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Mechanisms of Disease: environmental factors in the pathogenesis of rheumatic disease

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SUMMARY

Most rheumatic diseases are complex disorders for which pathogenetic mechanisms are poorly understood. Nonetheless, increasing evidence suggests that many of these illnesses result from one or more specific environmental exposures in genetically susceptible individuals. Although much progress has been made over the past few decades in advancing our knowledge of the genetics of rheumatic diseases, few studies have assessed environmental features and understanding of which exposures are important in pathogenesis remains limited. In this article, we review the difficulties inherent in deciphering the interacting environmental and genetic risk factors for rheumatic diseases, the current state of knowledge of infectious and noninfectious risk factors, possible mechanisms by which environmental exposures might induce pathologic processes and future directions. The advances in technologies and statistical approaches, development of collaborating consortia and focused resources that have resulted in the explosion of genetic information must now be applied to environmental studies so we can eventually interrupt pathogenesis before the onset of disease and transform the practice of medicine from curative to pre-emptive paradigms.

KEYWORDS environment, exposures, occupation, rheumatic disease, risk factors

REVIEW CRITERIA

We systematically searched in MEDLINE, EMBASE, ISI Web of Science and major textbooks for original articles or reviews published between 1996 and 2006 that discussed case-controlled investigations assessing environmental risk factors for systemic rheumatic diseases. Key search terms used included "rheumatoid arthritis", "systemic lupus erythematosus", "dermatomyositis", "polymyositis", "scleroderma" and "vasculitis"; these terms were searched for alone and in combination with "epidemiology", "incidence", "prevalence", "frequency", "occurrence", "etiology", "environment", "infectious" and "occupation". All papers identified were English-language, full manuscripts. We also searched the reference lists of identified articles for additional relevant papers.

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INTRODUCTION

Despite the growth in knowledge of the genetics of systemic rheumatic diseases, understanding of the role of the environment in the pathogenesis of these conditions is limited. In this article, we discuss appropriately controlled studies of the association between environmental agents and the development of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, myositis and vasculitis syndromes. Environmental risk factors for a disease are typically identified when a new clinical disorder is recognized that develops after an exposure, with the disorder often resolving when the exposure is removed (dechallenge) and recurring after re-introduction of the same exposure (rechallenge). Standard methods for identifying and defining risk factors for environmental illnesses have been proposed;[1] however, a systematic approach has yet to be implemented by all investigators. Other difficulties associated with defining environmental risk factors for rheumatic diseases include a low number of validated exposure biomarkers and other environmental assessment tools, the limited formal training physicians receive in environmental medicine, the rarity of most rheumatic diseases and the lack of organized national databases for rheumatic diseases that would facilitate epidemiologic investigations. Hence, appropriately powered epidemiologic studies for identifying environmental risk factors can require large sample sizes, resulting in costly or impractical studies for most of these illnesses.

The concept of phenotypic disease heterogeneity is central to deciphering pathogenesis. As depicted in Figure 1, not only do rheumatic diseases differ, but they can also share many signs and symptoms, resulting in overlapping disease states.[2] Viewing each rheumatic disease as a collection of many discreet phenotypes or elemental disorders, each of which is defined by unique symptoms, signs and laboratory findings, might, therefore, be more appropriate. By use of this approach, each elemental disorder would develop after the required interactions

between genetic and environmental factors have occurred. Data suggest that genetic and environmental risk factors and gene–environment, environment–environment and gene–gene interactions are all important for disease expression.[3] The presence of susceptibility factors, as well as the absence of protective factors, probably have crucial roles in defining disease development.[4] In addition to their role in initiating disease processes, environmental exposures might be important in modulating the expression or severity of rheumatic diseases.

Despite the difficulties in defining environmental risk factors, the many clear cases of drug-induced SLE spurred investigations that led to the association of a number of factors with rheumatic diseases.[5] The evidence comes from diverse sources, including case reports, cohort studies, investigations of the effects of environmental agents *in vitro* and in animal models, and case–controlled studies. Here, we limit our discussion to publications that provide epidemiologic data on environmental risk factors from controlled studies reporting on relative risks or odds ratios with CIs. Importantly, these epidemiologic studies provide estimates of risk by association but do not establish causality.

Environmental exposures vary widely and could be considered to include all nongenetic factors. Commonly, infection, chemicals or drugs are considered to be characteristic environmental factors; however, stressful life events, other lifestyle factors and incidental exposures, such as ultraviolet light, might also be environmental risk factors for rheumatic diseases. We will discuss risk factors for rheumatic diseases in three categories: occupational, infectious and nonoccupational and noninfectious.

OCCUPATIONAL EXPOSURES AND RHEUMATIC DISEASES

The epidemiologic evidence for the association between occupational risk factors and systemic rheumatic diseases is summarized in Table 1. Because exposures are frequently of long duration, there is growing interest in studying health hazards in the workplace, to provide a working environment that is not detrimental to health. As is the case for many exposures, however, most individuals are not aware of the specific agents to which they have been exposed during the working day and, without validated biomarkers, many of these studies rely on indirect estimates of exposure.

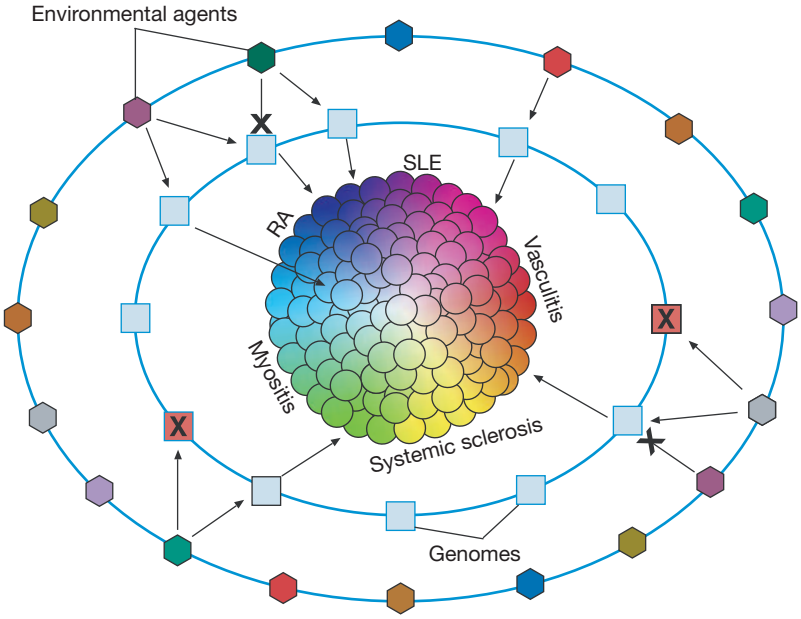


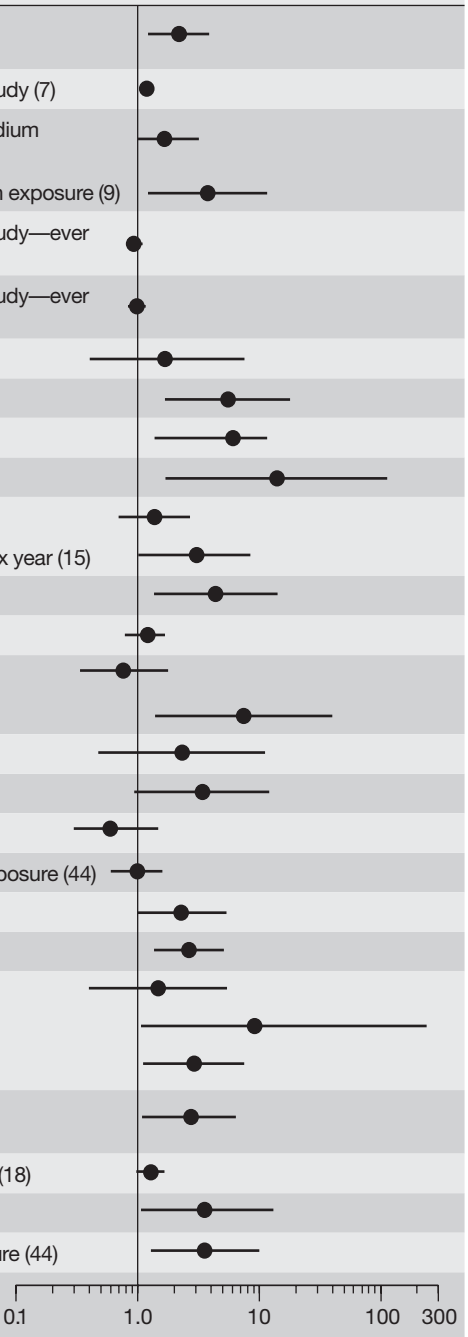
Figure 1 Possible phenotypes of rheumatic diseases resulting from different gene–environment interactions. Systemic rheumatic diseases can be composed of multiple phenotypes or elemental disorders, represented here as spheres, each of which might be defined by unique combinations of symptoms, signs and laboratory abnormalities. Each phenotype could result from different pathogeneses, as a result of the interactions between genetic and environmental risk factors. Each box represents an individual's genome and each hexagon represents a particular environmental exposure. Some combinations of genotypes and environmental exposures induce certain disease phenotypes, whereas other combinations might have no effect or could be protective (as indicated by an 'X'). RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

People who work in industries involving soil and rock, such as quarry work and mining, can have high levels of exposure to crystalline silica. Exposure to this substance is associated with silicosis, chronic obstructive pulmonary disease, pulmonary tuberculosis and lung cancer. Although some of the first descriptions of the environmental factors of rheumatic diseases nearly 100 years ago involved silica exposure and systemic sclerosis,[6] later studies suggested that silica exposure is associated with many other rheumatic diseases, including RA, SLE and vasculitis.

Support for an association between exposure to silica and development of RA comes from two large studies that examined data from the US National Occupational Mortality Surveillance (NOMS) system or identified cases in a defined area of Sweden.[7,8] In addition, a population-based, case-controlled study of 265 SLE cases in southeastern US observed an effect of the intensity of silica exposure (medium and high) in patients with SLE.[9] Conversely, the NOMS study did not find an association between

Table 1 Epidemiologic studies of occupational exposures and systemic rheumatic diseases.

Exposure	Rheumatic disease	Comments (reference)	Odds ratio or relative risk (bars, 95% CI limits)
Crystalline silica	RA	Swedish study—exposed men (8)	
	RA	US National Occupational Mortality Surveillance Study (7)	
	SLE	Southeastern United States study, 265 cases—medium exposure (9)	
		Southeastern United States study, 265 cases—high exposure (9)	
	SLE	US National Occupational Mortality Surveillance Study—ever exposure (7)	
	Systemic sclerosis	US National Occupational Mortality Surveillance Study—ever exposure (7)	
	Systemic sclerosis	Italian study, 55 selected cases (11)	
	Systemic sclerosis	French study, 80 consecutive cases (10)	
	Wegener's vasculitis	Italian study, 16 cases (12)	
	ANCA + glomerulonephritis	Belgian study, 16 cases (14)	
	Primary systemic vasculitis	UK study, 75 cases, high silica exposure ever (15)	
		UK study, 75 cases, high silica exposure in the index year (15)	
	ANCA + small-vessel vasculitis	US study, 51 cases (13)	
Pesticides	RA	US study, 135 cases, mixing or applying (16)	
	SLE	Carolina Lupus Study, *n* = 265, applying (44)	
		Carolina Lupus Study, *n* = 256, mixing (44)	
	ANCA + small-vessel vasculitis	US study, 51 cases (13)	
	Wegener's granulomatosis	US study, 101 cases (58)	
Solvents	RA	US Agricultural Health Study, 135 cases (16)	
	SLE	Carolina Lupus Study, *n* = 265, high or moderate exposure (44)	
	Systemic sclerosis	Italian study, 55 selected cases (11)	
	Systemic sclerosis	French study, 80 consecutive cases (10)	
	Systemic sclerosis	Italian study, organic solvents (17)	
		UK study, organic solvents (17)	
		South Carolina study, men-only association (17)	
	Primary systemic vasculitis and Wegener's granulomatosis	US study, 75 cases, high ever exposure (15)	
Mineral oil	RA	Swedish study, 1,419 cases, men-only association (18)	
Fumes	Systemic sclerosis	French study, 80 consecutive cases (10)	
Mercury	SLE	Carolina Lupus Study, *n* = 265, self-reported exposure (44)	



Abbreviations: ANCA, antineutrophil cytoplasmic antibody; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

exposure to silica and development of SLE or systemic sclerosis.[7] A French and Italian study found mixed associations between silica exposure and development of systemic sclerosis.[10,11] Three investigations examined silica exposure and vasculitis in relatively small populations and reported an association.[12–14] A study that included 75 cases of primary systemic vasculitis did not find a high level of exposure to silica at any time during a working lifetime was a risk factor for developing vasculitis; however, a high level of exposure to silica during the year

symptoms of vasculitis were first experienced was a risk factor.[15]

Other occupational exposures that have been studied as possible risk factors for rheumatic disease include pesticides, solvents, mineral oil, fumes and heavy metals. Pesticides are chemical substances used against pests, insects and plant or human pathogens; these compounds are toxic to humans but must be prepared before application, which can result in exposure. Published studies of the relationship between pesticides and rheumatic diseases are few and have reported mixed findings. The Carolina Lupus Study represents the largest case-controlled study, including 265 cases of SLE. The study did not report an association between applying pesticides and development of SLE, but it did find that mixing pesticides was a risk factor for development of SLE.[9]

Solvents are liquids that dissolve a solid, liquid or gas and include organic solvents used in dry cleaning (e.g. tetrachloroethylene), alcohols, aromatic hydrocarbons and paint thinners (e.g. toluene and turpentine), nail polish and glues (e.g. acetone, methyl acetate and ethyl acetate) and degreasers (e.g. hexane and petrol ether). In epidemiologic studies, solvents have been associated with RA, SLE, systemic sclerosis and vasculitis (Table 1).[10,11,15–17]

Exposure to mineral oils, complex mixtures of petroleum products that include motor oils and other lubricating oils results in a 30% increased risk of developing RA.[18] The observed risk was primarily reported for men with rheumatoid-factor-positive RA**.** An increased risk for systemic sclerosis was observed in workers who had been occupationally exposed to welding fumes (odds ratio [OR] 3.74, 95% CI 1.06–13.18).[10] Occupational exposure to mercury, which induces autoimmunity in animal models, was noted to be a risk factor for SLE, but, owing to the small number of exposed subjects, this effect could not be separated from exposures to other potential risk factors.[19]

INFECTIONS AND RHEUMATIC DISEASES

The seasonal onset and geographic clustering of some rheumatic diseases has suggested a possible role for infectious agents as triggers of disease. There are many descriptions in the literature of individual patients with rheumatic diseases that are suspected to have been caused by a microbe, but epidemiologic evidence for the role of specific infections in rheumatic diseases is relatively sparse. The evidence offered is generally the presence of a serologic response, recovery of an organism or identification of part of the amplified genome of a microbe; however, many studies did not include appropriate control populations. No infectious agent that has been identified consistently induces any rheumatic illness in a specific population. Hepatitis B, for example, is known to be associated with polyarteritis nodosa in only 1–5% of infected individuals.[20] The associations between infectious agents and rheumatic diseases based on epidemiologic data, are listed in Table 2.

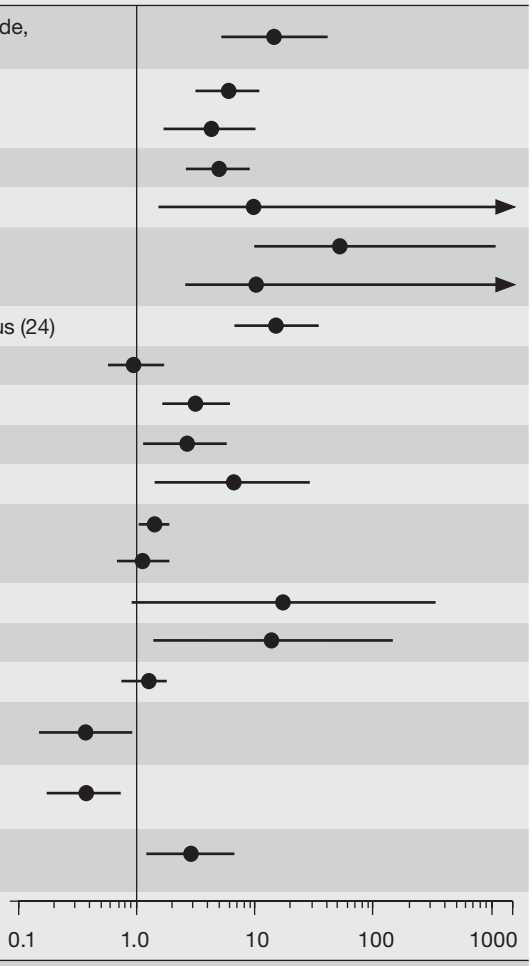
Several appropriately controlled studies suggest an increased risk of RA and SLE after measuring the presence of antibodies to various viral components of the Epstein–Barr virus (EBV), cytomegalovirus, or and human herpesvirus in patients' sera,[21–24] or using questionnaires and interviews to gather information from patients.[25–27] Some of the strongest evidence for infectious associations with rheumatic diseases come from studies of EBV. This ubiquitous virus has been implicated in numerous illnesses. The evidence that suggests EBV is associated with rheumatic diseases includes an increased presence of antibodies to viral peptides and the ability to amplify EBV genomes by polymerase chain reaction (PCR) in more patients with rheumatic disease than controls. Our increased knowledge of EBV and genes encoding autoantigens has strengthened the evidence for an association between EBV and SLE.[28,29]

Parvovirus is well known for inducing reactive polyarthritis that spontaneously resolves in most cases, but several investigations have suggested parvovirus might be an etiologic agent in RA.[30,31] In addition, in a study of children with an acute onset of arthritis, those with IgM antibodies to parvovirus B19 developed a chronic arthritis indistinguishable from juvenile RA, whereas those who lacked IgM antibodies to parvovirus B19 did not progress to a chronic form of RA.[32] In a carefully conducted study, however, Mamyrova *et al.*[33] did not find an association between serum IgG antibodies to parvovirus B19 and juvenile dermatomyositis.

The 'hygiene hypothesis' posits that the increase in the prevalence of immune-mediated diseases in developed countries might be related to an early-life environment that is relatively deficient in microbial flora. This hypothesis predicts that some types of infection could be protective for autoimmune diseases and, in fact, a history of recent upper respiratory tract infection was found to be protective for polymyositis and dermatomyositis (OR 0.35, 95% CI 0.17–0.71).[34]

Table 2 Epidemiologic studies of infectious agents and systemic rheumatic diseases.

Exposure	Rheumatic disease	Comments (reference)	Odds ratio or relative risk (bars, 95% CI limits)
EBV	RA	Antibodies to antiviral citrullinated peptide, 300 cases (21)	
	SLE	IgA to EBV, African American (22)	
		IgA to EBV, White >50 years (22)	
	SLE	EBV presence by PCR (23)	
	SLE	IgG to EBV—viral capsid antigen (28)	
	SLE	IgG to EBV—viral capsid antigen (29)	
		EBV viral DNA (29)	
Cytomegalovirus	SLE	Seropositiivity to human cytomegalovirus (24)	
	SLE	IgG to human cytomegalovirus (28)	
Human herpesvirus	SLE	Questionnaire—VZV past exposure (25)	
	SLE	Questionnaire—VZV past exposure (26)	
	SLE	Chart review and interview VZV (27)	
	SLE	IgG to HSV-1 (28)	
		IgG to HSV-2 (28)	
Parvovirus B19	RA	B19 DNA in synovium (30)	
	RA	IgM to B19 >6 months duration (32)	
	JIA	76 monozygotic twins, IgG to B19 (31)	
	Juvenile dermatomyositis	No association with IgG to B19 (33)	
URI (one year prior)	Polymyositis and/or dermatomyositis	Questionnaire, case–sibling control (34)	
Streptococci (household exposure)	Childhood myositis	Case review (35)	



Abbreviations: EBV, Epstein–Barr virus; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SLE, systemic lupus erythrematosus; URI, upper respiratory infection; VZV, varicella zoster virus.

Conversely, bacteriologically confirmed cases of streptococcal infection could increase the risk of childhood myositis.[35] Further carefully designed and adequately powered studies are needed to better define the infectious agents that might be risk or protective factors for rheumatic disease.

OTHER ENVIRONMENTAL EXPOSURES AND RHEUMATIC DISEASES

Although the list of nonoccupational, noninfectious agents that could be involved in the development of rheumatic diseases is large, surprisingly few controlled epidemiologic studies have been published in this area (see Supplementary Table 1 online). On the basis of dechallenge–rechallenge scenarios in case reports or series, drugs are some of the best-characterized nonoccupational, noninfectious risk factors. The classic examples of causal agents in drug-induced lupus-like disorders are hydralazine and procainamide, although many other drugs have been implicated.[5] Acetylator status appears to be important in development of these drug-induced disorders, because slow acetylators are at increased risk.

Female hormones have been associated with SLE through several lines of evidence that include studies in animal models, a reportedly reduced risk of SLE after hysterectomy[36] and an increased risk of SLE with menstrual irregularity or menarche at 15 years or older.[37,38] Case-controlled studies examining the use of oral contraceptives and hormone-replacement therapy suggest a weak influence of exogenous female hormones.[27,39,40]

Ultraviolet (UV) radiation has been associated with increased disease activity in both SLE and dermatomyositis, but few studies have assessed the role of UV radiation as a trigger for disease onset. One investigation found that repeated sunburn might be a risk factor for the development of SLE.[41] Additionally, a worldwide study of polymyositis and dermatomyositis referral centers demonstrated that, of the environmental variables evaluated, the global intensity of surface UV radiation most strongly contributed to the relative proportion of dermatomyositis cases and was strongly related to the proportion of the dermatomyositis-associated Mi-2 autoantibodies.[42] These data suggest that UV radiation exposure might modulate the clinical and immunologic expression of autoimmune diseases in different populations around the world.

Vaccines, which out of necessity share many structural features with the infectious agents that they are designed to protect against, have long been considered as possible environmental triggers of various diseases. Although the Institute of Medicine of the National Academies, Washington, DC, concluded that certain strains of the rubella vaccine can cause polyarthritis and epidemiologic data suggest associations between vaccinations and polymyositis, dermatomyositis and systemic vasculitis (see Supplementary Table 1 online), the benefit of vaccination clearly outweighs this possible risk.[43]

Curiously, hair dye has been quite well studied, being the focus of attention of six controlled studies examining the link between this potential risk factor and SLE; these trials have mostly produced negative results.[44] Smoking is an important environmental agent, but data are limited to studies of the association between smoking and RA, SLE and vasculitis. Studies suggest a greater risk of RA in those who carry shared epitope alleles, and the combined presence of shared epitope alleles and smoking confers a risk to patients with autoantibody-positive RA (i.e rheumatoid factor and anti-cyclic citrullinated peptide antibodies) but not those with autoantibody-negative RA. This risk increases further with the increasing number of copies of HLA–DRB1 shared epitope alleles the individual carries.[45,46] Diet has been implicated as a risk factor for RA by the finding that a greater intake of meat and protein is associated with development of RA and that high dietary intake of vitamin D might be associated with a lower risk of RA in older women.[47,48]

Less-well-studied environmental factors that are believed to potentially influence the onset of rheumatic diseases include stress and microchimerism. The known neuroendocrine–immune interactions, in addition to anecdotal cases of rheumatic disease developing soon after stressful life events, resulted in uncontrolled trials in this area. These studies suggested that there is the role for stress in disease pathogenesis, but it is unclear whether stress is a risk factor for developing RA, juvenile RA or SLE.[49] Microchimerism is the persistence of a low level of nonhost cells in an individual. A possible role for microchimerism in the pathogenesis of some disorders (e.g. systemic sclerosis, SLE and juvenile myositis) has been suggested by research.[50] Intriguing investigations indicated that myositis patients with and without Jo-1 myositis autoantibodies have different seasonal onsets.[51] Similar to infections, many occupational or noninfectious exposures can be seasonal, including exposures to certain pesticides, chemicals in sunscreens and some air or water pollutants. Further studies are needed to define the risk factors and mechanisms responsible for seasonal onset of rheumatic diseases.

POSSIBLE MECHANISMS

The precise mechanisms responsible for the development of environmentally-induced rheumatic disorders are unknown. Although many hypotheses for the occurrence of autoimmune phenomena after various environmental exposures have been proposed, none of the hypotheses is completely supported by direct causal evidence. Also, mechanisms thought to be involved in the initiation of the disease process might differ from the mechanisms believed to exacerbate an established illness. Discussion of all the proposed mechanisms is not within the scope of this article, so we have summarized the major categories of potential mechanisms that are supported by the most extensive evidence.

Interference with immune tolerance

Loss of self-tolerance, causing an auto-inflammatory state, is crucial for the development of systemic rheumatic diseases. Numerous studies suggest that environmental exposures affect tolerance at various stages. First, the hapten hypothesis proposes that a drug, or its reactive metabolites, binds to certain proteins, thereby changing the immunogenicity of the

proteins and triggering an immune response. T-cell recognition of the hapten–protein complex is altered in such a way as to interfere with immune tolerance. Second, alteration of self-antigens or ineffective removal of apoptotic cells has been suggested as a mechanism for photosensitivity in rheumatic diseases. UV light induces apoptosis in keratinocytes that accumulate in the skin; the clearance of these apoptotic cells is delayed in people with rheumatic disease compared with normal individuals.[52] Furthermore, the extractable nuclear antigens SS-A/Ro and SS-B/La are induced on the surface of human keratinocytes by UV light, resulting in antibody binding, which might be an important inducer of antibody-dependent keratinocyte damage in patients with photosensitive cutaneous lupus.[53] Human lymphocytes that have been stimulated by silica express high levels of the death receptor Fas (CD95) and then undergo apoptotic cell death, which could result in human cells releasing, concentrating and altering autoantigens, thereby focusing an autoimmune attack.[54] Third, post-translational modifications of proteins might be involved. Citrullination, a post-translational modification of a protein by which the amino acid arginine is changed to citrulline by means of an enzymatic process, occurs in bronchoalveolar lavage cells after exposure to cigarette smoke and is believed to have a role in the generation of anticitrullinated autoantibodies following smoking. As mentioned previously, the combined presence of these antibodies in individuals with the appropriate genetic risk factors can confer a risk to patients with RA who smoke[45]

Activation of the immune system

Evidence that environmental exposures might directly activate the immune system and result in autoimmune disease comes from several lines of investigation. First, it is probable that many cases of rheumatic disease that occur after therapeutic cytokine administration and resolve on dechallenge are the result of direct immune activation by those cytokines. Second, studies show that respirable silica particles are phagocytized by alveolar macrophages, leading to cellular activation and the release of soluble mediators, such as chemokines and proinflammatory cytokines, including tumor necrosis factor, interleukin-1β and transforming growth factor β.[55] Incubation of silica and silicate with isolated human T cells can cause polyclonal lymphocyte activation *in vitro*.[54] Third, drugs can alter gene activity by influencing DNA. In general, DNA methylation acts to suppress gene activity and serves to regulate genes that are potentially harmful to the functions of the cell. Both hydralazine and procainamide are examples of DNA methylation inhibitors that promote expression of genes that normally are silenced.[30]

Molecular mimicry

Molecular mimicry is characterized by an immune response to an environmental agent that cross-reacts with a host antigen. The best epidemiologic evidence for molecular mimicry in human disease is the example of β hemolytic streptococcus infection and subsequent rheumatic fever.[56] Perhaps some of the strongest data in the rheumatic diseases come from investigations of EBV and SLE. James *et al.*[28] described an increased prevalence of antibodies to EBV in patients with SLE, compared with matched healthy controls. Further investigations found a cross-reactivity between SmB' and SmD1 lupus autoantigens and sequences of EBV nuclear antigens (EBVNA). Rabbits immunized with small sequences of either of the two cross-reacting antigens Ro or EBVNA produced antibodies to both antigens and developed leukopenia and thrombocytopenia.[57] Because of the epidemiologic association between EBV and SLE, it is possible that molecular mimicry could explain how an EBV-induced immune response to EBVNA could result in lupus autoantibodies and subsequent disease.

It is almost certain that a single mechanism does not account for how all environmental exposures trigger disease and it could be that combinations of the above mechanisms result in the pathogenic effects in different disorders. As studies of autoimmunity have shown, most perturbations of the immune system alter many other processes. These alterations involve antigen recognition and processing, cell signaling and cytokine production, for example. Advances in systems biology approaches have led to the use of combinations of comprehensive genomic, proteomic and metabolomic assays, making it plausible that the complex molecular signatures of a number of environmental exposures could soon be revealed. Such information could assist us in understanding the etiologic mechanisms of environmentally induced disease.

CONCULSIONS AND FUTURE DIRECTIONS

Case reports, case series, *in vitro* studies, experiments in animal models and epidemiologic investigations all support a role for the environment in development of rheumatic diseases. Nevertheless, our understanding of the link between environmental risk factors and rheumatic diseases is limited for a number of reasons, including the phenotypic and pathogenetic heterogeneity of rheumatic diseases and a poor capacity to quantitatively assess environmental exposures and the probable role of gene–environment, gene–gene and environment–environment interactions in the etiology of these complex illnesses.

There are many approaches that could enhance the capacity to understand environmental risk factors for rheumatic disease, as follows: improving global collaborations to make the best use of limited patients and resources and exploiting the naturally occurring variation in environmental and genetic factors around the world; careful phenotyping of larger populations of rheumatic disease patients and developing more detailed databases and specimen repositories for collaborative use; standardizing and validating biomarkers and questionnaires, to reliably quantify environmental exposures; incorporating environmental studies into genetic investigations to understand gene–environment interactions; and focusing additional resources in novel coordinated ways into all these areas. Just as whole-genome scans have revolutionized our understanding of genetic risk factors for disease, the possibility of whole-environmental scans—which might be approximated by 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 the capacity to define environmental risk factors in the future. Although such approaches will require significant additional research efforts and dedicated resources over an extended period, this should be a cost-effective investment that will eventually provide the understanding needed to evolve to an era in which medicine will be predictive, personalized and pre-emptive, ultimately enabling the prevention of many diseases.

Supplementary information in the form of a table is available on the *Nature Clinical Practice Rheumatology* website.

KEY POINTS

- Complementary lines of evidence point to the role of environmental factors in the pathogenesis of rheumatic diseases
- In addition to well-described cases of drug-induced disease, epidemiologic data support a role for inhaled silica, solvents, pesticides, tobacco smoke and DNA viruses in triggering many rheumatic diseases
- Mechanisms are ill-defined for all environmentally-associated rheumatic diseases
- Integrated collaborative approaches, focused resources and better tools, including validated exposure biomarkers and questionnaires, are needed to define additional environmental risk factors and, ultimately, prevent the development of certain forms of rheumatic disease

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Competing interests

The authors have declared no competing interests.

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