated during the innate response, such as IL-1, TNF, and complement, are required for the development of myocarditis, whereas IFN-γ is protective. IL-4 and IL-12 are also essential for the development of autoimmune disease, and IL-10 is a pivotal factor in recovery (Kaya *et al*, 2002).

TREATMENT AND PREVENTION OF AUTOIMMUNE DISEASE

At present, treatment of autoimmune disease is directed to remedying the particular defect or modifying the entire immune response.

If the autoimmune damage is relatively well circumscribed, it is possible to replace the missing function. For example, administration of insulin to diabetics or thyroid hormone to patients with Hashimoto's disease will alleviate most signs of the disease. Removal of the thyroid gland will remedy the hyperthyroidism of Graves' disease. Often, the ramifications of autoimmune damage are widespread and systemic treatment is required. Antimetabolites and steroids as treatments for lupus and rheumatoid arthritis are examples where the immune response is globally suppressed. Neither therapeutic approach is entirely satisfactory, and a new approach is greatly needed (Rose, 2002b) whose goal is to terminate the damaging aspects of the autoimmune response without impairing the general immune defense. Immunizing with the T cell receptor (TCR) or with the hypervariable portion of the TCR might abort the pathogenic autoimmune response. This approach has been successful in a number of experimentally induced autoimmune diseases, such as allergic encephalomyelitis and experimental thyroiditis. In humans, unfortunately, it is rarely possible to delineate the particular antigen responsible for the initiation of an autoimmune disease. By the time a patient is clinically ill, the autoimmune response has escalated and the initiating antigen is no longer easily identified.

An intermediate step is to inhibit the mediators of the pathologic autoimmune response. The current success of agents to block TNF illustrates the power of this approach (Davidson and Diamond, 2001). On the other hand, many immunomodulators have different effects in different autoimmune diseases or even different effects in the same disease at different times. There is already some disturbing preliminary evidence that anti-TNF agents may exacerbate multiple sclerosis or increase the production of antinuclear antibodies. A whole new pharmacology of autoimmune disease will be necessary before physicians can safely and reliably use these powerful medicines.

A major impetus for devising new therapies is the development of biomarkers to determine inordinate susceptibility to disease before the process is too far advanced (Rose, 2002b). As our understanding of the natural history of autoimmune disease grows, it may be possible to intervene before the disease has had its devastating, irreversible effects. Primary prevention is the ultimate goal of public health and achieves the greatest benefit for the least cost. Early interventions include opportunities for aborting or terminating the pathologic immune response or identifying and eliminating the environmental trigger. A striking example of success of the latter approach is the virtual disappearance of rheumatic fever, once the leading cause of death among young people in the United States, purportedly through the prompt treatment or prevention of streptococcal infections. The next few years promise to be a period of unparalleled progress in alleviating the burden of autoimmune disease.

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