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Genetic and environmental risk factors for rheumatoid arthritis

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Abstract

Multiple genetic and environmental factors have been associated with an increased risk for rheumatoid arthritis (RA). Of these, the strongest associations have been seen with female sex, a family history of RA, the genetic factor the ‘shared epitope’ and with exposure to tobacco smoke. There is also renewed interest in mucosal inflammation and microbial factors as contributors to the development of RA. However, the identification of a ‘preclinical’ period of RA that can be defined as local or systemic autoimmunity as measured by autoantibodies and other biomarkers prior to the development of clinically-apparent synovitis suggests that the risk factors for RA are acting long prior to first clinical evidence of IA. As such, a major challenge to the field will be to investigate the full spectrum of the development of RA, from initiation and propagation of autoimmunity during preclinical RA and transition to clinically-apparent synovitis and classifiable RA, in order to determine which genetic and environmental factors are important at each stage of disease development. Understanding the exact role and timing of action of risk factors for RA is especially important given the advent of prevention trials in RA, and the hope that a full understanding of genetic and environmental factors in RA could lead to effective preventive interventions.

Keywords

Rheumatoid arthritis genetic risk factors; Rheumatoid arthritis environmental risk factors; Rheumatoid arthritis prevention; Preclinical rheumatoid arthritis; Mucosal inflammation; Microbiome

Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune inflammatory disease that affects ~0.5 to 1% of the overall population (1). The disease is defined as inflammatory arthritis (IA) that fulfills established classification criteria that include the 1987 American College of

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Rheumatology (2) and 2010 ACR/European League Against Rheumatism criteria (3). Furthermore, RA is typically divided into two subtypes designated ‘seropositive’ and ‘seronegative’ disease, with seropositivity being defined as the presence of serum elevations of the autoantibodies rheumatoid factor (RF) and the more recently described antibodies to citrullinated protein/peptide antigens (ACPAs) (1).

Multiple genetic and environmental factors have been associated with increased (or decreased) risk for RA. A major advance in understanding how these factors impact the development of RA has been the emergence of a model of RA development, and in particular seropositive RA development, where there is typically a period of circulating autoantibody elevations which may last several years prior to the first appearance of IA (reviewed in (4)). This period can be termed ‘**Preclinical RA**’, and its presence has raised the issue that a subset of the genetic and environmental factors that drive RA are likely acting years prior to the first appearance of IA (Figure 1). This process of disease progression is not universal, though, as some studies have identified a small percentage of patients where IA presents prior to the appearance of circulating autoantibodies (5). However, for the great majority of cases of seropositive RA, there is a preclinical stage that can be operationally identified by the presence of circulating RA-related autoantibodies that include RF and ACPA, as well as other autoantibodies such as antibodies to carbamylated proteins (4, 6). Importantly, the understanding of the genetic and environmental factors that contribute the development of RA, and in particular Preclinical RA, has taken on new importance because of multiple pharmacologic prevention trials that are underway (7–10), and these factors may be used in prediction models for future RA as well as to identify targets for prevention.

With these issues in mind, in this review we will take the approach of first discussing the known genetic and environmental factors associated with the risk of developing RA (11). We will follow that with a discussion of the phenotypes manifest by individuals who appear to be in the preclinical stage and how these factors fit within the Preclinical RA model. Finally, we will discuss future directions for research that can ultimately lead to improved treatment and potentially effective preventive approaches for RA.

Genetic and familial risk factors for RA

Several factors have strongly suggested that genetics are a major influence on the development of RA. These factors include the general increased prevalence of RA within families, leading to estimations of familial risk contribution to seropositive RA of ~40–50% of seropositive RA, with strongest risks seen in first-degree relatives (FDRs) (12). In addition, genetic factors in RA are suggested by increased prevalence of disease within certain racial groups such as North American Natives, who exhibit prevalence rates of RA of 5–7% (13–15).

Following this, although there may be non-genetic familial or cohort factors that play a role in family or racial/ethnic group risk, multiple specific genetic loci have been identified that are associated with increased risk for RA, and in some cases decreased risk (Table 1). The strongest of the genetic risk factors is a set of alleles within the Major Histocompatibility

Complex (MHC) that encode amino acid sequences that predict structural similarities in the Human Leukocyte Antigen (HLA) peptide-binding groove and are termed in aggregate the 'shared epitope', or SE (16, 17). As a group, SE alleles are thought to contribute up to ~40% of genetic risk of RA, although other studies suggest less contribution (15–20). Notably, there are numerous alleles considered to contain the SE, with many of these alleles in the HLA DRB1 region, and prior nomenclature has reflected that (e.g. HLADRB1*0404 is a high-risk allele). However, the nomenclature and classification system for the SE has undergone revision recently, with the new system being based on the importance of the amino acids at positions 70 and 71 in conferring risk for RA (21, 22). As such, the new groups divide the risk SE alleles into five groups: S1, S2, S3P, S3D, and X. S2 and S3P are considered high risk for RA, and the other groups lower risk.

Importantly, multiple studies show that the presence of the SE (and based on the new system, the S2 and S3P groups) is most strongly associated with ACPA positive RA (15, 21, 22), and higher levels of autoantibodies, although in some studies non-SE alleles have also been associated with high ACPA levels (23, 24). Furthermore, some studies have shown that citrullinated proteins/peptides, as compared to their arginine-containing counterpart, preferentially bind in the SE and are more efficiently presented to T cells (25). As a result, it is hypothesized that the SE plays an important part of the pathogenesis of RA, and in particular ACPA positive RA; these relationships will be discussed in more detail below.

Multiple other genetic factors have also been associated with RA, with genome-wide studies identifying more than 100 loci that are associated with RA and that in aggregate may explain ~5% of the genetic association with RA (12, 15, 26–29). Importantly, however, most of these loci have low effect sizes, with odds ratios typically less than 2 and often less than 1.5, and with variability across races (29, 30). One of the strongest associations is with a polymorphism in the PTPN22 gene that is thought to lead to a lowered threshold for immune activation of T cells, as well as other cells (31–33). Recent studies have also suggested that this polymorphism may also lead to hypercitrullination because of altered PTPN22 interactions with peptidylarginine deiminase (PAD), an enzyme responsible for citrullination, although it is unknown whether this hypercitrullination is targeted by immune responses, or functionality drives other processes that lead to autoimmunity (34, 35). Other associations exist with genes that are in inflammatory pathways implicated in RA (e.g. CTLA4 (36), STAT4 (37), IL-6 (38), NF-kB (39)), and with genes related to enzymes that conceivably could participate in autoimmune responses, including the PAD enzymes that mediate citrullination (29, 36, 40).

Notably, polymorphisms within non-coding regions have been associated with RA. In particular, studies that have identified genetic factors associated with specific immune cell types have identified that super-enhancers in T cells are associated with RA (41). In addition, non-coding regions with the TRAF-C5 genetic region are associated with RA (42). Multiple genetic factors are also associated with certain biologic pathways in patients with established classified RA, typically relating to response to therapy, or toxicity, although how these factors influence the earliest stages of RA development remains to be determined (43, 44). Finally, several genetic factors are associated with decreased risk for RA, or the

development of ACPA in RA (19). In particular, the HLA DRB*1301 allele appears protective against ACPA positive RA (45).

There is also a growing understanding that epigenetic changes are associated with RA, and in particular disease activity (46). Specifically, methylation changes in several regions in the genome of fibroblast-like synoviocytes (FLS) from RA joints have been associated with more aggressive RA (47, 48). These methylation changes are hypothesized to alter gene expression and increase disease activity in patients with RA, although it is not yet clear when in the course of disease these changes occur, and it may be that they are late changes and unrelated to disease initiation.

There are, therefore, multiple genetic factors associated with RA. The strongest is the presence of the SE, although there are important differences in the association of this factor with seropositive and specifically ACPA positive RA. Furthermore, it is thought that the other genetic factors also more strongly associate with seropositive RA. However, overall, it is thought that heritability only accounts for ~40–50% of seropositive RA, and ~20–30% of seronegative RA (12).

Importantly, the known genetic factors (and environmental factors) contribute less than 100% of this heritability (49). What makes up the difference between the heritable risk and known genetic risk is as of yet unknown, but it is likely that is due to unknown genetic as well as environmental factors and potentially stochastic effects (12, 49).

In this regard, it may also be the case that there are subtle genetic/familial factors such as predisposition to inflammation that serve as a permissive background for the development of RA-related autoimmunity and arthritis. In particular, elevation of the cytokine MCP-1 has been identified in autoantibody negative FDRs of patients with RA from Native American populations as well as in individuals who later developed seropositive RA, although it is not clear if this is a genetic factor, or a biomarker of some response to an environmental factor (50, 51). Furthermore, detailed cellular function studies in arthritis-free FDRs of patients with RA have noted abnormalities of several inflammatory pathways as well as increased intracellular citrullination related to PTPN22 function in the absence of the known risk allele for autoimmunity associated with this protein (34). In addition, there is growing evidence that subtle genetic factors that may more indirectly influence immunity (e.g. autonomic dysfunction) may play a role in RA risk (52).

Despite a greater understanding of genetic factors associated with RA, it is still not clear what functional role(s) most genetic factors plays in the overall development of RA. Specifically, the understanding of how the SE may contribute to RA includes a model where SE-related factors lead to citrullinated antigen presentation and also models where the SE may alter intracellular function contributing to autoimmunity and inflammation, such as NFκB activation (19). It is therefore as-of-yet unclear if genetic factors such as the SE are associated with the initial generation of autoantibodies in RA. Nevertheless, cross-sectional studies as well as longitudinal studies suggest that the SE plays an important role in the transition of subjects from an ACPA positive Preclinical RA state to the development of clinically apparent synovitis and classified RA (53–55). Specifically, in a longitudinal study

of 100 ACPA positive subjects without IA at basline, the presence of SE was associated with ~2-fold increase in risk of developing IA and classifiable RA (55). Even though the exact mechanisms and timing of action of genes that are associated with RA are not known, it is reasonable to assume that some factors are likely to play more of a role in the early initiation of autoimmunity, others play a role in the propagation of autoimmunity, and finally other factors play a role in disease severity and/or response to therapy.

Environmental risk factors for RA

Multiple environmental, dietary and lifestyle factors have been associated with RA (Table 2). While many of these associations are only seen in single studies, or there are discrepant results across multiple studies, there are several environmental factors that have relatively consistent associations with RA, and the strongest of these is exposure to tobacco. Multiple studies have found odds ratios of association between smoking and RA of greater than 2, and estimates are that exposure to smoking accounts for ~20–30% of environmental risk for RA (56). Importantly, there are several features of the relationship between smoking and RA that could mediate the increased risk for RA development. Primarily, smoking is most strongly associated with ACPA positive RA, and especially ACPA positive RA in the setting of the SE (56). Furthermore, smoking has long been associated with the presence of RF even in the absence of RA (57). This suggests that there may be biologic interactions between these factors that drive the development of RA, or at the very least RA-related autoimmunity. As one relevant example, it has been proposed that smoking may lead to increased citrullination which in the setting of the right genetic background, leads to presentation of citrullinated proteins and the generation of ACPA although there are many other local and systemic effects of smoking tobacco that may influence immunity (57–59).

As to where the site of action of smoking is in the development of RA, that remains to be determined. However, smoking is associated with increased periodontal disease and lung disease, so it may be that this factor drives inflammation and autoimmunity at these sites, and this will be discussed further below. In addition, there are systemic effects of smoking and it may be that these lead to changes within joints that drive RA. In this regard, in a study of FDRs of patients with RA, joint tenderness and swelling was associated with smoking even in the absence of RA-related autoantibodies, raising the possibility that smoking may have early direct joint effects that could be related to the future development of inflammatory arthritis (60). In addition, it has emerged in several large-scale epidemiology studies that smoking appears to be a stronger risk factor for RA in men compared to women (61, 62); this feature could indicate that there are sex-related differences in effects of smoking, or that women have other, stronger risks for developing RA.

Furthermore, because smoking has also been associated with increased disease activity, its actions may be beyond initiation of RA (63). Thus, a major unanswered question regarding the role of smoking in RA is where it acts in the natural history of RA. Specifically, does exposure to tobacco smoke act to trigger initial autoimmunity, or does it drive propagation of autoimmunity to the point of classifiable disease? Data from twin studies in Sweden suggest that smoking’s effects may be after the initial generation of RA-related autoimmunity, and related to prolonged ‘high-dose/intensity’ smoking as measured by pack-years, although

other studies suggest that it is more the duration of smoking rather than intensity that imparts risk for RA (53, 64). These issues will need to be investigated thoroughly, especially given the potential for smoking to be a modifiable risk factor and therefore a potential preventive intervention in RA development.

Beyond tobacco smoke exposure, multiple studies have also consistently demonstrated an association between exposure to occupational silica/dust and RA, and in particular ACPA positive RA (65–68). There have also been findings linking increased exposure to inhaled particulate air pollution and increased risk for RA. However, the findings have been mixed, perhaps in part due to the complexity of assessing the true exposure to air pollution as well as accounting for other factors such as specific components of pollution that may vary by locality. In addition, these findings are likely affected by confounders such as increased lower socioeconomic status, a purported risk factor for RA in its own right, in individuals who are also exposed to greater amounts of pollution (69–75).

Multiple dietary or other factors such as supplements or medications have also been variably linked to RA risk. These include lower intake of vitamin D and antioxidants, and higher intake of sugar, sodium, red meats, protein and iron, with increased risk for RA (76–82). In addition, in a large-scale prospective study of nurses in the United States, a generally healthy diet has been associated with a decreased risk for seropositive RA, although specific dietary factors were not identified (83). Furthermore, a finding that has been relatively consistent across many studies is that a higher intake of fish as well as omega-3 fatty acids have been consistently linked to decreased risk for RA across a number of studies, including studies where dietary data was collected prior to incident RA (84–88). Furthermore, in FDRs of patients with RA who at the time of study did not have classifiable RA, self-reported intake of supplements containing omega-3 fatty acids, as well as biomarkers of fatty acids, found that increased intake and higher blood levels of fatty acids were associated with decreased risk for RF and ACPA positivity (89, 90). Notably, there appeared to be a greater protective effect in individuals who were positive for at least one allele containing the SE, suggesting that there may be an interaction between these factors in mediating RA risk (89). These findings coupled with clinical trials where fatty acid intake is associated with decreased RA activity in established disease suggest there could be a direct protective relationship of fatty acids across the spectrum of RA development (91).

In addition, healthy lifestyles including lower body mass index and healthier diets that are defined differently across studies but in general are low in sugar and animal fats, and high in fruits, whole grains and vegetables, have been associated with decreased risk for RA (83, 88, 92). In one study of 55 autoantibody positive individuals without IA at baseline, high body mass and ongoing smoking were associated with the highest risk for developing future RA (93), suggesting that these factors may act as additional risks for progression from autoimmunity to classifiable disease.

However, these relationships are complex and some prospective studies have not found a significant relationship between smoking and transition from autoantibody positivity to RA (54, 55). In addition, the relationship between obesity and RA risk is conflicting. One study has shown that an increasing body mass index (BMI) was protective against RA

development in men, although there was no significant relationship with RA risk in women (94). Another study showed that an increasing BMI was a risk factor for RA in both men and women, but less so in women (95). In addition, and in contrast to the above mentioned prospective study where obesity was a risk factor for progression to RA in ACPA(+) individuals (93), in another cohort of ACPA(+) individuals without baseline IA, Rakieh and colleagues found no significant relationship between a high BMI (>=25) and the development of future IA/RA (55). While one could hypothesize that the known systemic metabolic, inflammatory and immunologic effects of obesity (especially omental fat) may predispose to autoimmunity and the development of RA (96), these conflicting studies indicate that additional research is necessary in order to understand the role between obesity and RA, especially as weight loss could be a preventive intervention in at-risk individuals.

Furthermore, in multiple epidemiologic studies and including studies where data regarding alcohol intake was collected prior to incident RA, modest alcohol consumption (in some studies 1–2 drinks daily) has been associated with decreased risk for RA (97–101), although not invariably (98). There have also been mixed results of the protective effect of alcohol in longitudinal studies of individuals who have presented to clinical care with musculoskeletal symptoms in absence of IA on examination at baseline. Specifically, a Dutch longitudinal study of 374 individuals who initially presented with arthralgias and ACPA and/or RF positivity but without IA at baseline found in multivariate analyses that alcohol consumption was a protective factor for the development of classified RA (54). In contrast, however, a British study of 100 ACPA positive subjects, alcohol use was not significantly protective (55). As such, additional studies will need to be done to understand the true role of alcohol in risk and prevention of RA. Finally, statin use has also been variably associated with risk for RA, with two large-scale studies suggesting a reduced risk of RA in statin users (102, 103), and one suggesting an increased risk (104). Given the proposed beneficial immunomodulatory actions of statins, a prevention trial for RA using atorvastatin is underway as of 2015 (10).

Female sex and rheumatoid arthritis

Because approximately two-thirds of individuals who develop RA are women, and a large number of epidemiologic studies point to sex-related factors in RA risk, it has long been considered that there are female-specific factors that influence risk for RA. Notably, though, the studies that have explored the relationship between sex and RA risk suggest at the very least a complex relationship between female sex and RA, with conflicting results potentially attributable to heterogeneous study design, recall bias if risk factors for RA were assessed after the clinically-apparent onset of disease, and changing composition of hormonal replacement therapy and oral contraception use over time (105–107). Despite these caveats, factors that have been associated with increased risk for RA include early menopause (108–110), the presence of polycystic ovary syndrome (111), and potentially pre-eclampsia (112). In addition, across several studies involving diverse populations, the rates of a first diagnosis of RA appear to be increased 1–2 years post-partum, although it is not known whether this phenotype is related to changes in hormone levels such as prolactin, or other factors such as transmission of cells/DNA from the fetus to the mother (microchimerism) (113–115). Protective factors include breast-feeding (108, 116–118), and variably, use of hormone

replacement therapy and oral contraception, with greater protection seen with longer-term use (e.g. >7 years) (119–121). Less clear is the relationship between parity and risk for RA, with one study showing no increased risk for seropositive RA based on one or more pregnancies (122), and other studies including a meta-analysis demonstrating a protective effect of pregnancies (123, 124).

Importantly, while prospective studies of the role of sex specific factors and the development of future RA are limited, oral contraceptive use has been shown to be associated with decreased rates of RF positivity in FDRs of patients with RA, suggesting there may be an early "preclinical" effect of hormones in the pathogenesis of RA (125). The mechanisms underlying the relationship between hormone use and decreased risk for RA are not known, although it may be that exogenous hormones lead to decreased endogenous hormone production, and it is that decreased endogenous hormone production that leads to decreased risk (105). This latter explanation may be supported by findings that there is a decreased risk for adult-onset RA in individuals with Turner's syndrome that is characterized by decreased endogenous oestrogen production (126). Complicating this issue further is that there are several potential mechanisms of immunologic activity that may be related to hormones including glycosylation of autoantibodies and alterations of T and B cell function, and these may be important in early development of RA as well as in established classified disease (105, 127). However, whether these changes are directly related to hormone effects, or other down-stream female-specific factors (e.g. genito-urinary structure and pregnancy) is not clearly known and needs further study (105).

Microbes and mucosal processes influencing RA development

There has been long interest that microbes may play a part in the development of RA. Early hypotheses were that some pathogen or other factor encountered by Europeans in their contact with the Americas led to the development of RA (128). Later studies suggested that specific organisms including *Proteus* and *Escherichia* species, among others, may be causative in RA (129–131).

In the past decade there has been renewed interest that microbes as well as mucosal inflammation play a strong role in the pathogenesis of RA, spurred in large part by deepening of understanding of the risks for RA associated with environemental factors such as smoking and occupational dust that may primarily affect mucosal surfaces, as well as advances such as 16S RNA sequencing that can identify bacterial species through culture-free methods (132). There is also a growing knowledge of how microbes influence human immunity both at mucosal surfaces and systemically. With relevance to RA pathogenesis, there is an emerging understanding of mucosal-associated immunoglobulin A (IgA)-related autoimmunity as a possible early factor in disease development that is based on autoantibody isotype studies as well as plasmablast studies (133, 134).

The general model underlying a hypothesis that mucosal surfaces (and potentially microbes) play a role in the pathogenesis of RA is as follows. At some point in Preclinical RA, at a mucosal surface (e.g. the oral cavity, lung, gut) interactions between microbes potentially other environmental factors (e.g. tobacco smoke) and host factors lead to mucosal inflammation and initial breaks in RA-related immune tolerance. This mucosal inflammation

may then facilitate local, then systemic, propagation of autoimmunity through mechanisms that may include molecular mimicry, or facilitation of development of direct autoimmunity to self-antigens (135).

Despite not yet knowing specific mechanisms, and although not consistent across all studies, epidemiologic and other observational studies have linked inflammation in the oral cavity and specifically periodontitis to the preclinical period of RA (136–138). In addition, studies of RA-related autoantibody positive individuals without IA have demonstrated the presence of airways inflammation and/or lung parenchymal abnormalities by imaging (139–141), with a number of subjects later progressing to clinically-apparent RA. The generation of RA-related autoantibodies to citrullinated proteins within the lung has been also demonstrated in sputum studies in individuals without RA (142). While not yet well studied in preclinical RA, there have also been microbiome differences in patients with early RA compared to controls (143). All of these factors suggest that mucosal surfaces, and in particular the periodontal region, lung and gut, may be sites of inflammation and potential generation of RA-related autoimmunity in the preclinical period of disease, although certainly other mucosal sites are also candidates and will need further study.

As to what may be driving mucosal inflammation and generation of RA-related autoimmunity in the early phases of RA, it could be multiple factors, including environmental factors that could directly affect mucosa (e.g. tobacco smoke (58)), or microbes or complex interactions between these factors. However, in the past several years, many hypotheses regarding early causes of mucosal-generated RA-related autoimmunity have centered on microbial factors, and in particular bacteria largely because techniques to evaluate micro-organisms have been optimized for bacteria (e.g. 16S RNA) and not fungi or viruses. Following this, several specific organisms have been considered as part of the pathogenesis of RA. In relation to periodontal inflammation potentially driving early RA-related autoimmunity, studies have identified *Porphyromonas gingivalis* (*P ging*) as a candidate organism in RA pathogenesis (144–146). This is because *P ging* is a common pathogen in periodontal disease, and furthermore, *P ging* generates a bacterial PAD called “PPAD” that can citrullinate human tissue, or bacterial products (e.g. enolase) that could be recognized by the human immune system. This PPAD driven citrullination could contribute to early breaks in tolerance in RA development (144, 146–148). Other support for some role for *P ging* in the early pathogenesis of RA, elevations of antibodies to *P ging* have been associated with elevations of RA-related autoantibodies in individuals without classifiable RA (149). Furthermore, individuals with periodontal disease in absence of classifiable RA have been demonstrated to have ACPA in their periodontal fluid (150).

In addition, other organisms that are related to periodtonal disease have been linked to RA. In particular, *Anaeroglobus* and *Prevotella* species have been found in patients with early, pre-DMARD RA (151). *Aggregatibacter actinomycetemcomitans* has also been shown to produce leukotoxin A that can induce citrullination in human neutrophils potentially creating autoantigens that can be targeted in RA, and antibodies to leukotoxin A have been found in serum in RA patients, suggesting a possible link between periodontal infection with this specific organism and RA, although to date this relationship has not been examined in preclinical RA (152).

As for other mucosal sites, cross-sectional studies of patients with RA and controls have suggested that other organisms are potentially related to early RA development. These include that bacterial diversity and abundance is altered in the fecal samples from patients with early RA compared to controls (143). In addition, specific organisms including *Prevotella* species have been identified in fecal samples from early RA (143). Furthermore, several organisms have differed at oral and gastrointestinal mucosal sites between patients with early RA and patients with established treated disease as well as healthy controls (153).

Overall, these findings suggest that microbiota and mucosal inflammation may influence the early immunologic changes that leading to classifiable RA. However, while it is exciting to think that mucosal inflammation and potentially microbes influence early RA development, especially since these sites and processes may be amenable to manipulation for prevention, these are early days in this scientific arena. Much more needs to be learned about the relationship between mucosal processes and the initiation and propagation of autoimmunity. In particular, given that there is a general understanding that an illness can alter an individual's microbiome even in absence of specific microbiome changes causes that illness (154), the causal link between microbiome changes and disease development needs to be firmly established in longitudinal studies where transition from preclinical to classified RA can be evaluated. Importantly, the specifics of how mucosal inflammation and microbial factors may drive autoimmunity need to be established. It may be molecular mimicry where there is cross-reactivity between a microbe and human antigen, such as is suspected in rheumatic fever (155). Alternatively, it could be that endogenous microbial factors lead to citrullinated proteins, such as proposed with *P ging.* General inflammation that triggers human citrullation, or non-specific permissive effects on immune dysregulation because of mucosal-driven systemic inflammation may also be the culprit. Furthermore, as the understanding expands regarding broader aspects of RA related autoimmunity, including metabolic processes that could be affected by the microbiome (156), and other autoantibody systems that may relate to mucosal immunity in RA pathogenesis (e.g. antibodies to carbamylated proteins and heat-shock proteins (157–159)), these aspects need to be included in models of disease development. Other processes that need to be explored include the role of neutrophil extracelluar traps (NETs) and inflammasomes in mucosal and systemic autoimmunity (160, 161), and emerging technologies that can elucidate single cell phenotypes (including IgA production) mucosally or systemically (134). Finally, it will be critically important to integrate all of these factors to understand how mucosal processes relate to other factors associated with RA such as genetics, familial factors, and sex, as well as environmental factors such as exposure to tobacco smoke, or dietary factors.

Summary and future directions

There are multiple genetic and environmental factors that have been associated with RA. The strongest of these are familial associations and in particular FDR status, although it is not yet clear if these associations are due to genetic or environmental factors, or both, or even possible increased diagnosis within families due to awareness of disease (12). Other strong and consistent factors include the presence of alleles containing the SE, female sex, exposure to tobacco smoke and some dietary factors such as intake of omega-3 fatty acids.

Importantly, given the implementation of prevention trials for RA, all of these risks must now be understood in the context of understanding how to identify individuals at-risk for future RA through accurate prediction models, and understanding the pathophysiology of disease so that RA-related autoimmunity can be modified across its stages of development to improve active disease as well as to develop effective preventive interventions (162).

In terms of prediction of future RA, at this time, the presence of RA-related autoantibodies and clinical features such as joint pain appear to be the most powerful predictors of future disease. Consequently, these are the factors being used as inclusion criteria in current clinical prevention trials for RA (7–9). Notably, however, as mentioned above, cross-sectional studies as well as longitudinal studies have suggested that the presence of the SE is a risk factor for transitioning from ACPA positivity to clinically-apparent RA (53, 55, 163, 164); therefore, the SE may be an important part of creating robust prediction models for future RA. Other models that incorporate various genetic and environmental factors (e.g. smoking) are being explored, and have thus far been able to predict risk for future RA with fair degree of accuracy (e.g. area under the curve for RA of ~0.7 (165)) although additional studies are needed to improve and validate these findings so that genetic and environmental factors can be routinely applied in prediction models for future RA (165, 166).

In terms of actionable prevention for RA, currently there is likely enough evidence to recommend that to reduce risks for RA that individuals should stop using tobacco, maintain optimal body weight, and have an overall healthy diet - especially since these interventions also have broad health benefits beyond RA. However, much more information needs to be obtained before interventions such as specific dietary, microbial or hormonal manipulation are used in RA prevention. Importantly, understanding specific roles that genetic and environmental factors play in disease development may provide targets for prevention beyond general lifestyle changes, and in particular may allow for implementation of ‘precision’ medicine that can be tailored for specific individuals. This is especially relevant given the known differences in risks factors for RA between women and men, as well as differences in risk factors for seropositive and seronegative RA.

To improve the understanding of the pathways and timing at which genetic and environmental factors influence RA development, longitudinal studies of at-risk individuals will need to be performed. The high specificity for RA of serum elevations of ACPAs, as well as the high positive predictive value for future RA of ACPA elevations in combination with other factors such as RF positivity, and joint symptoms (54), allow for the identification of individuals who are at high-risk for future RA. Therefore, it is incredibly valuable to identify and study these subjects to learn more about how RA develops. Importantly such subjects can contribute to the knowledge of RA even if their autoimmunity resolves or does not progress to classified RA. Such individuals are admittedly difficult to identify, but hopefully a collateral benefit of the current prevention trials in RA will be to establish the interest as well as the infrastructure and methodologies to identify such individuals (167, 168). In addition, longitudinal studies will also need to be done in individuals before autoimmunity develops so that the initial genetic and environmental factors that lead to triggering of autoimmunity can be identified, especially in absence of confounding that may exist in our current understanding of risk factors for RA because of studies performed in

patients with established classified RA. Given the relatively rarity of incident autoimmunity, these will need to be large-scale studies. These studies of RA development preferably will also involve multiple races/ethnicities in order to make findings most broadly applicable as well as to identify factors that may be unique to certain groups, especially since the majority of genetic and epidemiologic studies in RA have been performed in Europe and the United States. Importantly, the genetic and environmental assessments as well as definitions of disease that are used in these studies will need to be harmonized to maximize comparability. In particular, it will be critical to establish homogenous classification and nomenclature for the various stages of RA development. To that end, terminology for the various stages of RA development has been developed, although has yet to be validated and widely adopted (169). Finally, these human studies will be helped by use of informative animal models to help understand specific mechanisms of genes and environment in human disease.

While addressing these issues is daunting, the fact that there are prevention trials underway should provide hope and encouragement that further study can lead to a major paradigm shift where prevention in RA becomes a reality.

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Practice Points

There are currently limited evidence-based effective preventive interventions for rheumatoid arthritis. However, there are several lifestyle changes that may be protective against the development of RA, as well as improve overall health:

- Avoidance or cessation of tobacco use
- Maintenance of a healthy body weight
- Healthy diet (although a specific diet is not known)

There are now a number of studies world-wide investigating the natural history and prevention of rheumatoid arthritis. Most of these studies particularly focus on individuals who are positive for antibodies to citrullinated protein antigens (ACPA) without clinically-apparent synovitis. If these types of individuals are identified, clinicians should consider referring them to research studies.

Research Agenda

- Natural history studies of the development of rheumatoid arthritis (RA) in order to identify and validate the genetic and environmental risk factors for each stage of RA development. These stages should include the initiation and propagation of autoimmunity in preclinical RA, the transition to clinically-apparent synovitis and classifiable disease, as well as response to therapy once classifiable disease has developed.
- Understanding specific mechanisms of genetic and environmental factors in the development of RA. These studies may include informative animal models.
- Widely accepted and validated nomenclature to define the stages of RA in clinical care as well as research studies.
- Development of the infrastructure to identify individuals who are high-risk for future RA.
- Development of accurate prediction models for future RA that incorporate genetic/familial, environmental, biomarker and clinical factors.
- Prevention trials that evaluate the effectiveness of pharmacologic as well as dietary and lifestyle factors in the prevention of RA

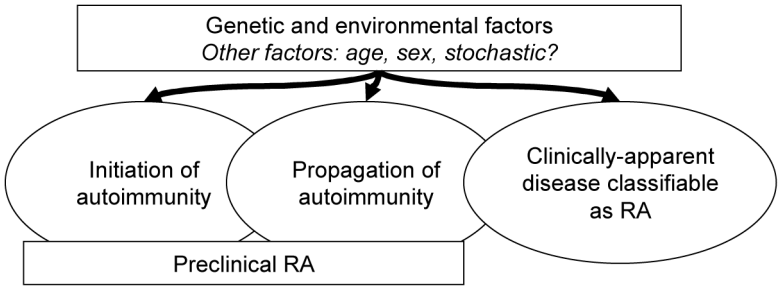

Figure 1. A general model of rheumatoid arthritis (RA) development

In this model, genetic and environmental factors interact to initiate autoimmunity, propagate autoimmunity and ultimately lead to clinically apparent tissue injury and inflammatory arthritis that is classifiable RA. The period of disease development during which there are detectable RA-related biomarkers without clear inflammatory arthritis can be termed 'Preclinical RA'. Importantly, the genetic and environmental factors that influence each of these stages of disease may be different.

Table 1

Major genetic factors associated with rheumatoid arthritis risk

Genetic region	Possible mechanism
MHC regions encoding HLA proteins collectively termed the ‘shared epitope’ where most risk is associated with amino acids at positions 70 and 71.	Preferential presentation of citrullinated antigens; intra-cellular effects leading to increased inflammation
Protein tyrosine phosphatase, non-receptor type 22 (PTPN22)	Generalized cellular hyperreactivity; may disrupt PTPN22 and PAD interactions and lead to hypercitrullination
Interleukin-6 receptor (IL6R)	Increased inflammation due abnormal IL6 metabolism
Tumor necrosis factor receptor-associated factor-1 (TRAF1/C5)	Increased inflammation
Signal transducer and activator of transcription 4 (STAT4)	Increased inflammation
Peptidylarginine deiminase 4 (PADI4)	Increased citrullination
Fc gamma receptor (FCGR)	Increased antigen presentation
CD40, CC chemokine ligand 21 (CCL21), CC chemokine receptor 6 (CCR6)	Increased cell activation and inflammation
DNA methylation changes	Methylation changes leading to increased inflammation from altered protein transcription
Protective? HLA DRB1*1301 (decreased risk for ACPA positive RA)	Decreased presentation of citrullinated antigens

Abbreviations: MHC=major histocompatibility complex; HLA=human leukocyte antigen; ACPA=antibodies to citrullinated protein/peptide antigens

Table 2

Environmental and other factors associated with rheumatoid arthritis risk*

Increased risk
Female sex
Exposure to tobacco smoke
Occupational dust (silica)
Air pollution
High sodium, red meat and iron consumption
Obesity
Low vitamin D intake and levels
Decreased risk
Fish and omega 3 fatty acid consumption
Moderate alcohol intake
Healthy diet
Statin use
Oral contraceptive use/hormone replacement

* Of note, many of these risk factors have conflicting associations with RA risk in the literature, or have only been seen in single studies. However, factors that demonstrate fairly consistent increased risk for RA include female sex, and exposure to tobacco smoke. Factors that demonstrate fairly consistent decreased risk include fish and omega 3 fatty acid consumption, and moderate alcohol intake.