# Aetiopathology of rheumatoid arthritis

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## Abstract

Rheumatoid arthritis (RA) has a multifactorial aetiopathogenesis with both genetic and environmental factors implicated, giving rise to immune dysregulation with resultant joint inflammation and tissue damage. The emergence of biologic and small molecular targeted therapeutics has validated the role of many key molecules and cells in the pathogenesis of RA. The major cellular components, cytokines and key signalling pathways of importance in RA pathogenesis are reviewed in this article. The 'microbiome' (the population of commensals at mucosal surfaces) is also increasingly recognized to play a potential role in the pathogenesis of RA.

**Keywords** Angiogenesis; anti-citrullinated peptide antibodies; B cell; co-stimulation; cytokine; dendritic cells; microbiome; MRCP; rheumatoid arthritis; T cell

## Key points

- Rheumatoid arthritis (RA) is a heterogeneous syndrome with multifactorial aetiopathogenesis
- Genetic mutations of HLA-DRB1 alleles account for a large proportion of genetic risk
- Further investigation of the microbiome may give further insight into the aetiology of RA
- A multitude of proinflammatory cytokines contribute to, and are the focus of many therapies for, RA

## Genetic factors

Genetic factors clearly play a role in the aetiopathogenesis of rheumatoid arthritis (RA)[1] (Figure 1). There is a slight increase in frequency of RA in first-degree relatives of RA patients, especially if they are seropositive for rheumatoid factor (RF). Furthermore, identical twins share RA in about 12–15% of instances, compared with 1% of the general population. The relatively low concordance suggests that RA is a polygenic disease, and that non-genetic factors also contribute to disease pathogenesis.

Over 100 risk loci have been described as predisposing to RA, the largest contribution coming from those encoding particular class II human leucocyte antigens (HLA). Here, the allele HLA-DRB1*04 was found to be present in 70% of white patients with RA, compared with about 30% of the healthy control population. Further characterization of the HLA locus identified multiple RA risk alleles within HLA-DRB1, encoding a conserved amino acid sequence at position 70–74, known as the 'shared epitope'.[2] The shared epitope has been widely demonstrated to be associated with erosive, destructive disease, and an increased likelihood of developing anti-cyclic citrullinated peptide antibody (ACPA) positive RA in association with cigarette smoking has been reported.

The molecular mechanisms accounting for the susceptibility to RA inferred by HLA-DRB1 are unclear, but include modifications in antigen binding, resulting in binding of autoantigens or environmental antigens, initiation of disease by specific binding of superantigens to HLA molecules, or modulation of the T cell repertoire by selection or tolerance.

## The microbiome

The mucosal surfaces of the oral cavity, upper respiratory tract and gut are colonized by commensal microorganisms; this population is known as the microbiome. Aberrations in the microbiome may facilitate developments in innate and adaptive immunity that predispose to RA.[3] For example, multiple studies have demonstrated an association between RA and periodontitis, often caused by the bacterium *Porphyromonas gingivalis*. Studies focussing on the gut microbiome in RA have suggested that an expanded presence of intestinal *Prevotella copri*, together with a reduction in other bacteria, including *Bacteroides* species, is more common in patients with new-onset RA compared with healthy controls. The true impact of the microbiome on RA pathogenesis is the subject of continuing investigation.

## Autoantibodies

RF is an antibody directed against the Fc portion of human immunoglobulin (Ig) G. It has long been established that patients with high RF titres are more likely to develop extra-articular disease than those negative for RF. Typically, RF is of IgM isotype, but IgG and IgA also occur. They are found in 75–80% of RA patients at some time during their disease course.

High-titre IgM RF is relatively specific for the diagnosis of RA in the context of a chronic polyarthritis, and was for decades the sole serological criterion widely used to diagnose RA. It has little predictive value in the general population, although the presence of RF, particularly at high levels, can antedate the clinical development of RA. RF can potentiate inflammation by activating Fc receptors on monocytes, inducing the production of

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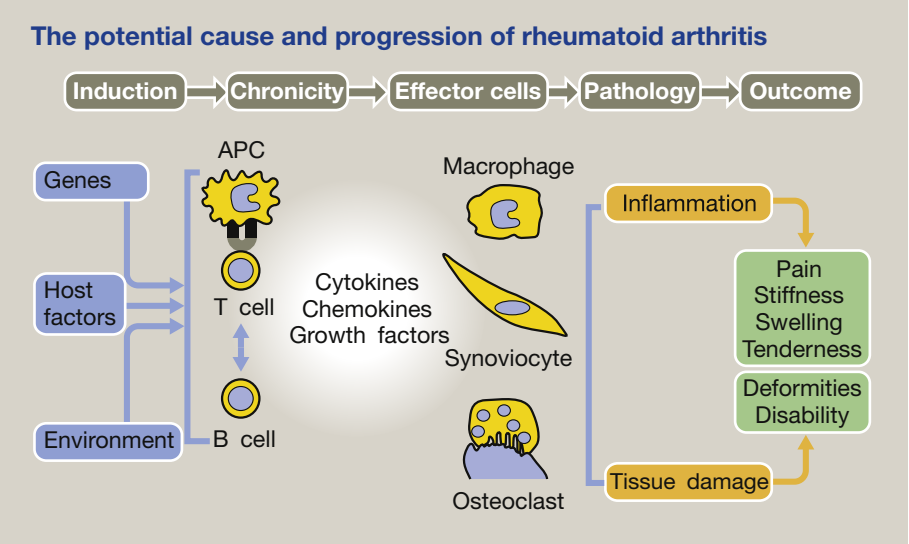


**Figure 1** The potential cause and progression of RA. In genetically susceptible individuals, host and environmental factors can result in activation of pathogenic T cells and a subsequent cascade of inflammatory events that fail to switch off. An example includes the increased occurrence of autoantibodies to certain citrullinated peptides in genetically susceptible individuals who smoke. Cytokines are involved in coordinating the immune response and in the recruitment and activation of effector cells, which results in not only inflammation, but also local tissue damage in the RA joint. APC, antigen-presenting cell.

proinflammatory cytokines such as tumour necrosis factor (TNF)-α. Immune complexes of RF can also activate complement, potentiating inflammation.

Over the last three decades, there has been increasing recognition of the importance of ACPA in the pathogenesis of RA. Unlike RF, which has little specificity for predicting RA in the general population, the presence of ACPA is more specific and sensitive to RA.

Citrullination involves the protein modification by the conversion of an arginine amino acid into a citrulline amino acid residue, through the action of the enzyme peptidyl arginine deiminase; this produces immunogenic epitopes, to which ACPA binds. A wide range of proteins, including vimentin, fibrin and fibrinogen, can undergo citrullination. ACPAs themselves can form immune complexes, leading to inflammation in the same way as RF.

## Cellular pathology

RA is characterized by chronic inflammation of synovial joints with synovial proliferation and infiltration by blood-derived cells, in particular, memory T cells, macrophages and plasma cells (B cells), all of which show signs of activation. Angiogenesis is a feature from the earliest stages of disease. The synovial tissue becomes markedly hyperplastic and locally invasive at the interface between cartilage and bone, usually with progressive destruction of these tissues. This invasive tissue is termed 'pannus'; it comprises mainly lining cells with the appearance of proliferating mesenchymal cells, with very little sublining lymphocytic infiltration. The accompanying destruction of bone and cartilage is mediated by degradative enzymes, notably matrix metalloproteinases. Although RA has its principal manifestation in joints, there is also evidence of systemic involvement, including up-regulation of acute-phase proteins and a variety of extra-articular features. These occur predominantly in patients who are RF-positive and carry the HLA-DR4 gene.

T lymphocytes are abundant in active RA, comprising 30–50% of cells in the inflamed synovium. Activated T cells contribute to the regulation of osteoclast activation and thus joint destruction. Co-stimulation is an essential component of T cell activation in RA

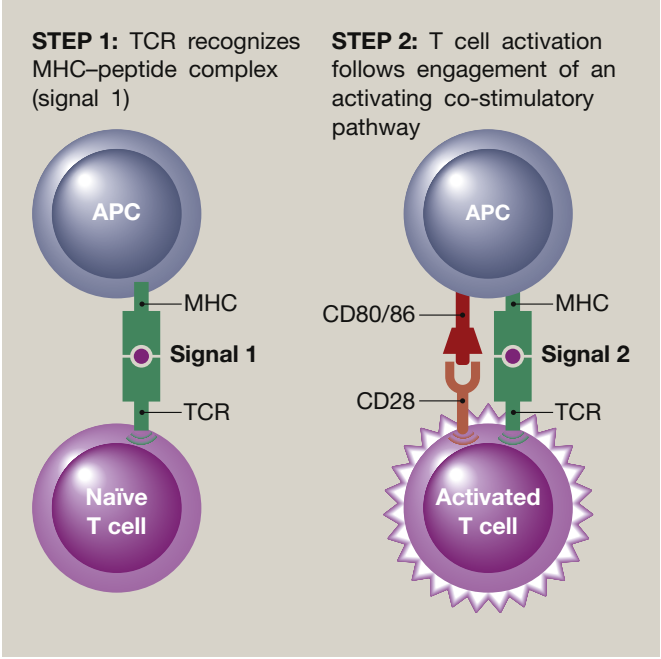


**Figure 2** The T cell receptor (TCR) binds to and recognizes components of both the major histocompatability complex (MHC) and peptide to elicit signal one. There are many different variants of both the T cell receptor and MHC molecules. However, this is insufficient to activate the T cell. Activation follows engagement of a co-stimulatory pathway. CD80/86:CD28 is the best characterized co-stimulatory pathway. CD28 is constitutively expressed on T cells and binds to CD80/86. CD80/86:CD28 facilitates T cell activation, proliferation, survival and cytokine production.




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