BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, September 2016. Vol. **13**(3), 1421-1428

Novel Approaches to Autoimmune Diseases: A Review of New Studies

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http://dx.doi.org/10.13005/bbra/2285

(Received: 21 July 2016; accepted: 01 September 2016)

In this review we have highlighted the most important of autoimmune disorders which occur when the body's immune system turns against the body itself, attacking it as if it were a foreign pathogen in human. More than 80% human diseases are due in part to an inappropriate immune system response that results in damage to an individual's organs, tissues, or cells. Autoimmune diseases can affect any part of the body, and produced an array of clinical manifestations that can often be difficult to diagnose. At the same time, autoimmune diseases share many features related to their onset and progression. In addition, overlapping genetic traits enhance susceptibility to many of the diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family. Although, treatments are available for many autoimmune diseases; cures for most have yet to be discovered. For these and other reasons, autoimmune diseases are best recognized as a family of related disorders that must be studied collectively as well as individually. Although individual autoimmune diseases are relatively rare, as a group they are among the most prevalent diseases in the United States, affecting between 14.7 and 23.5 million people, i.e. approximately eight percent of the population, and are a leading cause of death among young and middle-aged women. For reasons that it is poorly understood, both the incidence and prevalence of autoimmune diseases is rising. The chronic and often debilitating nature of many autoimmune diseases increases the burden on patients, their families, and society in terms of medical costs, a reduction in the quality of life, and lost productivity. The total societal disease burden for autoimmune disorders is difficult to estimate because some of these are chronic and debilitating diseases, while others are less serious; arthritis on its own though is estimated to cause a $65 billion disease burden. The aim of this review is to provide an update on the current status and trends in autoimmune disorders, which as a group, constitute some of the most expensive diseases currently faced by humans. Not surprisingly then, these diseases are the subject of extensive research worldwide, in both academic and medical laboratories.

Keywords: Humans, Autoimmune diseases, Morbidity and Mortality, Genetic Factors, Prevention and Treatment.

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With the exception of rheumatoid arthritis and autoimmune thyroiditis, auto immune diseases are individually rare; together however, they affect

approximately five percent of the population in Western countries[1,2], and provide a fascinating, if generally poorly understood group of diseases. Here, we define an autoimmune disease as a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection, or other discernible cause. We will discuss a classification of autoimmune disease that distinguishes diseases caused by generalized defects in lymphocyte selection or by homeostasis from those caused by aberrant responses to particular antigens. We will consider genetic susceptibility to autoimmune disease, environmental and internal triggers of auto-reactivity, changes in pathologic processes as the disease progresses, and multiple mechanisms of tissue injury. Finally, we will conclude with a survey of new therapeutic approaches to these highly problematical diseases.

More than 80 human diseases are due at least in part to an inappropriate immune system response which results in damage to an individual's organs, tissues, or cells. Autoimmune diseases can affect any part of the body, and have myriad clinical manifestations that can be difficult to diagnose. At the same time, autoimmune diseases share many features related to their onset and progression. In addition, overlapping genetic traits enhance susceptibility to many of the diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family. While treatments are available for many autoimmune diseases, cures for most have yet to be discovered. For these and other reasons, the autoimmune diseases are best recognized as a family of related disorders that must be studied collectively as well as individually[3].

Though each of the autoimmune diseases is relatively rare, as a group they are among the most prevalent in the United States, affecting between 14.7 and 23.5 million people up to eight percent of the population. They also are a leading cause of death among young and middle-aged women. For reasons that are poorly understood, the incidence and prevalence of autoimmune diseases is rising. The chronic and often debilitating nature of many autoimmune diseases increases the burden on patients, their families, and society in terms of medical costs, reduced quality of life, and lossof productivity.

Autoimmune diseases include a diverse group of chronicdisorders associated with substantial public health impact[4].Anecdotal evidence suggests that autoimmune diseasestend to coexist both within individuals and within families,and the concept of an autoimmune diathesis is widely accepted.However, patterns of association among autoimmune diseases have not been evaluated in a systematic fashion,and it remains unclear whether clinical reports of comorbid autoimmune diseases represent chance findings or true associations.

Common features in the immunoepidemiology of various autoimmune diseases are recognized, and reports ofshared risk factors are emerging[5,6]. However, the etiologiesof most autoimmune diseases remain poorly understood.Because autoimmune diseases are conventionally treated byseparate medical specialties according to type of organ involvement, there are missed opportunities to study thesediseases as an entity. We areinterested here in the premise thatinteraction between genetic background and early life programming due to environmental exposures may result in general susceptibility to autoimmune disease. Characterization of theextent to which particular combinations of autoimmune diseasesoccur, in excess of that expected by chance, may offer insights intothe existence of shared pathophysiological mechanisms.

In pediatrics, as well as in young adults, AIH often presents acutely and exhibits a more aggressive course than is seen in middle-age and elderly patients. In children, there are two liver disorders in which liver damage is likely to arise from an autoimmune attack, namely classical AIH and AIH/sclerosing cholangitis overlap syndrome (autoimmune sclerosing cholangitis [ASC]), the latter being characterized by both bile duct damage and interface hepatitis. A possible autoimmune pathogenesis has also been postulated for the so-called ''post–liver transplant *de novo* AIH,'' a condition originally described in children and later confirmed to occur in adults.

Type 1 diabetes, rheumatoid arthritis, multiple sclerosis and Crohn's disease are all examples of autoimmune diseases, which can be triggered when the body's immune system begins to attack healthy cells. Treating these diseases

requires an understanding of how to turn off an immune system attack, which might seem an unusual goal since most immune onslaughts are aimed at viruses, bacteria or other biological invaders to the body. But when the immune system's attack is aimed at healthy cells, the ability to apply the immune 'off switch' becomes very important[7].

Several common autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis, are genetically linked to distinct human major histocompatibility complex (MHC) class II molecules and other immune modulators. In addition, autoimmunity often clusters families, indicating the potential for a broad-spectrum genetic defect in immunological tolerance mechanisms. However, the genetic factors which lead to the development of immune responses against specific antigens in a tissue and/or organ-specific manner remain largely unknown. Among the environmental factors, infections have been particularly implicated in the onset and/or promotion of autoimmunity[8].

For many years, the central dogma of immunology focused on the clonal deletion of autoreactive cells, and ignoring a repertoire of T cells and B cells that recognize specific foreign antigen. However, our present view acknowledges that a low level of autoreactivity is physiologic[9] and crucial to normal immune function. Autoantigen helps to form the repertoire of mature lymphocytes, and the survival of naive T cells[10] and Bcells[11] in the periphery requires continuous exposure to auto-antigens. Since there is no fundamental difference between the structure of self antigens (or auto-antigens) and that of foreign antigens, lymphocytes evolved not to distinguish self from foreign (as some have speculated), but to respond to antigen only in certain microenvironments, generally in the presence of inflammatory cytokines[12]. Since autoreactivity is physiologic, the challenge is to understand how it becomes a pathologic process and how T cells and B cells contribute to tissue injury.

We undertook a systematic literature review to quantifythe coexistence of selected autoimmune diseases within in individuals and families. We reviewed the associations among four autoimmune diseases: insulin-dependent diabetes mellitus(IDDM), autoimmune (Hashimoto) thyroiditis (AIT), rheumatoid arthritis (RA), and multiple sclerosis (MS). We choseto focus on these diseases for several reasons. Firstly, evidence ofassociations between these diseases in animal models impartsplausibility for their coexistence in humans. Moreover, thesediseases are sufficiently common, in contrast to many otherautoimmune diseases, to provide a reasonable expectation ofdetecting them when they occur in combination.

Incidence, Prevalence, Morbidity, and Mortality of Autoimmune Diseases

Incidence is the rate at which new cases of a disease occur relative to population size and the passage of time. At present, few data exist that can be used to estimate the incidence of autoimmune diseases on a national scale. While some studies provide estimates for individual autoimmune diseases, these studies have been relatively small and geographi-cally limited. Because of these limitations, scientists cannot extrapolate from these studies to generate national incidence data.

Prevalence is the ratio of the number of existing cases of a disease (active and in remission) in a population at a specific point in time to the total number of persons in the population. Prevalence estimates take into account both the occurrence of new cases and duration of the disease, and therefore reflect both the natural history of the disease and the availability of treatments. Because autoimmune diseases are chronic, prevalence rates are usually high despite the occurrence of relatively low annual incidence rates.

Household survey data have been used to estimate the prevalence of a number of the more common autoimmune diseases. Many of these surveys, however, are limited because of the relatively small sample size, particularly in the case of the less common autoimmune diseases. In addition, because most household surveys rely on self-reporting of disease, they can often lead to over-reporting or under-reporting.

The lack of reliable figures on the incidence and prevalence of autoimmune diseases significantly hampers research on these disorders. It is important to know the populations and individuals that are most susceptible to autoimmune diseases in order to understand the

genetic and environmental factors that contribute to their onset. Moreover, without better disease surveillance studies, progress in the treatment and prevention of these diseases will be constrained.

Morbidity refers to the severity and complications of illness. Commonly used measures of morbidity include the number of days of hospitalization due to a specific disease, days lost from work or school, physician visits associated with a disease, and days of restricted activity. These measures can be used to estimate the impact of a disease, both in monetary and non-monetary terms.

Unfortunately, we currently lack rigorous quantitative estimates of morbidity for most autoimmune diseases. The National Hospital Discharge Survey provides data on primary and secondary diagnoses, as well as reasons for hospitalization. These data, however, may not reflect the true morbidity associated with autoimmune disease because most patients are seen in an outpatient setting. Due to the scarcity of data sources, most of our under-standing of the morbidity associated with autoimmune disease is based upon the impressions of physicians and patients.

Mortality is the number of deaths caused by a specific disease, including any deaths that result from treatment of the disease. This information is typically assembled from death certificates. Information is often lacking, however, about the underlying factors that led to a person's death but are not listed as the immediate cause. It is likely, therefore, that estimates of autoimmune disease mortality which are based on death certificates alone understate the true magnitude of the problem.

Etiology of Autoimmune Diseases

Fundamentally, all autoimmune diseases are a consequence of impaired immune function resulting from interactions of both genetic and environmental factors. Despite significant progress, much remains to be learned about these factors and their interactions. Advances in this area are however, providing a foundation for more effective therapies and prevention strategies.

Genetic Factors

The tendency to develop an autoimmune disease is in part hereditary. Initially, clinicians observed that a single patient may develop more than one autoimmune disease and that related members of the same family may share an autoimmune disease. These observations led to rigorously controlled epidemiologic studies comparing the occurrence of autoimmune diseases in genetically identical twins to the occurrence of these diseases in non-identical twins. Several such studies reported a concurrence rate between identical twins of 15 percent to 50 percent, with a mean of approximately 30 percent. In contrast,non-identical twins have about the same risk of developing an autoimmune disease as any other sibling, i.e. about two to five percent. As a result, heredity is estimated to account for about one-third of the risk of developing an autoimmune disease. In contrast to other inherited diseases (such as cystic fibrosis, Tay-Sachs disease, or sickle cell disease) which result from disease-causing mutations in a single gene, most autoimmune diseases result from the combined effects of several genes acting in concert to determine disease susceptibility. The disease-related versions of these genes may be relatively common in the population, but unless present in combination they are not usually associated with disease.

Some genes affect the immune response itself, whereas others increase the vulnerability of the target organ to autoimmune attack. Of all such genes identified to date, the most com-pletely characterized are members of the family of genes of the major histocompatibility complex, or MHC. These genes are determinants of tissue compatibility and are thus responsible for tissue graft rejection. This group of genes when present in humans is referred to as HLA (human leukocyte antigens) also controls key steps in the immune response, especially those related to recognition by T cells of specific antigens presented to them by antigen-presenting cells.

Environmental Factors

Certain environmental agents play a clear role in instigating autoimmune processes. For example, drugs such as procainamide and hydrolyzine can induce a lupus-like syndrome in genetically-susceptible individuals,which then undergoes remission when the drug is discontinued. Other drug-induced autoimmune diseases have been described, including some of the hemolytic anemias, thrombocytopenias, and

leukopenias. The possible role of exposure to various metals in autoimmune disease has been explored, primarily through laboratory and animal studies. With notable exceptions, metals generally inhibit immune cell pro-liferation and activation. Mercury, gold, and silver, for example, can induce lymphocyte proliferation and subsequent autoimmunity. Genetically susceptible mice develop a lupus-like condition when dosed with mercury, silver, or gold. It is likely, however, that the autoimmune disorders that result from exposure to various metals occur through distinct mechanisms.

Other environmental exposures have been studied in relation to immune disease, but associating such exposures with specific disorders is difficult. Some epidemiologic information suggests an association between dietary iodine and iodine-thyroiditis, and between silica and both scleroderma and lupus in people living in certain industrial settings. Additional research has explored possible relationships between autoimmune disease and exposures to organic compounds, principally the halogenated hydrocarbon trichloroethylene (TCE) and polychlorinated biphenyls (PCBs). TCE metabolites have also been associated with systemic lupus erythematosus, systemic sclerosis, and other autoimmune disorders; the evidence for PCB effects remains sparse however. Similarly, a few epidemiologic studies have examined occupational exposures to dioxins; however, firm epidemiologic evidence of a cause and effect association has yet to be shown. Similarly, investigations of exposure to pesticides and estrogenic compounds in relation to autoimmune diseases are areas of considerable research interest, but require additional exploration.

Exposure to ultraviolet radiation from the sun can exacerbate disease symptoms in patients with systemic lupus erythematosus. Other epidemiologic studies suggest that ultraviolet exposure may be protective in multiple sclerosis and rheumatoid arthritis; however, conflicting animal studies indicate that ultraviolet exposure may increase autoimmune disease risk in genetically-predisposed individuals.

Despite these leads, the exact mechanisms by which infection induces a particular autoimmune disease are unknown. In the case of the bacteria *Streptococcus*, it is believed that a bacterial antigen resembles an antigen present in the heart, and that a cross-reactive immune response to the infecting bacteria causes immune-mediated damage to the heart. This phenomenon is referred to as molecular mimicry. In other instances, microorganisms or local inflammation may alter antigens of the host so that the immune system sees them as foreign. Infections may also increase immune cell expression of co-stimulatory molecules and thus promote autoimmune responses.

Lifestyle Factors

Lifestyle factors may also contribute to the development or progression of autoimmune diseases. For example, nutritional factors that affect immune function and interactions between dietary factors and other exposures are potentially important. Antioxidants may play a role in immune function, particularly with respect to autoimmunity. Lupus-prone mice show delayed symptom onset or prolonged survival when given antioxidant supplements, as well as when total fat and caloric intake are reduced or dietary fatty acid (e.g., omega-3 fatty acids) content is manipulated. The potential role of diet in autoimmune disease remains an important issue for patients and clinicians. Several studies have shown that smoking is associated with an increased risk of rheumatoid arthritis, but inconsistent results have been found in relation to smoking and lupus. Smoking might however be associated with a reduced risk of ulcerative colitis, an inflammatory bowel disease. Clearly, it is important to understand the mechanisms through which smoking may affect autoimmune disorders and why different effects are seen across the spectrum of diseases.

Diagnosis of Autoimmune Diseases

The first step in managing patients with any disorder is to produce a proper diagnosis. Diagnosing autoimmune diseases can be particularly difficult, however, because these disorders can affect any organ or tissue in the body, and produce highly diverse clinical manifestations, depending on the site of autoimmune attack. Moreover, disease symptoms are often not apparent until the disease has reached a relatively advanced stage.

The diagnosis of an autoimmune disease typically begins with a careful health history, including assessment of possible occupational and environmental exposures. Many of the early symptoms of these disorders, such as fatigue, joint

and muscle pain, fever, or weight change are nonspecific. While these symptoms alone may not point to a particular autoimmune disease, when considered in retrospect they can help to pinpoint the point at which the disease process began. Added diagnostic clues may be revealed through family history and the presence of autoimmune disease in a patient's should be considered as a diagnostic indicator. Similarly, a social and occupational history may identify exposures associated with a particular autoimmune disorder.

Recent studies suggest that autoantibody detection may be valuable in earlier diagnosis of autoimmune diseases, thereby allowing treatment to be initiated sooner. Research has shown that individuals who go on to develop clinical manifestations of type 1 diabetes, for example, often have had multiple antibodies to the insulin-producing islet cells for some time before disease is evident. The presence of such antibodies, especially if coupled with a family history and genetic factors associated with the disease, increases the likelihood that symptoms will appear in the future. In some instances it may be possible to use anti-bodies to monitor responses to treatment or to forecast an exacerbation of a disease in remission. However, because some autoimmune diseases are caused by infiltrating cells rather than autoantibodies, practical tests for cell-mediated autoimmune reactions are needed as a high priority.

Imaging technology can also be a valuable diagnostic tool. For example, imaging tests that reveal areas of demyelinization in the brain (plaques) have been useful for diagnosing and staging multiple sclerosis and for monitoring responses to therapy. Other specialized imaging technologies are of increasing value in following the course of several autoimmune disorders.

Prevention of Autoimmune Diseases

Arresting the autoimmune process at its outset before irreversible tissue injury occurs remains the long range goal of much autoimmune disease research. Yet,in order to effectively develop and implement prevention strategies, scientists must first be able to identify individuals or populations at risk for developing an autoimmune disorder. Since about one third of autoimmune disease risk is inherited, it is important to define the genetic makeup of the most susceptible individuals in order to target prevention strategies. This effort has been aided by our increasing knowledge of the human genome and the genes that contribute to autoimmune susceptibility.As is the case with prevention, research in other diseases such as cancer, efforts to learn about a disease in highly affected families often lead to the design of prevention strategies that are effective in populations with no known genetic vulnerability

Many autoimmune disorders involve environmental factors, and identifying these is a major focus of prevention research. Environmental triggers may include infectious agents, normal dietary components (e.g., celiac disease symptoms can be avoided by eliminating gluten in the diet), supplements and food contaminants such as mercury, or occupational or other environmental exposures. As we learn more about environmental influences in autoimmune disease, it may be possible to prevent the onset of disease even in the most vulnerable individuals. For example, identifying those at high risk for type 1 diabetes depends on a combination of genetic factors and the appearance of islet autoantibodies. The presence of these autoantibodies precedes clinical symptoms, but is a strong indicator of relatively rapid progression to frank diabetes

Treatment of Autoimmune Diseases

Treatments to reduce the symptoms of most autoimmune diseases are available, but definitive cures have yet to be developed. In general, two approaches to treatment are currently available. The first involves replacing or repairing impaired function. For example, patients with type 1 diabetes mellitus can take insulin to replace the hormone that is not produced by their damaged pancreatic islet cells. Similarly, patients with autoimmune thyroiditis can be treated with thyroid hormones. These approaches do not however, arrest the auto-immune process, although the patient may undergo remission while receiving symptom-based treatment. In most cases, however, the patient must depend on the use of replacement therapy throughout his or her lifetime.

A damaged organ can be sometimes replaced by transplantation, e.g. the use of islet cell transplant as a treatment for diabetes. Patients with end-stage renal disease or dilated cardiomyopathy may also be candidates for a kidney or heart transplant. In the future, stem cell

therapies might allow replace, or repair, damaged organs. Replacement therapy is most likely to be successful if the impaired function is localized to a single organ system. The second type of treatment approach centers on suppressing the destructive autoimmune response. Systemic autoimmune diseases often require the general suppression of the immune response. Immunosuppressive drugs reduce the overall immune response and thereby ameliorate the manifestations of the disease. However, because these drugs also reduce the individual's resistance to infection, they must be used with great caution; additionally they often produce adverse side effects. Such treatments are most often used in debilitating diseases such as lupus and rheumatoid arthritis.

Considerable effort has in recent years been devoted to developing more focused therapies than global immunosuppression. Most of these approaches target a specific step in the tissue-damaging inflammatory response. A number of promising new biologic agents, which are capable of producing more targeted immunosuppression are already in advanced clinical trials. They include mono-clonal antibodies that decrease T cells or B cells specifically, act on only activated T cells, inhibit particular cytokine mediators of inflammation, or block the recruitment and localization of lymphocytes to the target organ. Although such targeted approaches usually produce fewer side effects, they may increase the patient's vulnerability to infection, and must therefore be used with caution. Unfortunately, a therapy that benefits one autoimmune disease may some-times make another disorder worse

Researchers are now using our growing knowledge of the biology of immune response to develop innovative new intervention strategies. These include bone marrow transplanta-tion and approaches aimed at enhancing a naturally-occurring regulatory mechanism (e.g., shifting immune response from a damaging T cell subpopulation to a less injurious one, or increas-ing the number of regulatory cells produced by the thymus). Other interventions may include new therapies and counseling related to the avoidance of exacerbating factors (e.g., certain infections, environmental agents)

Application of new technologies

Biomarker Development

Discovering and validating biomarkers of the disease process is an overarching need in most areas of clinical research. Biomarkers are clinical indicators, or routine laboratory studies, that have been shown to correlate with clinical status. As such, they can contribute to patient management decisions and facilitate the conduct of clinical trials. Biomarkers can also include specific gene expression patterns and genetic polymorphisms, or immunologic assays of an investigational nature.

The discovery of biomarkers depends on an understanding of the genetic, infectious, environmental, and immunologic factors which contribute to the pathogenesis of the disease; the natural history of the disease as seen in large epidemiology studies; novel high-throughput assays; and clearly defined clinical phenotypes of autoimmune diseases. The discovery of biomarkers requires multidisciplinary and creative teamwork, as well as the validation of candidate biomarkers,an approach which entails rigorous clinical evaluation.

An expanded set of validated biomarkers for autoimmune diseases will allow: (1) the earlier and more rapid diagnosis of disease, thereby resulting in earlier treatment; (2) intervention with the most effective therapies for particular stages of the disease process or for application to patients with a par-ticular genetic background or immunologic background; (3) shorter, smaller, and less costly clinical trials; and (4) more informative monitoring of drug efficacy leading to earlier discontinuation of ineffective therapies. Biomarkers could also be used to detect exposures to environmental factors that might increase the risk or severity of autoimmune disease

Bioinformatics of New Technologies

Various new technologies are being applied to research on autoimmune diseases. For example, disease processes can now be characterized at a molecular level through the use of micro-array technologies that reveal patterns of gene expression in tissue samples. Proteomics–the study of protein shape, function, and patterns of expression–can enable scientists to characterize the status of proteins in tissues and antibodies in serum. High-throughput technologies allow investigators to acquire large amounts of genomic and proteomic data and record the biologi-cal responses and activities of systems under study. Constructs called MHC-tetramers now allow

scientists to sort and analyze T lymphocytes based on their recognition of specific antigens. These powerful tools are increasingly being applied, not only in the laboratory, but also within clinical research. Finally, mining and analysis of data derived from such studies depends on a variety of advanced computational tools.

The above mentioned approaches are beginning to show results in the area of cancer diagnosis and management. A dedicated effort to apply these technologies to the family of autoimmune diseases is only beginning, but holds great promise.

The availability of the reference human genome sequence will greatly accelerate the identification of disease susceptibility and resistance genes. In addition, ongoing efforts to fully sequence the genomes of animal models, such as the mouse and the rat, will be enormously important in understanding the genetics of autoimmune diseases. Similarly, clinical data-bases, disease registries, and repositories will hopefully greatly accelerate such efforts.

Looking to the Future

Since the publication of the 2002 ADCC Autoimmune Diseases Research Plan, substantial progress has been made to quantify and better understand the burden of autoimmune diseases and to a) define the factors that lead to their development; to improve the diagnosis, treatment, and prevention of autoimmune disorders and b) to strengthen the autoimmunity research workforce and disseminate research findings to patients, clinicians, and the community. Numerous specific initiatives are now underway in relation to many of the areas highlighted in the Research Plan. These solicited research programs are producing a wealth of new knowledge as well as enhancing collaboration among basic-research scientists, clinical investigators, and individuals from a host of other technological disciplines ranging from bioinformatics to imaging approaches. Over the next several years, the NIH will exploit every opportunity to build upon its new found progress in autoimmune disease research, and will hopefully yield new knowledge, leading to new and exciting interventions aimed at improving the lives of all those who are suffering under the yoke of autoimmune disease.

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