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Genetic and environmental risk factors for rheumatoid arthritis

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A B S T R A C T

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 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, 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.

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that affects ~0.5%–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 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 that may last several years prior to the first appearance of IA (reviewed in Ref. [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 (Fig. 1). This process of disease progression is not universal, although 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 and 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 and 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 for 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 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

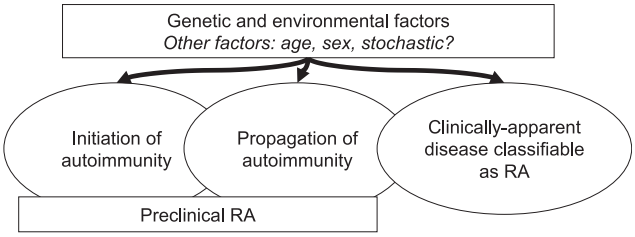

Fig. 1. A general model of rheumatoid arthritis (RA) development. In this model, genetic and environmental factors interact to initiate autoimmunity, propagate autoimmunity, and ultimately lead to clinically apparent tissue injury and inflammatory arthritis that is classifiable as RA. The period of disease 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.

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