
Etiology of Rheumatoid Arthritis: A Historical and Evidence-Based Perspective

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, and destructive polyarthritis with numerous autoimmune features and the potential for extra-articular and systemic complications. Its etiology is still unknown but much progress has occurred in defining important mechanistic components of RA, leading to significant advances in its treatment. RA is a multifactorial and multistage disease, beginning with preclinical autoimmunity that arises in a genetically predisposed individual who encounters one or more environmental triggers, progressing to the clinical appearance of inflammation in joints and sometimes in other organs, and leading (if effective treatment is unavailable) to destruction of the articular cartilage and adjacent bone. This chapter will consider historical, epidemiologic, genetic, environmental, autoimmune, and inflammatory aspects of the development and progression of RA.

Epidemiology and Historical Aspects of RA

In a Caucasian population sample in the United States, the incidence and prevalence of RA have fluctuated over the past five decades [1]. As of 2005, the incidence per year per 100,000 of population was 27.7 in men and 53.1 in women, with an overall prevalence of 0.72 %. The incidence of RA rises in frequency from early adulthood into the seventh decade, before declining in the eighth decade and beyond [1]. In this context, and in view of the lifelong persistence of RA in most affected individuals, the lifetime risk of developing RA is strikingly high: 3.64 % in women and 1.68 % in men [2].

Individuals with RA have an approximately 50 % increase in premature mortality (after adjustment for comorbidities and risk factors such as smoking), which equates to a reduction in life expectancy of 3–10 years [3]. Multiple factors appear to contribute to this “mortality gap” versus the general population, with accelerated cardiovascular disease identified as the most significant component [4].

The historical epidemiology of RA is intriguing and, if accurately understood, could provide clues to etiology [5]. Recognizable descriptions of RA in the medical literature are recent, beginning about 200 years ago, but some earlier European paintings show what appear to be RA-like deformities. A few skeletal remains from

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both the New World and the Old World, dated to points in time over the past four millennia, have shown damage interpreted as potentially due to RA (reviewed in [5]). RA may have been present in ancient times but was likely rarer than at present. If this assessment is correct, it may indicate changes in the presence of environmental triggers and/or genetic changes in the human population over time that have increased propensity to RA.

Genetics of RA

The importance of inherited risk alleles in the pathogenesis of RA is highlighted by increased concordance for RA in monozygotic compared to dizygotic twins and by the familial clustering of RA. The most important region of the human genome in RA susceptibility is the major histocompatibility complex (MHC), which encodes for genes that are essential to immune responses, notably the HLA-A, HLA-B, HLA-C, and HLA-D proteins. These structures are expressed on the surface of antigen-presenting cells and are required for recognition of peptide antigens by T lymphocytes, leading to initiation of immune responses. The RA-associated MHC allele was initially identified as HLA-DR4 [6] and later localized to a five-amino-acid sequence from residues 70–74 of the beta chain of subtypes of HLA-DR4 and selected other DR alleles, termed the “shared epitope,” which is located within the MHC peptide-binding cleft [7]. More recently polymorphisms that govern additional amino acid variations in HLA-DR that are located outside the shared epitope have also been strongly associated with susceptibility to RA [8, 9]. The mechanism for MHC predisposition to RA remains to be established—while presentation of a pathogenic autoantigen by RA-associated alleles is an attractive theory, other possibilities exist, for example, unique pro-inflammatory properties of the shared epitope itself [10].

Genome-wide association studies have identified more than 100 other loci that affect susceptibility to RA, each of which has a modest effect [8, 11]. The specific genes associated with these loci mostly function in cells that mediate immune responses, such as lymphocytes and antigen-presenting cells,

Table 2.1 Examples of RA-associated genes

Gene	Function
HLA-DR (shared epitope)	Antigen presentation, lymphocyte activation
PTPN 22 (protein-tyrosine phosphatase non-receptor type 22)	Regulation of T cell receptor signaling
PADI4 (peptidyl arginine deiminase 4)	Posttranslational conversion of arginine to citrulline
CCR6 (chemokine receptor 6)	Attraction of Th17 cells to sites of inflammation
STAT4 (signal transducer and activator of transcription 4)	Signaling downstream of cytokine receptors

reinforcing the concept that RA is an autoimmune disease (Table 2.1). The known loci associated with RA, both MHC and non-MHC, are more strongly linked to seropositive RA, i.e., RA in which either rheumatoid factor (RF) or antibodies to citrulline-containing proteins (ACPA) are present. The most influential RA-associated non-MHC gene is PTPN22, which encodes a tyrosine phosphatase that is expressed in lymphocytes, regulates signaling through the T cell receptor for antigen, and influences lymphocyte development [12].

Epigenetic mechanisms control gene expression in a potentially heritable manner and include DNA methylation, histone modifications such as acetylation, and microRNA control of posttranscriptional stages of gene expression. Understanding of the role of epigenetics in RA is still in its infancy, but such mechanisms are likely to be of great importance, especially in the connection of environmental triggers to changes in gene expression [8, 13]. Epigenetic changes often occur distinctly in specific cell types, such as lymphocytes or synovial fibroblasts [13, 14], increasing the complexity of analysis in a disease such as RA that involves multiple cell populations.

Environmental Triggers of RA

Smoking is the best-established environmental risk factor for RA and is receiving attention as a potential trigger for the development of RA-associated autoimmunity. Although the association of smoking with RA was suspected 25 years ago [15], this link has become much better

established within the past decade [16, 17], with smoking shown to increase the risk for seropositive RA by more than twofold. Smoking synergizes with the presence and gene dosage of the MHC shared epitope allele to greatly increase the risk of developing RA [18]. Preliminary evidence suggests that cigarette smoking can induce expression in the lungs of the enzymes responsible for citrullination of various proteins, thus creating antigen targets of autoantibodies that are tightly associated with RA [18, 19]. Smoking is also associated with resistance to successful treatment of RA and more rapid disease progression [20]. Thus, smoking cessation should be viewed as part of both prevention and treatment of RA.

Infection has long been viewed as a potential trigger of RA, even though direct infection of RA joints has not been demonstrated (reviewed in [21]). A variety of bacterial and viral pathogens have been implicated, but not definitively [21]. Recently attention has refocused on the clinical association of RA and periodontal disease [22, 23]. *Porphyromonas gingivalis* (*Pg*) is a gram-negative bacterium that is strongly linked to periodontal disease. Uniquely among bacteria, it possesses the enzymatic machinery to generate citrullinated proteins, and such RA autoantigens are indeed detected in the gingival tissue of subjects with periodontitis [22, 23]. Smoking and periodontal disease are also positively associated [23].

Investigation of the microbiome is a new area of inquiry in RA and other autoimmune diseases, and is a complex task in view of the multiple microbiomes present on the skin and in the respiratory and gastrointestinal tracts and the multiple influences that can skew the composition of each microbiome. One report identified a higher level of *Prevotella copri* in feces of patients with new onset RA. This RA group was seropositive for RF and/or ACPA, and expansion of *Prevotella* was more pronounced in the subset that lacked the MHC shared epitope compared with those who were shared epitope positive [24]. This finding will require confirmation and further exploration of implications for the pathogenesis of RA.

Stages of RA

RA-associated autoimmunity precedes clinical onset of RA, and joint inflammation precedes damage to the cartilage and bone. The sequence of systemic and articular events in RA can be conceptualized as discrete stages of RA. Holmdahl et al. have delineated these stages as autoimmune priming, tissue attack, and chronic inflammation [25]. The hallmark of autoimmune priming is the appearance of RA-associated autoantibodies, especially RF and/or ACPA.

Rheumatoid factors (RFs) are antibodies that recognize a domain of the IgG Fc portion as their target antigen. Recognized since the 1950s as present in about 70 % of patients with RA, RF is however highly nonspecific and is found in many other immune-mediated and infectious conditions as well as in some apparently healthy older individuals. The presence and titer of RF correlate positively with disease severity and extra-articular manifestations, and RF has plausible roles in the pathogenesis of RA synovitis (reviewed in [21]).

ACPA recognize proteins that have undergone posttranslational conversion of arginine to citrulline at one or more arginine residues [26], a reaction that is catalyzed by peptidyl arginine deiminase (PAD). ACPA are much more specific for RA than in RF and are thus useful diagnostically [27]. The presence and titer of ACPA also predict disease severity, including the degree of joint destruction [28]. Both RF and ACPA can appear years before the clinical onset of RA [25, 29–31]. At this stage, elevated serum biomarkers of inflammation can also be detected, including pro-inflammatory cytokines [30, 31].

The high specificity of ACPA for RA has prompted consideration of a potential role for these autoantibodies in RA etiology and pathogenesis. As mentioned previously, citrullinated antigens can be formed in the lung and oral cavity as a result of cigarette smoking or by *P. gingivalis*, respectively, environmental triggers that are epidemiologically associated with risk of RA. Thus, local extra-articular inflammatory processes could create immunogens for development

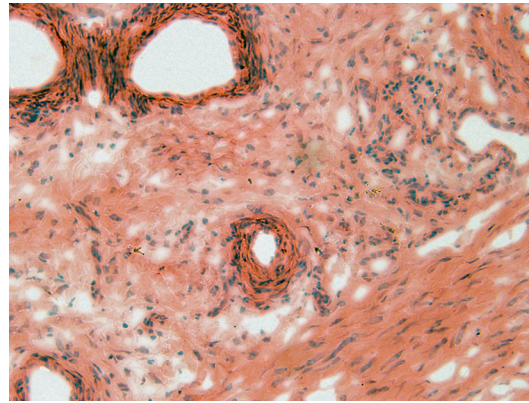
Table 2.2 Key elements in the pathogenesis of RA synovitis and tissue damage

Autoantibodies	RF, ACPA
T cells	Th17 (?Th1)
Cytokines	TNF, IL-6, IL-1, IL-17
Synovial fibroblasts	Cartilage damage, interactions with lymphocytes
Osteoclasts	Bone destruction
Endothelial cells	Angiogenesis

of RA-associated autoantibodies, capable of recognizing citrullinated proteins in the joint at a later stage of disease [32].

The second stage of RA is the appearance of clinical arthritis due to a level of joint inflammation that is sufficient to generate clinical symptoms and signs. The specific trigger or triggers that localize the systemic autoimmune process to the joint are unknown and could be heterogeneous, including local trauma, transient infection of the joint itself, systemic infection that alters permeability of the synovial microcirculation, noninfectious tissue damage that generates ligands of innate immune receptors, and increase in the magnitude and affinity of autoreactive B and T lymphocyte responses that react against articular antigens. A curious feature of RA is the tendency toward symmetry of joint involvement. This mapping of the disease, which differs from other forms of inflammatory and degenerative arthritis, can be interpreted to implicate pathogenic events in the local mesenchymal cells [synovial fibroblasts (FLS), also known as type B synoviocytes] in the control of disease onset in specific joints in RA.

Synovitis is the hallmark of clinical RA (Table 2.2), and a detailed molecular understanding of this process has led to remarkable advances in the treatment of RA with both biologic and non-biologic pharmaceutical agents. The three most abundant cell populations in RA synovium are type A synoviocytes (of monocyte-macrophage lineage), FLS, and T cells. Other important participants include dendritic cells (potent antigen-presenting cells), B lymphocytes, plasma cells, endothelial cells, mast cells, neutrophils (primarily in synovial fluid rather than synovial tissue), and osteoclasts. Normal synovium is

**Fig. 2.1** Photomicrograph (20×) of chronic rheumatoid synovitis. Note the synovial fibroblast hyperplasia (lower right), extensive arterial and venous vascularity, and inflammatory cell infiltrate

not known to be a location for initiation or propagation of immune responses, but in RA the synovium assumes characteristics of a tertiary lymphoid organ. The massive infiltration of leukocytes in RA synovium is accompanied by (and likely causes) marked hypertrophy of the synovial lining layer (Fig. 2.1). Numerous cytokines and other inflammatory mediators are produced in RA synovium as an outcome of the complex interactions between the various cellular constituents [33]. These interactions are both cognate (resulting from direct cell-cell contact mediated by various receptor-ligand pairings) and paracrine (due to local release of soluble pro-inflammatory mediators). Angiogenesis is a critical process in supporting synovial expansion and inflammation in RA, by providing avenues for the ingress of inflammatory cells and the nutrients to sustain them.

The third stage of RA is chronic inflammation that is destructive of cartilage, bone, and other structures including tendons and ligaments, leading to deformities that may require surgical intervention. Cartilage is directly invaded by chronically inflamed synovial tissue termed pannus, with a key role for FLS. Although FLS can secrete a variety of proteases and other mediators that may contribute to tissue damage in RA, a critical role has emerged for the membrane-anchored matrix metalloproteinase on the FLS surface known as MMP-14 or MT1-MMP in the

invasion and destruction of collagenous structures [34]. Bone is eroded in RA through the activation of osteoclasts in the adjacent bone and through differentiation of monocyte precursors into osteoclasts in the inflamed synovial tissue, processes that are cytokine driven [35].

The distinctions between these three stages become blurred when one examines underlying mechanisms. Thus, ACPA can bind directly to citrullinated structures on the surface of osteoclasts, leading to osteoclast activation that would promote bone erosion. Sensitive imaging techniques confirm that joint damage can occur very early in clinically diagnosed RA and that osteopenia is present at the time of diagnosis in ACPA-positive patients [35]. The concept that joint destruction begins as soon as (or even before) recognizable synovitis is present reinforces the necessity for early diagnosis and aggressive treatment to minimize cartilage loss, bone erosion, soft tissue disruption, deformity, and consequent functional disability.

Cytokines and T Cells in RA

An essential role for pro-inflammatory cytokines is well established in RA, and RA has become the prototypic autoimmune disease in which cytokine blockade by biologic agents has revolutionized disease management. Of the nine biologics approved in the United States for use in RA, seven neutralize key cytokines in RA synovium—tumor necrosis factor (TNF), interleukin-1 (IL-1), or interleukin-6 (IL-6). (Of the other two biologics approved for RA, one impairs T cell activation and one depletes B lymphocytes.) Moreover, other agents that are effective in RA, such as a Janus kinase inhibitor, act primarily by blocking signaling downstream of cytokine receptor activation [36]. Cytokines appear to be important at all stages of RA, although it is possible that shifts in cytokine networks occur as RA evolves.

The search for additional cytokine targets in RA has focused in part on the cytokines secreted by differentiated effector cell subsets of CD4+ T lymphocytes. T cells have long been viewed as

central to the pathogenesis of RA (reviewed in [21]). T cells in the joint respond to various local tissue antigens and interact with FLS in ways that can promote activation of both cell types [33]. Activated subsets of CD4+ cells can be defined by their cytokine products: Th1 cells secrete interferon-gamma, Th2 cells secrete interleukin 4, and Th17 cells secrete various isoforms of interleukin 17. Though Th2 cells are critical for allergic diseases, many autoimmune conditions, including RA, appeared to be driven by Th17 cells, Th1 cells, or by cells that overlap the Th1/Th17 subsets [37]. Manipulation of the function of these cells and neutralization of their secreted cytokines are current areas of clinical investigation that may shed further light on disease pathogenesis.

Future Directions

Although the cause, cure, and prevention of RA are not yet known, significant and accelerating progress has been achieved toward each of these goals. Plausible models for the development of RA that integrate genetic predisposition, environmental triggers, autoimmunity, synovial inflammation, and tissue damage have been proposed [29–32, 38]. At the same time, the notion of molecular heterogeneity of RA is gaining traction, based on distinct patterns of synovial gene expression that can predict clinical response or lack of response to various biologics and ultimately guide individualized treatment approaches [39]. Perhaps most exciting, the improving ability to define risk for RA before onset of disease is laying the groundwork for clinical trials of RA prevention [40, 41].

References

1. Myasoedova E, Crowson CS, Kremers HM, Thorneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. *Arthritis Rheum.* 2010;62(6):1576–82. Pubmed Central PMCID: 2929692.
2. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The lifetime risk

- of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis Rheum.* 2011;63(3):633–9. Pubmed Central PMCID: 3078757.
3. Myasoedova E, Davis 3rd JM, Crowson CS, Gabriel SE. Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. *Curr Rheumatol Rep.* 2010;12(5):379–85.
 4. Crowson CS, Liao KP, Davis 3rd JM, Solomon DH, Matteson EL, Knutson KL, et al. Rheumatoid arthritis and cardiovascular disease. *Am Heart J.* 2013;166(4):622–8.e621. Pubmed Central PMCID: 3890244.
 5. Entezami P, Fox DA, Clapham PJ, Chung KC. Historical perspective on the etiology of rheumatoid arthritis. *Hand Clin.* 2011;27(1):1–10. Pubmed Central PMCID: 3119866.
 6. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. *N Engl J Med.* 1978;298(16):869–71.
 7. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum.* 1987;30(11):1205–13.
 8. Viatte S, Plant D, Raychaudhuri S. Genetics and epigenetics of rheumatoid arthritis. *Nat Rev Rheumatol.* 2013;9(3):141–53. Pubmed Central PMCID: 3694322.
 9. Okada Y, Kim K, Han B, Pillai NE, Ong RT, Saw WY, et al. Risk for ACPA-positive rheumatoid arthritis is driven by shared HLA amino acid polymorphisms in Asian and European populations. *Hum Mol Genet.* 2014;23(25):6916–26. Pubmed Central PMCID: 4245039.
 10. Ling S, Cline EN, Haug TS, Fox DA, Holoshitz J. Citrullinated calreticulin potentiates rheumatoid arthritis shared epitope signaling. *Arthritis Rheum.* 2013;65(3):618–26. Pubmed Central PMCID: 3582785.
 11. Kochi Y, Suzuki A, Yamamoto K. Genetic basis of rheumatoid arthritis: a current review. *Biochem Biophys Res Commun.* 2014;452(2):254–62.
 12. Stanford SM, Bottini N. PTPN22: the archetypal non-HLA autoimmunity gene. *Nat Rev Rheumatol.* 2014;10(10):602–11.
 13. Klein K, Gay S. Epigenetics in rheumatoid arthritis. *Curr Opin Rheumatol.* 2015;27(1):76–82.
 14. Nakano K, Whitaker JW, Boyle DL, Wang W, Firestein GS. DNA methylome signature in rheumatoid arthritis. *Ann Rheum Dis.* 2013;72(1):110–7. Pubmed Central PMCID: 3549371.
 15. Hernandez Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. *Epidemiology.* 1990;1(4):285–91.
 16. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum.* 2004;50(10):3085–92.
 17. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* 2006;54(1):38–46.
 18. Makrygiannakis D, Hermansson M, Ulfgren AK, Nicholas AP, Zendman AJ, Eklund A, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis.* 2008;67(10):1488–92.
 19. Kilsgard O, Andersson P, Malmsten M, Nordin SL, Linge HM, Eliasson M, et al. Peptidylarginine deiminases present in the airways during tobacco smoking and inflammation can citrullinate the host defense peptide LL-37, resulting in altered activities. *Am J Respir Cell Mol Biol.* 2012;46(2):240–8.
 20. Saevarsdottir S, Rezaei H, Geborek P, Petersson I, Ernestam S, Albertsson K, et al. Current smoking status is a strong predictor of radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial. *Ann Rheum Dis.* 2014;4.
 21. Fox DA. Etiology and pathogenesis of rheumatoid arthritis. In: Koopman WJ, Moreland LW, editors. *Arthritis and allied conditions.* Philadelphia: LWW; 2004. p. 1089–115.
 22. Bingham 3rd CO, Moni M. Periodontal disease and rheumatoid arthritis: the evidence accumulates for complex pathobiologic interactions. *Curr Opin Rheumatol.* 2013;25(3):345–53.
 23. Scher JU, Bretz WA, Abramson SB. Periodontal disease and subgingival microbiota as contributors for rheumatoid arthritis pathogenesis: modifiable risk factors? *Curr Opin Rheumatol.* 2014;26(4):424–9. Pubmed Central PMCID: 4128331.
 24. Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, et al. Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *eLife.* 2013;2:e01202. Pubmed Central PMCID: 3816614.
 25. Holmdahl R, Malmstrom V, Burkhardt H. Auto-immune priming, tissue attack and chronic inflammation – the three stages of rheumatoid arthritis. *Eur J Immunol.* 2014;44(6):1593–9.
 26. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest.* 1998;101(1):273–81. Pubmed Central PMCID: 508564.
 27. van Jaarsveld CH, ter Borg EJ, Jacobs JW, Schellekens GA, Gmelig-Meyling FH, van Booma-Frankfort C, et al. The prognostic value of the antiperinuclear factor, anti-citrullinated peptide antibodies and rheumatoid factor in early rheumatoid arthritis. *Clin Exp Rheumatol.* 1999;17(6):689–97.
 28. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies

- recognizing a cyclic citrullinated peptide. *Arthritis Rheum.* 2000;43(1):155–63.
29. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? *Curr Opin Rheumatol.* 2014;26(1):64–71. Pubmed Central PMCID: 4033623.
 30. Holers VM. Autoimmunity to citrullinated proteins and the initiation of rheumatoid arthritis. *Curr Opin Immunol.* 2013;25(6):728–35. Pubmed Central PMCID: 3895448.
 31. Deane KD. Preclinical rheumatoid arthritis (auto-antibodies): an updated review. *Curr Rheumatol Rep.* 2014;16(5):419. Pubmed Central PMCID: 4059414.
 32. Klareskog L, Malmstrom V, Lundberg K, Padyukov L, Alfredsson L. Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. *Semin Immunol.* 2011;23(2):92–8.
 33. Fox DA, Gizinski A, Morgan R, Lundy SK. Cell-cell interactions in rheumatoid arthritis synovium. *Rheum Dis Clin North Am.* 2010;36(2):311–23. Pubmed Central PMCID: 2879397.
 34. Sabeh F, Fox D, Weiss SJ. Membrane-type I matrix metalloproteinase-dependent regulation of rheumatoid arthritis synoviocyte function. *J Immunol.* 2010;184(11):6396–406.
 35. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat Rev Rheumatol.* 2012;8(11):656–64. Pubmed Central PMCID: 4096779.
 36. Fox DA. Kinase inhibition—a new approach to the treatment of rheumatoid arthritis. *N Engl J Med.* 2012;367(6):565–7.
 37. Sarkar S, Fox DA. Targeting IL-17 and Th17 cells in rheumatoid arthritis. *Rheum Dis Clin North Am.* 2010;36(2):345–66.
 38. Boissier MC, Semerano L, Challal S, Saidenberg-Kermanac'h N, Falgarone G. Rheumatoid arthritis: from autoimmunity to synovitis and joint destruction. *J Autoimmun.* 2012;39(3):222–8.
 39. Dennis Jr G, Holweg CT, Kummerfeld SK, Choy DF, Setiadi AF, Hackney JA, et al. Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. *Arthritis Res Ther.* 2014;16(2):R90. Pubmed Central PMCID: 4060385.
 40. Karlson EW, van Schaaardenburg D, van der Helm-van Mil AH. Strategies to predict rheumatoid arthritis development in at-risk populations. *Rheumatology (Oxford).* 2016;55(1):6–15.
 41. Hunt L, Emery P. Defining populations at risk of rheumatoid arthritis: the first steps to prevention. *Nat Rev Rheumatol.* 2014;10(9):521–30.

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