CHAPTER 6

ENVIRONMENTAL AGENTS AND AUTOIMMUNE DISEASES

Frederick W. Miller

National Institute of Environmental Health Sciences, National Institutes of Health, HHS, Bethesda, Maryland, USA
Email: millerf@mail.nih.gov

Abstract: Autoimmune diseases, which comprise over 80 clinically distinct conditions, are characterized by the presence of autoantibodies or autoreactive T cells directed against self structures (autoantigens). While these often incurable disorders appear to be rapidly increasing in recognition throughout the world, their rarity, heterogeneity and complex etiologies have limited our understanding of their pathogeneses. The precise mechanisms for the development of autoimmune diseases are not known, however, evidence from many complementary lines of investigation suggests that autoimmune diseases result from the interactions of both environmental and genetic risk factors. While considerable progress has been made in understanding multiple genetic risk factors for many autoimmune diseases, relatively little information is now available regarding the role of the environment in the development of these illnesses. This chapter examines the limited but growing evidence for the role of the environment in the development and progression of autoimmune diseases, the specific exposures that have been suspected of being involved, the possible mechanisms by which these agents may induce and sustain autoimmune processes and the approaches needed to better understand these issues in the future. Identifying the necessary and sufficient genetic and environmental risk factors for disease holds the promise of allowing for the prevention of some illnesses through avoidance of environmental risk factors by genetically susceptible individuals or via gene or other therapies to correct the effects of deleterious genetic risk factors in the case of unavoidable environmental agents.

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INTRODUCTION

Autoimmune diseases are pathologic conditions associated with self-reactive components of the immune system. Most of these illnesses are defined by clinical signs, symptoms and laboratory features that include characteristic autoantibodies or self-directed T-cell responses. Data regarding their incidence and prevalence are limited, but many investigators believe they are increasing for unknown reasons.[1,2] Collectively, over 80 different autoimmune diseases (Table 1) afflict 14-23 million Americans, an estimated 5 to 8 percent of the population.[3] Autoimmune diseases can affect one or more organs in any part of the body and have many clinical manifestations, making them difficult to

Table 1. Diseases with evidence supporting an autoimmune etiology. Source: American Autoimmune Related Diseases Association (http://www.aarda.org/)

- Acute Disseminated Encephalomyelitis (ADEM)
- Acute necrotizing hemorrhagic leukoencephalitis
- Addison's disease
- Agammaglobulinemia
- Allergic asthma
- Allergic rhinitis
- Alopecia areata
- Amyloidosis
- Ankylosing spondylitis
- Anti-GBM/Anti-TBM nephritis
- Antiphospholipid syndrome (APS)
- Autoimmune aplastic anemia
- Autoimmune dysautonomia
- Autoimmune hepatitis
- Autoimmune hyperlipidemia
- Autoimmune immunodeficiency
- Autoimmune inner ear disease (AIED)
- Autoimmune myocarditis
- Autoimmune pancreatitis
- Autoimmune retinopathy
- Autoimmune thrombocytopenic purpura (ATP)
- Autoimmune thyroid disease
- Axonal and neuronal neuropathies
- Balo disease
- Behcet's disease
- Bullous pemphigoid
- Cardiomyopathy
- Castleman disease
- Celiac sprue (nontropical)
- Chagas disease
- Chronic fatigue syndrome
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Chronic recurrent multifocal ostomyelitis (CRMO)
- Churg-Strauss syndrome

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Table 1. Continued

- Cicatricial pemphigoid/benign mucosal pemphigoid
- Crohn's disease
- Cogans syndrome
- Cold agglutinin disease
- Congenital heart block
- Coxsackie myocarditis
- CREST disease
- Essential mixed cryoglobulinemia
- Demyelinating neuropathies
- Dermatomyositis
- Devic's disease (neuromyelitis optica)
- Discoid lupus
- Dressler's syndrome
- Endometriosis
- Eosinophilic fasciitis
- Erythema nodosum
- Experimental allergic encephalomyelitis
- Evans syndrome
- Fibromyalgia**
- Fibrosing alveolitis
- Giant cell arteritis (temporal arteritis)
- Glomerulonephritis
- Goodpasture's syndrome
- Graves' disease
- Guillain-Barre syndrome
- Hashimoto's encephalitis
- Hashimoto's thyroiditis
- Hemolytic anemia
- Henoch-Schonlein purpura
- Herpes gestationis
- Hypogammaglobulinemia
- Idiopathic thrombocytopenic purpura (ITP)
- IgA nephropathy
- Immunoregulatory lipoproteins
- Inclusion body myositis
- Insulin-dependent diabetes (type1)
- Interstitial cystitis
- Juvenile arthritis
- Juvenile diabetes
- Kawasaki syndrome
- Lambert-Eaton syndrome
- Leukocytoclastic vasculitis
- Lichen planus
- Lichen sclerosus
- Ligneous conjunctivitis
- Linear IgA disease (LAD)
- Lyme disease
- Meniere's disease

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Table 1. Continued

- Microscopic polyangiitis
- Mixed connective tissue disease (MCTD)
- Mooren's ulcer
- Mucha-Habermann disease
- Multiple sclerosis
- Myasthenia gravis
- Myositis
- Narcolepsy
- Neuromyelitis optica (see Devic's)
- Neutropenia
- Ocular cicatricial pemphigoid
- Optic neuritis
- Palindromic rheumatism
- PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus)
- Paraneoplastic cerebellar degeneration
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Parry Romberg syndrome
- Parsonnage-Turner syndrome
- Pars planitis (peripheral uveitis)
- Pemphigus
- Peripheral neuropathy
- Perivenous encephalomyelitis
- Pernicious anemia
- POEMS syndrome
- Polyarteritis nodosa
- Type I, II, and III autoimmune polyglandular syndromes
- Polymyalgia rheumatica
- Polymyositis
- Postmyocardial infarction syndrome
- Postpericardiotomy syndrome
- Progesterone dermatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Psoriasis
- Psoriatic arthritis
- Idiopathic pulmonary fibrosis
- Pyoderma gangrenosum
- Pure red cell aplasia
- Raynauds phenomenon
- Reflex sympathetic dystrophy
- Reiter's syndrome
- Relapsing polychondritis
- Restless legs syndrome
- Retroperitoneal Fibrosis
- Rheumatic fever
- Rheumatoid arthritis
- Sarcoidosis

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Table 1. Continued

- Schmidt syndrome
- Scleritis
- Scleroderma
- Sjogren's syndrome
- Sperm and testicular autoimmunity
- Stiff person syndrome
- Subacute bacterial endocarditis (SBE)
- Sympathetic ophthalmia
- Systemic Lupus Erythematosus
- Takayasu's arteritis
- Temporal arteritis/Giant cell arteritis
- Thrombocytopenic purpura (TTP)
- Tolosa-Hunt syndrome
- Transverse myelitis
- Ulcerative colitis
- Undifferentiated connective tissue disease (UCTD)
- Uveitis
- Vasculitis
- Vesiculobullous dermatosis
- Vitiligo
- Wegener's granulomatosis

diagnose. Autoimmune diseases also may share many clinical features and risk factors, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family. Since all the autoimmune diseases are mediated by the immune system, the basic treatment is similar and involves the use of immunosuppressive agents and sometimes adjunct or supportive management with occupational or physical therapy. For these and other reasons, the autoimmune diseases should be thought of as a family of related disorders that should be studied collectively as well as individually.[4]

Mechanisms for the development of autoimmune diseases remain obscure despite intense investigation, yet a consensus is emerging that they likely occur as a result of chronic inflammation after selected environmental exposures in genetically susceptible individuals.[5] Despite the great progress that has been made in understanding a number of major histocompatibility complex (MHC) and nonMHC genetic risk factors for autoimmune diseases,[6] relatively little information is now available regarding the role of specific environmental agents in the development of these disorders. This is partly the result of the rarity of these conditions, the lack of easy-to-use and validated exposure biomarkers and environmental assessment tools, difficulties inherent in defining which of many environmental exposures that occur frequently are related to disease, the little formal training in environmental medicine, the few resources dedicated to this area and the lack of consensus approaches for the definition of environmentally associated diseases. As a result, the specific environmental triggers remain unknown for most autoimmune conditions.

It appears that multiple genes need to be present in an individual to induce autoimmune disease[7] and similarly, multiple environmental exposures may also need to occur in a

particular sequence, or in tandem, to provoke the chronic immune activation that leads to autoimmunity.[8] Thus, lessons might be learned from studies of similar diseases, such as cancers, which like autoimmune diseases, are complex conditions in which many genetic and environmental risk factors must interact in a correct sequence, before development of disease.[9] For example, a genetic, epigenetic or immune regulatory change induced by one exposure may be necessary before a subsequent exposure can have its effect. Alternatively, mixtures of exposures, including possible combinations of infectious and non-infectious agents, perhaps occurring during critical physiologic windows when persons may be more susceptible to them, may be necessary in order to overcome immune tolerance and induce autoimmunity. Additional general principles from the study of cancer that might be relevant to autoimmunity include: (1) the clinical, pathologic and pathogenetic heterogeneity of different entities as currently defined; (2) the low effect sizes from many environmental exposures requiring large samples for most studies; (3) the possible requirement for inducers, promoters and sustainers of disease at different points in the pathogenetic process; (4) the requirement for interaction with key genetic susceptibility factors; and (5) possible long latencies from exposure to pathogenic agents to the development of immune system alteration and then additional delays to the development of pathology.[10] This latter principle is supported by studies suggesting that cytokine and chemokine elevations, immune activation and autoantibodies precede the development of clinical disease by months to years.[11-13]

In the context of this chapter, environmental exposures will be considered to be all those factors that are not inherited. These are often divided into two general categories, infectious agents—which include viruses, bacteria and parasites—and non-infectious agents—including foods, drugs, devices, occupational exposures, lifestyle patterns, chemical components of air and water, radiation and other incidental exposures.

EVIDENCE SUGGESTING ENVIRONMENTAL AGENTS PLAY A ROLE IN THE DEVELOPMENT OF AUTOIMMUNE DISEASE

The evidence that environmental agents may play a pathogenic role in autoimmune disease comes from many complementary lines of study (Table 2). Although some of these are indirect or anecdotal evidence, taken together, the findings strongly support the notion that most autoimmune diseases do have an important environmental component.[5,14]

An important line of evidence for the role of the environment is that for autoimmune diseases there is generally much less than 50% disease concordance in monozygotic twins.[14,15] Although this may possibly be due to stochastic or other events, this consistent low level of disease concordance in genetically identical persons among all autoimmune disorders studied, as well as the many other lines of evidence implicating environmental factors, argues against this. These findings suggest that even if all the genetic risk factors for a given autoimmune disease were identified, it would not allow for prediction of disease with any greater accuracy than the flip of a coin without the incorporation of environmental, epigenetic or other factors.

The definition of an environmental disease in a person can be achieved by identifying a clinical disorder, which develops soon after a novel exposure (challenge), resolves when the exposure is removed (dechallenge) and then recurs after reintroduction of the same exposure (rechallenge).[16] Classic cases of this type include exposures to defined chemical entities such as drugs, foods, or inhaled toxicants whose effects are short-lived

Table 2. Lines of evidence supporting the role of environmental agents in the development of autoimmune disease

1. Low disease concordance in monozygotic twins
2. Temporal associations with some environmental exposures and later disease onset (challenge)
3. Disease resolution or improvement after removal of the suspect agent (dechallenge)
4. Disease recurrence or worsening after re-exposure to the suspect agent (rechallenge)
5. Seasonality in birth dates in some autoimmune diseases or phenotypes
6. Seasonality in disease onset in some autoimmune diseases or phenotypes
7. Geographic clustering with the onset of disease or disease prevalence
8. Changes in the prevalence or incidence of disease over time
9. Changes in disease frequency when genetically similar cohorts move to different geographic locations
10. Biologic plausibility from animal models that develop disease after specific exposures
11. Genetic risk factors for autoimmune disease regulate immune responses to environmental agents
12. Higher rates of disease in certain occupations
13. Higher rates of disease after higher doses of or more prolonged exposure (a dose-response effect)
14. Epidemiologic associations between particular exposures and certain diseases

Modified from reference 62.

and resolve if the agent is removed. Many xenobiotics (compounds found in an organism but which are not normally produced or expected to be present in it), however, cannot be removed after exposing an organism to them and in these cases this approach is not usually helpful. Exposures in this category include inhaled silica, vaccines, some petrochemicals and medical implants.

The unusual time-space associations of disease onset with some autoimmune illnesses also imply that nongenetic factors play a role in disease development. Examples here are more preliminary and sometimes have not been reproduced, allowing for the possibility that referral or other biases might explain the findings. Nevertheless, investigations have found that certain autoimmune disorders have a seasonal onset[17] or that there is a seasonal association with disease onset in subsets of patients based upon disease-specific autoantibodies.[18,19] Furthermore, studies of Type 1 diabetes have found significant associations with birth dates[20,21] implying that certain exposures at certain times of the year may alter the target tissues or immune systems of fetuses or neonates resulting in later autoimmunity. Infections are often presumed to be the source of seasonal or geographic associations, yet the immune system, like other organ systems, has cyclic patterns[22] that are likely related to light exposure and mediated by melatonin or other neurohormones.[23] Additionally, many non-infectious exposures are seasonal, including exposures to pesticides, chemicals in sunscreens and certain air or water pollutants, so non-infectious agents could account for some of these findings. Geographic clustering or gradients in disease prevalence or incidence have also been found for some autoimmune diseases. These investigations include associations with latitude, suggesting a role of ultraviolet radiation or other associated effects in either inducing disease, as may be the case for dermatomyositis,[24,25] or protecting from disease, as may be the case in multiple sclerosis and Type 1 diabetes.[26]

Changes in the incidence or prevalence of disease over time also suggest a nongenetic etiology given the slow rate of genetic change in a population. Type 1 diabetes, multiple sclerosis, myasthenia gravis, primary biliary cirrhosis Crohn's disease,SLE and myositis all appear to be increasingly prevalent, while rheumatoid arthritis may be decreasing in frequency in some populations.[1,27-31] Studies of genetically similar populations who move to live under different conditions are also interesting. The incidence of both multiple sclerosis and Type 1 diabetes changed as members of a population moved to new regions with higher incidence rates.[32,33]

Unfortunately, the gold standard approach to defining associations of environmental agents with disease—carefully controlled and adequately powered epidemiologic studies—are limited.[5] Large, well-designed, multicenter and sometimes international studies, using appropriate controls and collecting adequate information to minimize confounding, are needed in the future to more fully define the specific environmental risk factors for each disease or phenotype.

DEFINING ENVIRONMENTALLY ASSOCIATED AUTOIMMUNE DISEASES

A general problem in the field of identifying environmental agents that may cause autoimmune disorders is the lack of consensus on the necessary and sufficient evidence needed to define an environmentally associated condition.[2] This is further complicated by medical-legal issues often involved in a number of environmental exposures. To address this problem, a group of experts in the field—members of the American College of Rheumatology Environmentally Associated Rheumatic Disease Study Group—developed consensus on a general structural framework to address this issue and divided the process into four stages.[16]

The first stage is the identification of a single case, or a series of cases, which are clinically suspected of resulting from an exposure (Table 3). The consensus of the group is that such first stage cases need to meet a number of criteria to assure a minimum number of attribution elements are present.[16] A total of at least four of eight possible attribution elements need to be present, including at least three of five primary elements. The five primary elements are: (1) temporal plausibility, taking into account the pharmacokinetics and pharmacodynamics of the agent, the minimum induction time and maximum latency that are thought to be possible; (2) exclusion of other likely causes for the case based on prior experience with the clinical entity and the agent in question; (3) dechallenge if possible (clinical evidence for resolution or improvement in the case after removing the suspect agent); (4) rechallenge if appropriate (clinical evidence for the reinitiation or exacerbation of the case if it is appropriate to give the agent to the patient again) and (5) biologic plausibility based on the known effects of the agent. An additional three secondary elements are: the publication of reports of similar cases (analogy); publication of nearly identical cases (specificity); and evidence that exposure to higher doses or for a more prolonged period is needed for development of disease (a dose-response effect). Also, information regarding the history and clinical examination, laboratory and biopsy results, demographic details, the family history of similar disorders, knowledge of prior infections or physiology-altering exposures, all prior clinical diagnoses and the type/route/dose/duration/source of the exposure should be detailed in the report.

The second stage involves testing the possible association via epidemiologic studies, using surveillance criteria, to evaluate the relationship between a given exposure

Table 3. Proposed stages for identifying and defining environmentally associated autoimmune diseases

Stage	Description	Proposed Nomenclature for the Syndrome (Example)
Stage 1—Proposing the association	Case reports, defined by adequate criteria, propose a possible association of a specific clinical syndrome with a given exposure	Syndrome following exposure (Rheumatoid Arthritis following Hepatitis B vaccination)
Stage 2—Testing the association	After a number of such cases are reported, surveillance criteria are proposed and epidemiologic and laboratory studies test that hypothesis	Cardinal signs, symptoms and labs but without the putative exposure (Eosinophilia Myalgia syndrome)
Stage 3—Defining criteria for the condition	If studies above support the association, then specific preliminary classification and other criteria are defined for that specific environmental disease	Exposure-associated disorder (L tryptophan-associated Eosinophilia Myalgia syndrome)
Stage 4—Refining criteria for the condition	Criteria are reassessed and refined as necessary as additional data are obtained about the disease to confirm the association	Exposure-induced disorder (Hydralazine-induced Lupus-like disorder)

Modified from reference 16.

and a given syndrome, or by in vitro, in vivo or animal studies as appropriate. Other approaches could be used, such as case-control settings, to determine if the cases that develop after the environmental exposure differ clinically or genetically from those with similar diseases without the exposure or differ from subjects similarly exposed who do not develop disease.

If convincing evidence is obtained that the association is plausible, then the third stage will develop preliminary criteria for that environmentally associated disease. Classification criteria will define, with reasonable sensitivity and specificity, groups of patients with one disorder from closely related diseases. Approaches involving Delphi or Nominal Group Techniques using expert committees and appropriate mathematical algorithms could be used to develop these criteria.[34] Symptom, sign and laboratory criteria should be expressed in clinically sensible and practical formats with precise definitions of constituent elements. The fourth stage repeats the same processes used in the third stage if new information is collected to warrant a redefinition of the disease.

This proposed staging structure has certain limitations, including that the decision as to when to progress from one stage to the next stage remain somewhat subjective, yet it does give an overall framework to plan for future studies and it allows the classification of the environmental agents into groups with levels of evidence for their association with specific syndromes. The current limited information in this field means that most environmental agents suspected of being associated with autoimmune diseases today remain in Stages 1 or 2.

ENVIRONMENTAL AGENTS ASSOCIATED WITH AUTOIMMUNE DISEASES

Infectious Agents

Viruses, bacteria and parasites have all been proposed as possible triggers of autoimmune diseases and yet they also may modulate immune function to possibly prevent the development of autoimmune disease.[35] In fact, the 'hygiene hypothesis' proposes that the recent increases in immune-mediated diseases in developed countries might be related to an early life environment that is relatively deficient in microbial flora.

While many case reports and small case series describe the development of various autoimmune diseases following infections, few epidemiologic investigations have addressed this issue.[36] Controlled studies suggest an increased risk for rheumatoid arthritis and SLE after certain infections by measuring the presence of antibodies to various viral components of Epstein-Barr virus (EBV), Cytomegalovirus (CMV) and Herpes virus in sera or via questionnaires.[5] The evidence that suggests EBV is associated with autoimmune diseases includes an increased presence of antibodies to viral peptides and the ability to amplify EBV genomes by PCR in more autoimmune disease subjects compared to controls, as well as similarities between the products of EBV genes and autoantigens.[37] For further reading on EBV effects on epigenetic control see Chapter 7.

Parvovirus B19 can induce a transient reactive polyarthritis, but several investigations have also suggested parvovirus might be an etiologic agent in autoimmune diseases.[5] In children with an acute onset of arthritis, those with IgM antibodies to B19 developed a chronic arthritis indistinguishable from juvenile rheumatoid arthritis, while those children who lacked IgM antibodies to B19 did not progress to a chronic form of arthritis.[38] In a carefully conducted study in juvenile dermatomyositis, however, investigators failed to find an increase in serum IgG antibodies to parvovirus B19.[39]

New immunologic and molecular screening technologies should allow for the assessment of larger numbers of autoimmune diseases in rapid and efficient ways that could allow for more definitive analyses of the pathogenic role of infections.[40-42]

Drugs

Drugs are some of the best recognized and most often reported agents associated with autoimmunity and autoimmune diseases (Table 4). It is not necessarily the case, however, that drugs are more likely than other chemicals to result in autoimmunity. Rather, it is likely that the widespread use and careful monitoring of drugs by many parties, along with the regulatory oversight and adverse event reporting systems in many countries, has focused more attention on drugs. Also, the rapid metabolism and ease of collection of dechallenge and rechallange evidence has allowed associations in individual patients to be more carefully documented. Hundreds of drugs have been associated in case reports or published case series with a number of immune-mediated or autoimmune illnesses, yet few have met the consensus criteria described above to allow exclusion of confounding factors. Both chemicals and biologic agents used as drugs have been associated with autoimmune disease.

Lupus-like disorders seem to be the most common autoimmune conditions to develop after drug use.[43] These are often characterized by autoantibodies to histones and single-stranded DNA, rather than autoantibodies to double stranded DNA as are found

Table 4. Selected drugs associated in multiple case reports or in case series with autoimmune disorders

Drug	Associated Autoimmune Disorders
α-methyldopa	lupus-like syndrome, hemolytic anemia, thrombocytopenia
allopurinol	lupus-like syndrome, vasculitis
anti-TNFα agents	lupus-like syndrome, hepatitis
bleomycin	scleroderma
captropril	lupus-like syndrome, vasculitis, membranous glomerulopathy
chlorpromazine	lupus-like syndrome, hemolytic anemia
D-penicillamine	lupus-like syndrome, myositis, hypothyroidism, Goodpasture's
estrogens	lupus-like syndrome, myositis
gold salts	lupus-like syndrome, membranous glomerulopathy
hydralazine	lupus-like syndrome, vasculitis
interferon-alpha/beta	lupus-like syndrome, antiphospholipid syndrome, arthritis, hemolytic anemia, thrombocytopenia, hepatitis, myositis, hypothyroidism
interferon-gamma	lupus-like syndrome, myositis, arthritis, hypothyroidism
interleukin-2	scleroderma, antiphospholipid syndrome, arthritis, hypothyroidism
iodine	hypothyroidism
isoniazid	lupus-like syndrome, arthritis, hepatitis, vasculitis, hypothyroidism
L-tryptophan	EMS, scleroderma, myositis, neuropathies
lipid-lowering agents	lupus-like syndrome, myositis, hepatitis
penicillins	hemolytic anemia, lupus-like syndrome
phenytoin	scleroderma, lupus-like syndrome, hepatitis, thrombocytopenia
procainamide	lupus-like syndrome
propylthiouracil	lupus-like syndrome, ANCA+ vasculitis, myositis
quinidine	lupus-like syndrome, arthritis, thrombocytopenia
rifampicin	thrombocytopenia, vasculitis
sulphonamides	lupus-like syndrome, vasculitis
tetracyclines	lupus-like syndrome, arthritis, vasculitis

Reviewed in references 71, 72, 77-80; ANCA: antineutrophil cytoplasmic antibodies; EMS: eosinophilia myalgia syndrome.

more often in idiopathic lupus. Drug related lupus also differs from idiopathic lupus in having more frequent arthritis and less frequent neurologic and renal involvement, as well as having possibly different genetic risk factors. This appears to be a general phenomenon in that many cases of drug-linked disorders often differ from the idiopathic forms in clinical, serologic or genetic features. Nonetheless, the data are very limited in this regard and there are examples where the drug-related cases do not differ from idiopathic ones.

In terms of possible mechanisms for drug-related autoimmunity, there are no common drug structures, binding sites, functions, pathways, metabolites or other features among them that consistently allow prediction of their toxicity. Therefore, a current understanding of the pathogeneses of these syndromes remains incomplete. Collecting adequate numbers of cases in repositories to decipher the genetic and other risk factors

that result in drug-induced diseases so that they can someday be predicted and prevented would be a fruitful approach in this area.

Occupational Exposures

Limited but growing epidemiologic and experimental data have linked a number of occupational exposures to autoimmune diseases (Table 5). Silica, solvents, pesticides and ultraviolet radiation are of particular concern.[5,10] Strong associations have been reported in investigations of silica dust and rheumatoid arthritis, lupus, scleroderma and antineutrophil cytoplasmic autoantibody (ANCA) associated glomerulonephritis.[44]

Table 5. Occupational exposures associated with autoimmune diseases in epidemiologic studies

Exposure	Disease	Summary of Results
Crystalline silica	Scleroderma	3-fold increased risk in 4 occupational cohort studies; mixed results in 5 population-based case-control studies
	Rheumatoid arthritis	3-fold (or higher) increased risk in 5 occupational cohort studies
	Lupus	>10 fold increased risk in 3 occupational cohort studies
	ANCA + vasculitis	4-fold increased risk in 3 case-control studies
Ionizing radiation	Autoimmune thyroid disease	~3.5 risk in females among 4299 workers in Pomerania.
Solvents	Scleroderma	Mixed results, but some evidence of 2-3 fold increased risk with specific solvents (e.g., paint thinners and removers, trichloroetheylene) and with "any" solvent
	Undifferentiated connective tissue disease	2-fold increased risk with paint thinners and removers, mineral spirits; 3-fold increased risk with specific solvent-related occupations
	Rheumatoid arthritis	Weak or no association with specific solvents, but 2-fold increased risk among spray painters and lacquer workers
	Multiple sclerosis	2-3 fold increased risk with solvent exposures in most studies
Mercury	Lupus	~3 fold risk in the Carolina Lupus Study
Mineral oil	Rheumatoid arthritis	Slight increased risk in Swedish men
Pesticides	Rheumatoid arthritis	Weak associations (relative risks <2.0 seen with pesticide exposure and in farmers and horticultural workers
	Lupus	~4 fold risk after mixing pesticides
Ultraviolet radiation	Multiple sclerosis	Reduced risk (OR 0.74) of multiple sclerosis and mortality with increased occupational exposure to sunlight

Reviewed in reference 10 and reference 5 with additional information from reference 81. OR: odds ratio; ANCA: antineutrophil cytoplasmic antibodies.

Less strong associations are seen for solvent exposures (in scleroderma, undifferentiated connective tissue disease and multiple sclerosis) and for farming or pesticide exposures (in rheumatoid arthritis).

Assessing the role of occupational exposures in disease presents a number of problems. These include: (1) there are few biomarkers for specific chemical exposures acutely and none that capture lifetime cumulative exposures: (2) few validated and easy to use occupational exposure questionnaires; (3) limited power of relatively small studies resulting in imprecise risk estimates; and (4) possible confounding from multiple exposures in occupations that makes it difficult to ascertain the primary associations.

Non-Occupational Exposures

Many other non-occupational exposures have been studied and have been proposed to be associated with autoimmune diseases (Table 6). Evidence supporting these proposed associations include case reports, case series, in vitro assays, animal model studies and epidemiologic investigations, yet most have not been confirmed by appropriate independent study.[45]

Smoking tobacco has been reported to result in increased risks of rheumatoid arthritis, autoimmune thyroid disease and Crohn's disease in several studies, but inconsistent results were found in studies of smoking and SLE. Of interest, smoking appears to be associated with a reduced risk of ulcerative colitis implying that different compounds in tobacco smoke may alter risk for different diseases in a variety of ways or have different effects in different genetic backgrounds.

Heavy metals, including mercury, cadmium, gold salts and beryllium have been associated with different diseases, some of which have features of autoimmunity. Also, animal models have convincingly demonstrated inflammatory and autoimmune responses to these compounds, which appear to differ in different genetic backgrounds.[46]

Vaccines have raised controversy relating to concerns about their involvement in a number of different diseases. Because they are foreign proteins often injected with adjuvants into muscle to induce immune responses, immune-mediated adverse events would not be unexpected.[47,48] A number of autoimmune diseases have been reported to develop following various vaccinations, yet only a few have been deemed associated with disease by the Advisory Committee on Immunization Practices[49] and are now compensated by the National Vaccine Injury Compensation Program (http://www.hrsa.gov/vaccinecompensation/). These include chronic arthritis after rubella virus vaccines, thrombocytopenic purpura after measles vaccines and brachial neuritis or Guillain-Barre syndrome after certain swine flu or tetanus vaccines. While other illnesses are possibly caused by immunizations, as suggested by case reports or animal models, most epidemiologic studies have not shown significant associations.[50]

Medical devices, particularly silicone breast implants, remain controversial agents that have been proposed to be associated with multiple autoimmune or connective tissue disorders. Studies have been hampered by litigation involved in adverse events following silicone implants and the lack of adequate regulatory review prior to their initial use. Nonetheless, most studies, although underpowered for rare disorders, have not found significant associations with common autoimmune diseases.[51,52] Yet, some investigators believe that rare or atypical autoimmune diseases and fibromyalgia remain inadequately studied.[53,54] An investigation of 37 patients with the rare autoimmune muscle disease called myositis that developed after a variety of silicone implants found significantly different

Table 6. Non-occupational exposures proposed as possible risk factors for autoimmune diseases

Exposure	Disease	Comments and References
Cigarette smoking	Rheumatoid arthritis	Studies suggest relative risks of 1.5-3 with a greater effect in men, seropositive disease and those with the shared RA epitope[82-84]
	Autoimmune thyroid disease	Meta-analyses suggest 2-3 fold increased risks of Grave's and Hashimoto's[85]
	Inflammatory bowel disease	Smoking increases risks for Crohn's disease but decreases risks for ulcerative colitis[86]
	Lupus	Increased risk in current smokers[87]
Dietary gluten	Celiac disease	Gluten-induces disease in genetically susceptible hosts[88]
Dietary meat and protein	Rheumatoid arthritis	Increased risk noted in a European study[89]
Heavy metals	Multiple syndromes	"Pink disease" (acrodynia) and glomerulopathy from mercury toxicity; related syndromes with elements of autoimmunity from cadmium and gold salt toxicity; granulomatous pneumonitis from beryllium exposure; support for genetic risk factors in animal models[90-92]
Hormones	Lupus	Mixed results but larger studies suggest a trend for estrogens[5]
Vaccines	Multiple syndromes	Arthritis after rubella virus vaccines; thrombocytopenia after measles vaccines; Guillain-Barre syndrome after swine flu vaccine and tetanus; controversy remains over others[50]
Collagen implants	Myositis	In one study OR = 5.1; 95% CI, 2.3 to 9.6 for all forms of myositis[56]
Silicone implants	Multiple syndromes	Most studies do not find associations with common autoimmune diseases;[51,52] rare or atypical connective tissue disease and fibromyalgia remain inadequately studied.[53,54]
Stress	Grave's disease	Stressful life events preceding the diagnosis were significantly higher than controls (OR = 6.3, CI = 2.7–14.7.[59]
Ultraviolet radiation	Lupus	Increased risk with >1 severe sunburn in youth[93]
	Dermatomyositis and anti-Mi-2 antibodies	Positive correlation of the proportion of dermatomyositis and anti-Mi-2 antibodies with global surface sunlight intensity on 4 continents [24] and in women in the US.[25]

OR: odds ratio; CI: 95% confidence interval; ANCA: antineutrophil cytoplasmic antibodies; Modified from reference 62.

immunogenetic backgrounds compared to 453 myositis patients without implants.[55] Of interest, collagen implants have also been associated with the development of myositis.[56] And, recent reports of multiple cases of scleroderma following silicone breast implants suggest that additional studies in this area may be warranted.[57]

Stressful life events may boost immune responses through induction of TNF-alpha, IL-1 and IL-8 and by inhibiting TGF-beta production.[58] Therefore, conditions that are associated with significant changes in stress system activity may modulate the neuroendocrine-immune axis and perturb systemic cytokine balances resulting in proinflammatory changes and disease induction. Anecdotal reports suggest that significant stressful life events have preceded the development of many autoimmune diseases. A large population-based, case control study of Grave's disease showed that patients had more negative life events in the 12 months preceding the diagnosis of Grave's and negative life-event scores were also significantly higher.[59] Other diseases have not been adequately studied.

THE IMPORTANCE OF GENE-ENVIRONMENT INTERACTIONS IN AUTOIMMUNE DISEASES

Most common human diseases likely arise from a combination of genetic and environmental risk factors and understanding these interactions is critical to defining risk and focusing preventative measures at the individual level.[14,60] The familial nature of many complex diseases suggests an underlying genetic susceptibility, but environmental or epigenetic factors must be important since in many conditions monozygotic twins are often not concordant for disease.[61] The current scientific view is that virtually all clinical traits will show gene-environment interaction when studied in adequate detail with appropriately powered analyses. Yet, these data are not available in adequate numbers of individuals to allow for these analyses to be performed for most diseases. Evidence of statistical interactions between genetic and environmental risk factors is often used as evidence for the existence of an underlying mechanistic interaction. Gene-environment interactions may be additive or multiplicative or they may be negative (or antagonistic) when protective genes or protective environmental exposures interact. Figure 1 depicts the possible interactions of environmental agents and genetics to result in the development of autoimmune phenotypes and emphasizes the role of possible protective factors.

The complex pattern of inheritance of most human diseases suggests that interactions of multiple unlinked genes and likely multiple environmental factors are needed to produce the phenotype.[8] Genetic hallmarks of complex phenotypes are: (1) that the alleles associated with implicated polymorphic genes are alone neither necessary nor sufficient for the development of disease and (2) that these alleles are not severe, null mutations, but rather are often functional and relatively common in the general population. Data suggest that most of these alleles have arisen because of random mutation and positive selection in past environments, but these same alleles are often disadvantageous in our current environments that include many drugs and other chemical compounds, as well as infectious agents, that were not present during most of human evolution.[62] Thus, the understanding of environmental factors and their effects should always consider the contributing roles of genetic risk and protective factors.[63]

POSSIBLE MECHANISMS BY WHICH ENVIRONMENTAL AGENTS MAY INDUCE AUTOIMMUNE DISEASE

The mechanisms for the role of environmental agents in inducing autoimmune diseases are poorly understood. Yet, a variety of theories have been put forward to explain how

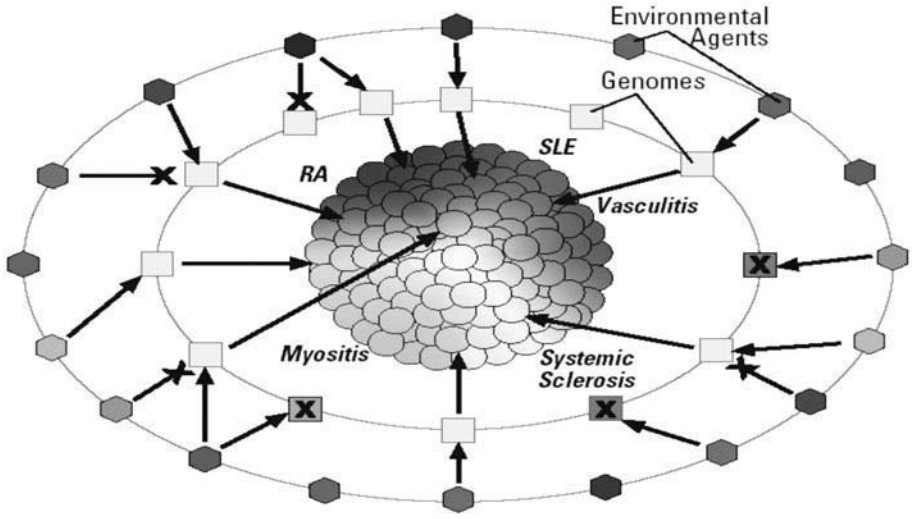

Figure 1. Possible phenotypes of autoimmune diseases resulting from different gene–environment interactions. Each autoimmune disease as currently defined is composed of multiple phenotypes, which in their indivisible form could be called elemental disorders. These are represented here as spheres, each of which would be defined by a unique combination of symptoms, clinical signs and laboratory abnormalities. Each elemental disorder could result from a unique pathogenesis as a result of the interactions between the necessary and sufficient genetic and environmental risk factors. Each box represents an individual's genome and each hexagon a particular environmental exposure. As shown, certain combinations of genotypes and environmental exposures induce specific disease phenotypes, while other combinations have no effect or can even be protective (as indicated by an X). RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. Reproduced with permission from reference 5.

xenobiotics and other exposures may induce disease.[45] The diversity of these theories themselves, however, points to the lack of understanding of even the most carefully-defined environmentally associated diseases. Evidence also implies that different pathogenic mechanisms are likely at work in different syndromes.

One popular theory for how chemicals may induce autoimmunity is their binding to self molecules to induce novel structures, which then overcome immune tolerance. This "hapten hypothesis" is supported by clinical and laboratory evidence in the case of drug-induced hematologic autoimmune disorders.[64] Agents may also alter the cellular level or location of autoantigens or decrease their removal. An example of this would be ultraviolet radiation, which is known to upregulate certain autoantigens, alter their subcellular distribution and induce apoptotic cells, which are cleared at a slower rate in autoimmune individuals.[65-68] Post-translational modification of proteins may also induce an immune attack. This has been postulated to occur when tobacco smoke alters broncho-alveolar cell proteins by inducing citrillination, changing the amino acid arginine to citrulline. Such citrullinated proteins are common targets for autoantibodies in rheumatoid arthritis.[69] Molecular mimicry is defined as an immune response to an environmental agent that cross-reacts with a host antigen and this process is likely responsible for rheumatic fever following β hemolytic streptococcus infection as well as ant-Sm autoantibodies in lupus patients following EBV infection.[5] Other studies have found that over expression of CD70, a T-cell costimulatory molecule encoded by the *TNFSF7* gene, on $CD4^+$

lupus T cells, as well as on procainamide- and hydralazine-treated T cells, is due to demethylation of a genetic element that suppresses CD70 expression when methylated.[70] These and other related findings suggest that epigenetic modifications following exposure to drugs, chemicals and other environmental agents may contribute to the induction of autoimmunity. Direct activation of the immune system occurs after the use of a number of therapeutic cytokines, including Type I interferons and interleukins and is the likely mechanism for the development of a number of autoimmune diseases following their use.[71,72] Other agents, including crystalline silica and certain silicones, also likely induce autoimmunity and autoimmune disorders via their direct effects on immune activation.[73]

An overall understanding of mechanisms for environmental effects needs to consider the concept of heterogeneity within the currently defined autoimmune diseases. A hypothesis that addresses this issue has been termed the "elemental disorder hypothesis". This concept posits that each autoimmune disease, as currently recognized, contains many stable and distinct phenotypes, which in their indivisible form are referred to as elemental disorders.[5,74] In this scenario, an elemental disorder is defined as a unique sign-symptom-laboratory complex that results from a distinct pathogenesis as a result of the interaction of the necessary and sufficient genetic and environmental risk factors (Fig. 1). If this concept is true, elemental disorders are likely complicating most studies of disease today via "comparisons of apples and oranges". Identifying elemental disorders should greatly increase the homogeneity of populations under study and significantly decrease the numbers of individuals needed for genetic, environmental, pathogenic and therapeutic studies. In the future, elemental disorder identification could allow for the prevention of some illnesses by avoidance of environmental risk factors or via gene or other therapy to correct deleterious genetic risk factors. The definition of genetic and environmental protective factors is equally important as these could also be harnessed to possibly prevent disease.

As mentioned before, many of the principles of carcinogenesis could be applied to the development of autoimmune diseases. The general concept here is that the pathogenic process could involve multiple sequential stages and that each stage may be dependent on the effects of prior agents. Beginning with genetic susceptibility, the action of one or more initiators of immune dysregulation that induce autoantibodies (autoimmunity) may first be necessary, followed by the subsequent effects of one or more promoters that would result in clinical pathology (autoimmune disease) and finally the effects of one or more sustainers of inflammation that would maintain autoimmune disease over time.[62]

CONCLUSION

Understanding the interactions of those elements that are necessary for autoimmune disease development offers the promise of preventing or treating autoimmune diseases in novel ways. To accomplish this, however, critical questions remain to be answered. Which particular gene-environment interactions lead to which specific clinical syndromes? What are the detailed pathogenic mechanisms involved? Is every autoimmune disease, as currently understood, actually composed of many subsets or "elemental disorders", each of which may be defined by a unique pathogenesis resulting from interactions of the necessary and sufficient risk factors? Can selected autoimmune diseases be better treated, cured, or even prevented through answers to some of the above questions?

Our complex and increasingly artificial environment complicates exposure assessments. Because more than 80,000 chemicals are registered for use in commerce in the United States to be included in our foods, personal care products, drugs, household cleaners and a host of industrial processes, we do not know the full range of environmental agents we are exposed to on a daily basis. Additionally, the long term effects of most of these chemicals on the immune system are unknown.

Parallel to whole genome scans, which have revolutionized our thinking about genetic risk factors for disease, the possibility of whole environmental scans should also be explored. Such global approaches appear daunting today, but new integrated systems biology methods, along with nanotechnology techniques for real-time individual analyte measurements in multiple tissues and worldwide geographic information systems and remote sensing measurements offer promise in this area.[75,76] Additionally, integrating validated exposure questionnaires with biomarkers for exposures from RNA expression signatures, proteomic or metabolomic analyses and antibody microarrays to capture the immune memory of a lifetime of exposures, could revolutionize our capacity to define environmental risk factors in the future.[62]

Many other challenges have prevented further understanding of the environmental risk factors that might trigger autoimmune diseases in genetically susceptible individuals. Nevertheless, a number of coordinated initiatives may be useful in overcoming these obstacles and making more progress in the future. These include: developing more validated exposure assessment tools and bioassays; increased training in the evaluation of environmental exposures; additional data on the incidence, prevalence and demographic information for autoimmune diseases; integrated databases and biorepositories; better coordination between animal model and human studies; increased worldwide integration of environmental exposures with geographic information systems. Critical for all these efforts is increased funding for understanding the environmental exposures that initiate, promote and sustain autoimmune disorders. These investments are likely very cost effective as they would have important clinical and financial implications for improving the public health.

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