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Environmental and gene-environment interactions and risk of rheumatoid arthritis

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Abstract

Multiple environmental factors including hormones, dietary factors, infections and exposure to tobacco smoke as well as gene-environment interactions have been associated with increased risk for rheumatoid arthritis (RA). Importantly, the growing understanding of the prolonged period prior to the first onset of symptoms of RA suggests that these environmental and genetic factors are likely acting to drive the development of RA-related autoimmunity long before the appearance of the first joint symptoms and clinical findings that are characteristic of RA. Herein we will review these factors and interactions, especially those that have been investigated in a prospective fashion prior to the symptomatic onset of RA. We will also discuss how these factors may be explored in future study to further the understanding of the pathogenesis of RA, and ultimately perhaps develop preventive measures for this disease.

Keywords

rheumatoid arthritis; environmental risk factors; gene-environment interactions

Introduction

While etiology of rheumatoid arthritis (RA) is unknown, a growing body of evidence suggests that it develops in individuals with inherited genetic risk factors after exposure to environmental triggers. The identification of autoantibodies and cytokines in the serum many years prior to the diagnosis of RA led to conceptualization of the development of RA as occurring in phases (Figure 1).[1–8] In this model of RA development there is an asymptomatic period of genetic risk in which environmental exposures are encountered, followed by an asymptomatic immune activation phase in which autoantibodies and

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inflammatory markers are found, likely followed by a phase of articular symptoms in absence of clearly definable arthritis, which is finally followed by the phase with signs of inflammatory arthritis (IA) that is perhaps initially unclassifiable but over time evolves to the point at which it is classifiable as RA by established criteria such as the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria.[9,10] Similar phases of development have been proposed in other autoimmune diseases such as type 1 diabetes and systemic lupus erythematosus (SLE).[11,12] This suggests a complex series of events in which a genetically susceptible host is exposed to environmental risk factors that trigger autoimmunity with autoantibody production, and a second or more event(s) or exposure(s) that might drive further immune dysregulation and eventual development of symptomatic inflammatory arthritis (IA). The interaction between genetic and environmental factors such as cigarette smoking within the subtype of ACPA positive RA[13] provides clues to disease pathogenesis, but much of the complexity of RA etiopathogenesis has yet to be delineated.

Epidemiologic research has produced convincing evidence for strong environmental risk factors for RA, including cigarette smoking[14–27], exogenous hormone use[28–36] and female reproductive factors.[28,37–41] Other exposures have also been identified as risk factors for RA including silica[42–46], air pollution[47] and periodontitis[48], and some exposures such as alcohol have been reported as protective factors[49,50] although these studies have not been widely replicated. Other factors are also associated with increased risk for RA including higher birthweight.[51,52] Furthermore, having a first degree relative (FDR) with RA increases RA risk 3- to 9-fold compared to that in the general population suggesting the influence of shared genetic and/or environmental factors.[53] Recent whole genome association studies in RA have identified > 30 novel risk loci confirmed by meta-analysis in addition to well established associations with the *HLA-DRB1* "shared epitope" (HLA-SE) alleles.[54] Gene-environment interactions between HLA-SE and potentially other risk alleles may contribute to RA pathogenesis.[5,13,55–57] Importantly, models that incorporate genetic, biomarker and lifestyle/environmental factors can now predict the risk of developing RA with greater precision than any of these factors alone.[56,58] This review will focus on validated environmental, lifestyle, and dietary exposures in the pre- RA phases prior to the objective signs of IA.

Defining the phases of development of autoimmunity, inflammatory arthritis and early rheumatoid arthritis

Multiple studies have shown that RA-related autoantibodies may be elevated up to years prior to the onset of clinically-apparent IA. Some of these studies were performed in a prospective fashion, with careful joint evaluations in currently asymptomatic individuals.[59–61] However, most of these studies are somewhat limited in their conclusions about the precise timing of elevations of RA-related autoantibodies before the onset of clinically-apparent IA because they were not performed as part of rigorous prospective evaluations of individuals at-risk for future RA.[2–8,59,62–66] Regardless, in sum these studies strongly suggest that RA develops in four distinct phases: 1) an "asymptomatic" phase of genetic risk; 2) an asymptomatic "immune activation" phase in which abnormalities of autoantibodies and biomarkers such as cytokines and chemokines are documented up to 14 years prior to RA[1–5, 7,8,66,67]; 3) a "pre-clinical" phase with abnormal biomarkers of inflammation and perhaps arthralgias[68,69]; and 4) clinically-apparent IA (symptomatic joint disease including pain, stiffness and swelling, and identifiable synovitis on examination) that may be undifferentiated arthritis (UA), or fulfill classification for RA (Figure 1).[70,71] Identifying the environmental factors associated with transitions between phases, key exposure windows leading to transition between phases, and the biologic mechanisms involved in these transitions is a challenge for the field.

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Epidemiologic study design

Studies of the environmental factors associated with RA are often conducted through a case control design in which cases with RA and healthy controls are surveyed retrospectively for environmental, lifestyle, and behavioral factors occurring prior to disease onset in cases and prior to a matched date (or age) for controls. This study design can be limited by recall bias, where cases recall and report exposures differentially than do controls.[72] Also, in case-control studies, results are reported as odds ratios which can approximate relative risk in settings where the sample size is high, but do not provide estimates of population risk. The prospective cohort design is considered less biased, as non-diseased subjects can be followed prospectively exposure assessment while asymptomatic prior to the development of RA. Examples of prospective cohort studies of RA include the US Nurses' Health Study[21], Iowa Women's Health Study[24,73], Malmo Diet and Cancer Study[39,41], and more recently Lifelines in the Netherlands. In the Norfolk Arthritis Register (NOAR, Great Britain) cohort study, risk factors for the development of Inflammatory Arthritis (IA) and RA that meets ACR criteria have been studied.[74] The advantage of prospective designs is analyses that produce relative risks, the ability to estimate population attributable risks, the ability assess repeated time-varying exposures and to study exposure windows prior to disease onset.

An alternative approach to understanding both timing of environmental exposures and their influence at points of transition in the phases of RA is prospective cohort studies of high risk individuals followed for the development of autoantibodies and immune markers. Two groups have led the field in studies of high risk first degree relatives (FDR): 1) the Studies of the Etiology of RA (SERA) in the United States[75] and 2) studies of North American Natives (NAN) in central Canada.[76] In each of these studies, FDRs are followed annually for environment, lifestyle and behavioral risk factors and the development of RA-related autoantibodies (RF and ACPA) and immune markers, as well as signs and symptoms of inflammatory arthritis (Table 1). Similar studies of FDRs are being launched in Europe.

Cigarette Smoking Exposure

Modifiable environmental factors contribute substantially to population risk of RA. Multiple case-control and prospective cohort studies have demonstrated that cigarette smoking is the strongest environmental factor linked with RA,[14,15,17–22,24–27,77] and its population attributable risk is 25% for all RA and 35% for seropositive rheumatoid factor(RF+) and anti-citrullinated protein antibody positive (ACPA+) RA.[23,27] Relative risks for cigarette smoking range from 1.6 for risk of all RA to 1.8 for risk of seropositive RA.[27] The association appears to be stronger for men than for women.[17,18,22,25,78] Furthermore, several studies demonstrate a dose-response between heavier smoking and RA, particularly seropositive RA with persistence of RA risk for 20 years after smoking cessation.[13,21,23,26,27,77] The specific mechanisms by-which smoking may be related to the generation of RA-related autoimmunity are unknown; however, there are several clues to pathogenesis. Smoking was shown to be associated with an increased levels of citrullinated proteins as well as expression of peptidyl arginine deiminase 2 (PADI2) in pulmonary cells obtained by bronchoalveolar lavage.[79] In addition, the risk of seropositive RA associated with smoking has been reported to be highest and in those who carry the *HLA-DRB1* shared epitope *(HLA-SE).*[13,77] Recent observations indicate that certain DRB1 alleles, in particular 0401 and 0404, are associated with a strong immunity to citrullinated peptides, such as vimentin or enolase peptides.[57,80–82] The specific time point in the development of RA that smoking acts to increase risk is unknown; however, in the prospective SERA project, smoking was associated with RF positivity in subjects enriched with *HLA-SE*, but no RA symptoms, suggesting that smoking may act early in immune dysregulation and may lead to future RA.[83] Smoking has been also been associated with more generalized immune

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abnormalities including alterations in T cell function[84,85], reduction in NK cells[86], impairment of humoral immunity[86,87] and elevated levels of inflammatory markers such as IL-6 and C-reactive protein[88,89] as well as elevations of rheumatoid factor (RF) in absence of RA[90]. While some of these effects associated with smoking such as impaired humoral immunity are somewhat paradoxical when trying to understand the relationship between smoking and development of RA, especially seropositive RA, in sum, these findings suggest that smoking may lead to auto-antigen generation and alteration of other inflammatory factors that in a permissive genetic background leads to the development of RA-related autoimmunity. However, the specific mechanistic details of how smoking triggers RA, including what anatomic site smoking may drive RA-related autoimmunity need further exploration, especially in prospective studies of preclinical RA. Furthermore, recent data suggesting decreased responsiveness to therapy in patients with established RA who are smokers suggests some relationship between disease development and smoking even after the onset of symptomatic IA, although the specific mechanisms of these relationships also need further exploration.[91,92]

Occupational Exposures

A case control study from Sweden, the Epidemiologic Investigation of RA (EIRA) reported an association between occupational silica exposure and RA among 276 male RA cases and 276 healthy controls with evidence for silica* smoking interaction.[42] Silica dust exposure was a risk factor only for RF+ and ACPA+ RA and not for seronegative RA. Exposure to silica dust though the respiratory tract in occupations such as rock drilling, mining and sand blasting, has been linked to RA risk in other epidemiologic studies.[43–46] High-level exposure to silica dust can cause chronic inflammation and fibrosis in the lung and other organs, and it may be that such inflammation leads to humoral immune responses and hence greater risk for seropositive RA. Furthermore, occupational exposure to other factors such as mineral oils (exposure pathways through the lung and skin) was also investigated in EIRA[93] and exposure was associated with increased risk of RF+/ACPA+ RA, and not of seronegative RA. Mineral oil can also act as an adjuvant capable of inducing experimental arthritis in rodent models and may have a similar action in humans.[94,95] Substantial exposure to inhaled organic solvents, in occupations such as upholstering, hair-dressing and concrete work, was associated with an increased risk of RA.[96] As with smoking, the specific details of how occupational exposures lead to the generation of RA-related autoimmunity, especially seropositive disease, need further study.

Reproductive and Hormonal Factors

Abundant epidemiological, clinical, and experimental evidence implicates hormones in the incidence and clinical expression of RA. Women are 2 to 4 times more likely than men to develop RA.[97,98] In women, RA frequently develops at times when sex steroid hormone levels are in flux, such as in the post-partum and perimenopausal periods.[99–102] In most[28–35,103], but not all studies[16,38,39,104–107], oral contraceptive use is protective against the development of RA. Studies such as the NHS demonstrated a strong trend of decreasing risk of RA with increasing total duration of breast feeding[38] with inverse findings for breast feeding and RA confirmed in 2 studies[39,108] while another study showed a positive association.[40] In the NHS irregular menstrual cycles and age at menarche ≤ 10 were associated with increased RA risk[38]; another study demonstrated that age at menarche ≤ 12 and younger age at menopause were inversely associated with RA risk.[41] Studies suggest that RA incidence rises with age[97,109] with a peak incidence at menopause.[38,99,110] However, exogenous estrogen therapy among post-menopausal women did not reduce RA risk.[36,38] In the SERA cohort, among subjects enriched with *HLA-SE* alleles, oral contraceptive pill use was associated with decreased risk for RF positivity, independent of age, education, and smoking. This finding may indicate that hormones or factors related to

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oral contraceptive use are acting early in RA-related immune dysregulation to reduce risk for formation of autoantibodies.

Infection and mucosal inflammation and the initiation of RA-related autoimmunity

RA-related autoimmunity has been associated with multiple organisms as well as tissue inflammation and injury at sites other than the joints, including the lungs, genitourinary tract and oral cavity/periodontal region. It has been typically thought that such infections and tissue inflammation are secondarily due to immunosuppression or autoimmune-related injury. However, the growing understanding of the preclinical phases of RA development[71], and recent findings show that circulating RF and ACPA elevations are present in the absence of synovitis on knee synovial biopsy provide support for the concept that RA may be generated outside of the joints.[111] Therefore, it may be that the infections that are associated with autoantibody formation, and inflammation at these extra-articular sites, are providing clues as to etiologic factors and sites that are driving the generation of initial RA-related autoimmunity.

As a specific example of infection and mucosal inflammation in association with RA, recent data has shown an association between established RA and periodontal disease.[112–115] The causal direction remains uncertain but recent discoveries suggest that gum inflammation and in particular infection with organisms such as *Porphyromonas gingivalis (P ging)* may be important in the pathophysiology of RA development.[113–115] The current hypothesis is that *P. ging*-mediated citrullination of human peptides may be responsible for the initial breakdown in self-tolerance that leads to the development of RA-related autoimmunity.[112,116] This is an intriguing concept, but it, as well as the role of multiple other infectious organisms and inflammation at other mucosal sites (including the respiratory tract, gut and genito-urinary tract) that have been implicated in the pathogenesis of RA, needs further exploration.[117–125] Importantly, such studies investigating the roles of infectious and mucosal factors in RA need to be performed in prospective study of the preclinical phases of RA development in order to identify the true temporal as well as mechanistic relationships between infections and mucosal inflammation in the early pathogenesis of RA.

Dietary factors

Dietary intake of vitamin D, antioxidants, fish and protein and iron may be inversely associated with RA risk although the data is mixed.[73,126–137] Vitamin D has been implicated as an etiologic and therapeutic factor in several autoimmune diseases including multiple sclerosis,[138,139] Type 1 diabetes[140], and SLE.[141] Vitamin D has pleotropic effects on the immune system, inhibiting pro-inflammatory cytokines, upregulating anti-inflammatory cytokines,[142] and regulating the innate and adaptive immune system through the vitamin D receptor.[140] Vitamin D prevents the development of inflammatory arthritis in collagen induced mouse models.[143] One study found a strong protective effect of high vitamin D intake in diminishing RA risk showing inverse associations for dietary and supplemental vitamin D[73]; another study revealed no association[136]. Furthermore, in a study of ~1200 healthy individuals at risk for future RA because of genetic factors (HLA DR4 allele enrichment and/or family history of RA), 76 of whom were positive for the RA-related autoantibodies anti-CCP and/or RF, there was no association of autoantibody positivity with plasma vitamin D levels.[144] Studies show an inverse relationship between higher vitamin D and lower disease activity in RA after diagnosis.[145,146]

Marine omega-3 fatty acids exert effects through the leukotriene and prostaglandin pathways, decreasing inflammatory mediators, and have multiple known anti-inflammatory properties.[147] Case-control and cohort studies reported a modest protective effect of fish

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intake on RA risk.[127,128,133,148] Consumption of fish has also been shown to improve RA symptoms and delay RA progression.[149,150]

Antioxidants—Observational case-control and cohort studies suggest that antioxidants may protect against the development of RA but the results for individual antioxidants are conflicting.[128–132,137,151–153] The Iowa Women's Health Study demonstrated an inverse association for β-cryptoxanthin and supplemental zinc, but only a weak inverse association for vitamin C, and no association for vitamin E and risk of RA.[129] In NOAR, Vitamin C was inversely associated with the risk of IA, but β-cryptoxanthin and zeaxanthin antioxidants showed only weak inverse associations after adjustment for Vitamin C.[130,131] Data from the NHS did not support any prospective association for antoxidants including vitamin C, vitamin E and β-cryptoxanthin.[137] Furthermore, data from a case-control study[128] and a randomized controlled trial[135] did not support an effect of Vitamin E on RA risk.

Protein and iron—In NOAR higher intakes of red meat and protein were associated with risk of IA while iron, another nutrient component of meat, showed no association.[130,132] However, no clear associations were observed between dietary protein, iron or meats, including red meat, and risk of RA in the NHS cohort.[134]

Alcohol

Case-control studies have suggested that alcohol consumption may decrease the risk for RA and RA progression.[49,50,154] Any alcohol vs. no alcohol use was associated with lower odds of seropositive RA in several case-control studies.[17,50,155] A dose dependent protected effect was demonstrated in two case control studies in which alcohol consumption was based on patient questionnaires regarding alcohol consumption in the previous week, previous habitual consumption prior to RA onset or consumption 10 years before inclusion.[49] Furthermore, there was evidence for alcohol*_HLA-SE_ interaction. However, there was no association between alcohol and RA in the IWHS, a prospective cohort study.[156] In the NHS, moderate alcohol intake (3–6 drinks per week) was associated with reduction in plasma biomarkers of inflammation, including CRP, sTNFR2, and IL-6, among women with pre-RA where blood was collected up to 12 years prior to first symptoms of RA suggesting an effect of alcohol on inflammation during the asymptomatic phases.[157]

There are several possible mechanisms for the inverse association of alcohol consumption with RA. Moderate alcohol consumption may be associated with reduced levels of inflammatory biomarkers reflective of underlying improved alterations of inflammatory pathways.[158] Alcohol has also been shown to diminish the response to antigens in animals as well as in humans,[159,160] and to suppress the synthesis of proinflammatory cytokines and chemokines, such as TNFα, IL-6 and IL-8 both in vivo and in vitro in alveolar macrophages and human blood monocytes.[161,162]

Inhaled Particulate Air Pollution

While the first cases of RA may date back thousands of years, the prevalence of RA appears to have increased in Europe in the 1800s.[163,164] This time period is associated with the introduction of tobacco from the New World and increased popularity of smoking and it also coincides with the Industrial Revolution and the advent of air pollution in Europe.[165] In the EIRA cohort, lower socioeconomic status is associated with an increased risk of RA.[166] This association remains strong after adjustment for cigarette smoking, suggesting the existence of an important environmental or lifestyle factor associated with lower socioeconomic status. This finding is particularly interesting given that exposure to air pollution is often much higher for those in lower socioeconomic classes.[167,168] Our evolving understanding of RA pathogenesis suggests that inhaled particulate matter may induce local lung

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inflammation as well as through systemic inflammation. Indirect support of this hypothesis comes from the observation that air pollution has been clearly linked with other diseases of local lung and systemic inflammation, including asthma[169] and chronic bronchitis[170,171], cardiovascular disease[172–174], lung[172,175,176] and laryngeal[177] cancers and increased all-cause mortality.[178–180] Studies from the NHS reported a higher relative risk of RA in the Northeast and upper Mid-West regions of the US, regions with high air pollution levels.[181,182] Further, data suggests a higher RA risk in women who live closest to major road, a proxy for traffic pollution.[47]

Family history

Twin studies demonstrate a high concordance of RA between monozygotic compared with dizygotic twins.[183] In a Swedish study involving 47,361 subjects with RA, standardized incidence ratios (SIR) were calculated as relative risk (RR) of RA in family members of RA patients as compared with RR in those with no affected family members.[53] Standardized Incidence Ratios (SIRs) for RA were 3.0 in offspring of RA-affected parents, 4.6 in siblings, 9.3 in multiplex families (both parent and sibling), and 6.5 in twins. The 3- to 9- fold increased familial risk of RA suggests strong influence of genetic or shared environmental effects or both.

Interactions between environmental and genetic factors and RA risk

There are several potential mechanisms by-which gene-environment interactions may 'trigger' RA-related autoimmunity. A gene–environment interaction between *HLA-SE* and smoking was first described in landmark studies led by Klareskog and colleagues.[13,77] This work has demonstrated that interaction between these two factors was strongly associated with specific phenotypes of ACPA+ and RF+, whereas no such association was seen for the risk of developing seronegative RA. Furthermore, the additive nature of the interaction suggested a biologic pathway to disease onset. Subsequent studies replicated and expanded upon these findings using two different methods: case–control analyses comparing RA cases stratified according to autoantibody phenotype with healthy controls[5] and case-only analyses comparing autoantibody-positive RA cases to autoantibody-negative RA cases, without involving healthy controls.[184,185] Gene environment interaction between *HLA-SE* in a case-control study was strongest for autoantibody positive RA with significant multiplicative interaction.[58] Further, there was a dose response in the gene-environment interactions for both allele dose and smoking does with highest risk among heavy smokers with double copy *HLA-SE*. Gene-environment interactions between *GSTT1* or GSM1 null polymorphisms (resulting in absence of the GSTT1 or GSTM1 enzymes that detoxify cigarette smoke), and the drug-metabolizing enzyme N-acetyletransferase-2 (NAT2) and smoking further supports the synergistic effect smoking and genetics on risk for RA.[186–189]

In an attempt to identify specific mechanistic pathways by-which exposure to tobacco smoke may induce RA-related autoimmunity, investigators have also examined broncho-alveolar lavage fluid from healthy non-smokers, healthy smokers and smokers with concomitant inflammatory lung diseases (such as sarcoidosis and Langerhan's cell histiocytosis).[13,79] They found that smoking increases PAD2 enzyme expression in human lungs and was associated with increased proportion of citrulline-positive BAL cells (mainly alveolar macrophages), whereas citrullinated cells were not found in nonsmokers.

Overall, this research has led to the hypothesis that smoking induces citrullination, with subsequent immune reactions to citrullinated antigens occurring in *HLA-SE*-positive individuals. This hypothesis is strengthened by the demonstration in *HLA-DRB1**0401 transgenic mice that citrullination of certain peptides renders them more prone to bind to HLA class II molecules with the *HLA-SE*, and to trigger a strong immune response to

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citrullinated self-antigens.[190] If similar mechanisms are occurring humans to drive the development of RA, based on the 'phased' model of RA development (Figure 1), the gene-environmental interactions that may lead to RA-related autoimmunity are likely occurring some time prior to the onset of symptomatic joint disease. However, the mechanisms as well as the specific sequence of gene-environment interactions such as smoking, the generation of citrullinated proteins and subsequent autoimmunity to those proteins, that lead to symptomatic RA are unknown. For example, it may be that some factor other than smoking initially interacts with HLA alleles to generate autoantibodies to citrullinated proteins, and that smoking is a permissive factor that later drives the development of symptomatic RA rather than the initiation of autoimmunity. To fully understand these issues, the development of RA needs to be explored in prospective studies that can in real-time evaluate the relationships between gene-environment interactions and the development of RA-related autoimmunity.

Pathologic roles for autoantibodies in RA

Despite their strong association with RA, it is unclear what precise role(s) for autoantibodies including RF and ACPAs have in the pathogenesis of RA, although it will be important to define these roles especially given the data discussed above associating the development of seropositive RA with gene-environmental interactions.[5,13,55–57,191] However, numerous studies suggest that autoantibodies are likely a key aspect of the development of RA.[192,193] In particular, the association of RF and ACPAs with more severe RA (or arthritis in non-RA conditions such as SLE) suggests that these autoantibodies are important contributors to joint disease.[63,192–195] Also, in animal models of arthritis, infusion of antibodies to citrullinated proteins leads to more severe arthritis suggesting these autoantibodies play a direct pathogenic role in disease development.[196] In addition, recent work demonstrating in both animal models as well as humans that circulating immune complexes containing ACPAs and citrullinated fibrinogen activate inflammation through interactions with Toll-like receptor 4 provides a potential mechanism by which circulating ACPAs may induce joint-specific inflammation – a process that is enhanced if RF is also present.[197,198] Finally, as discussed above, the findings in multiple human studies of elevated RF and ACPAs prior to the onset of RA suggest that autoimmunity to citrullinated proteins is an important factor in the development of RA in the period prior to the appearance of symptomatic synovitis. In sum, these data suggest that autoantibodies are an important aspect of the pathogenesis of RA; therefore, the area of gene-environment interactions that may lead to the development of these autoantibodies is a fertile ground for investigations in the pathogenesis of RA.

Animal studies linking environmental factors to development of autoantibodies

Emerging data from animal models of disease that have explored the role of environmental factors such as smoking in the pathogenesis of IA may provide insight into specific mechanism by-which environmental exposures may 'trigger' RA-related autoimmunity. In particular, in a murine model of collagen-induced arthritis, Okamoto and colleagues induced IA by exposing the mice nasally to cigarette smoke condensate.[199] However, other studies have shown that exposure to cigarette smoke delayed collagen-induced arthritis in mice, perhaps due to immunosuppressive constituents of cigarette smoke.[200] Therefore, additional work is needed to develop models that can help explain the pathophysiologic mechanisms by-which exposure to environmental risk factors such as cigarette smoke may trigger RA. As for potential infectious triggers of RA, multiple animal models of collagen-induced arthritis have shown more severe arthritis in the setting of environments where organisms are present.[201,202] Furthermore, in 2011, Kinloch and colleagues reported in a *HLA DR4*-transgenic murine model of arthritis that immunization with both citrullinated and uncitrullinated forms of enolase from *P ging* led to autoantibodies to the citrullinated mammalian form of this enzyme as well as arthritis.[203] This latter discovery needs further

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work to determine the direct applicability to human disease; however, it does support a hypothesis that bacterial factors may be an important part of development of RA.

Remaining questions and future directions

The identification of autoantibodies and cytokines present many years prior to RA onset, and the association of many environmental factors with RA development provides an exciting opportunity to intervene during the pre-clinical phase to prevent the development of symptomatic RA. However, it is critical to understand the critical exposure windows to design interventions, especially if such interventions are to include modification of environmental exposures. Further research into the environment and gene-environment determinants of RA risk will provide important data for individualized studies in order to target potentially toxic therapy at individuals of highest risk, with such data preferable obtained through detailed, prospective studies of the natural history of RA so that we can understand the precise temporal as well as mechanistic relationships between genetic and environmental factors and the development of RA-related autoimmunity. The concept that RA is initiated at some mucosal site distal to the joints, potentially in relationship to environmental factors such as smoking, alcohol or infection, is fascinating and may lead to a significant break-through in our understanding of how this disease develops, and needs additional study.

The ability to accurately predict an individual's risk of developing clinical RA would be an enormous advance in this area, enabling risk factor modification and earlier introduction of effective therapies to abrogate the destruction and disability of this disease. Thus predictive modeling incorporating RA genetic susceptibility alleles, hormonal, environmental, and behavioral risk factors, and their interactions is a key step in the progress towards an RA prevention clinical trial.

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KEY POINTS

- Individuals with inherited genetic risk factors who are exposed to environmental triggers are at higher risk of RA.
- Multiple environmental factors including exposure to tobacco smoke, occupational exposures, hormones, infections and dietary factors are associated with RA risk.
- Circulating RA-related autoimmunity is evident in some patients prior to the appearance of the first joint symptoms and clinical findings of RA. This asymptomatic phase of disease development suggests that important gene and environmental interactions leading to initiation of RA-related autoimmunity occur long prior to the onset of clinically-apparent disease.
- Natural history studies of the asymptomatic phase of RA development are needed to determine the mechanistic role(s) that environmental factors play in the initiation of RA.
- Animal studies link autoantibodies to RA pathogenesis and going forward may provide insight to the mechanisms of environmental and genetic factors in the pathogenesis of RA.

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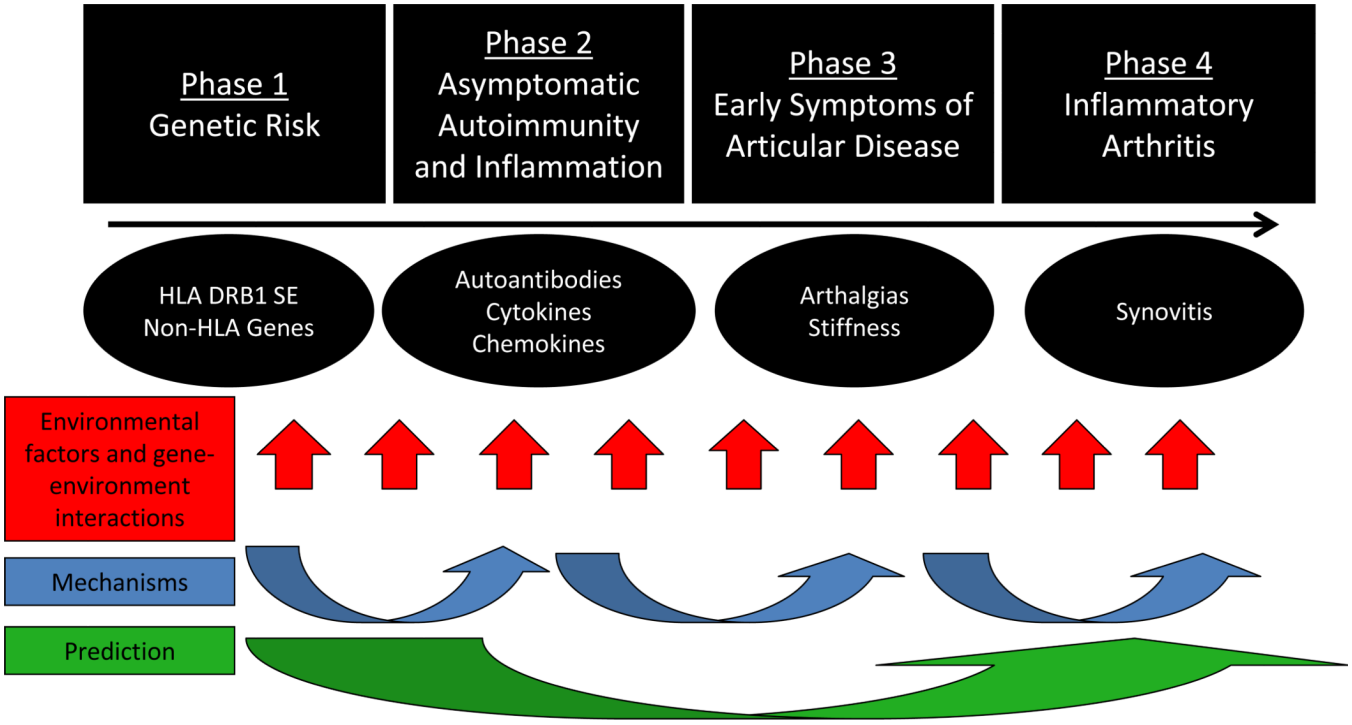

Adapted from Deane et al, Rheumatic Disease Clinics North America, 2010

Figure 1. Phases in the Development of Rheumatoid Arthritis

Phase 1) "asymptomatic" phase of genetic risk; Phase 2) asymptomatic "immune activation" phase with autoantibodies and elevated biomarkers such as cytokines and chemokines; Phase 3) "pre-clinical" phase with abnormal biomarkers of inflammation and perhaps arthralgias; and Phase 4) clinically-apparent inflammatory arthritis (defined as symptomatic joint disease including pain, stiffness and swelling, and identifiable synovitis on examination) that may be undifferentiated arthritis (UA), or fulfill classification for RA. Identifying the environmental factors associated with transitions between phases, key exposure windows leading to transition between phases, and the biologic mechanisms involved in these transitions is a challenge for the field.

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Table 1

Environmental, behavioral and lifestyle risk factors for rheumatoid arthritis, inflammatory arthritis, or autoimmunity in prospective cohort studies

Site	Population	Cohort	Smoking	Silica	Air pollution	Reproductive factors	Birth Weight	Alcohol	Diet	Periodontal Disease
Boston	Nurses	NHS	X		X	X	X	X	X	X*
Iowa Women's Health Study	Women	IWHS	X			X			X	
Sweden	General	Malmo Diet and Cancer Study	X			X		X		
Netherlands	General	Lifelines	X	X		X	X	X	X	X**
United Kingdom	General	NOAR	X			X			X	
Colorado	FDR	SERA	X	X		X		X	X	X*
Manitoba	FDR	NAN	X	X		X		X		X**
Geneva	FDR	Geneva	X	X		X	X	X		X*

X – Exposure ascertained by survey

*Subjects complete survey regarding periodontitis symptoms

**Subjects undergo dental examination for periodontitis