Aetiopathology of rheumatoid arthritis

Peter C Taylor

Abstract

Although the aetiology of rheumatoid arthritis remains unknown, there have been considerable advances in our understanding of its aetiopathogenesis in the last two decades. The role of genetic and environmental interactions in giving rise to immune dysregulation and the key cellular and cytokine mediators, as well as the signalling pathways involved, have been extensively studied. These insights have led to major advances in therapeutic options in the pharmacological management of this condition.

Keywords Aetiopathogenesis; angiogenesis; anti-citrullinated peptide antibodies; B cell; co-stimulation; cytokine; dendritic cells; rheumatoid arthritis; T cell

What's new?

- Biologic therapies are protein based and do not penetrate inside cells. They have been developed to target extracellular or cell surface-related targets. Blockade of TNF, IL-6R, CD20 and co-stimulation molecules are all effective treatments for RA available in the clinic
- An alternative approach to inhibition of the action of pro-inflammatory cytokines is the development of small molecular therapies that penetrate cells and prevent intracellular signalling through cytokine receptors. Many small molecules that target signalling enzymes, including inhibitors of p38 MAP kinase, SYK and JAK, have been investigated in trials. Of these, one JAK inhibitor has recently been approved for use in the clinic in North America by the FDA but has not received approval by EMEA for use in Europe as of late 2013

Genetic factors

Genetic factors became implicated in the aetiopathogenesis of rheumatoid arthritis (RA) because of the slight increase in the frequency of RA in first-degree relatives of RA patients, especially if seropositive for rheumatoid factor. In identical twins, concordance rates for disease are around 30% compared with 5% in non-identical twins. Such observations suggest that RA is a polygenic disease, and that non-inherited factors are also of great importance.[1]

Over 100 risk loci have been described for predisposition to RA, the largest contribution coming from those encoding particular class II human leucocyte antigens (HLA). This discovery arose with the observation that 60–70% of Caucasian patients with RA are HLA-DR4 positive compared with 20–25% of control populations. Furthermore, patients with more severe RA, especially those with extra-articular complications such as vasculitis and Felty's syndrome, are even more likely to be HLA-DR4 positive than patients with disease confined to joints.

Class II HLA molecules are expressed on the surface of antigen-presenting cells. They play a key role in the presentation of processed linear peptide antigens to T cells. Antigen is bound to the HLA-binding cleft formed by the α and β chains of the HLA class II molecule. This tri-molecular HLA–antigen complex binds, in turn, to the variable portion of the T-cell receptor.

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The nucleotide sequence of HLA DR β_1 exons coding the five amino acid residues 70–74 predicts susceptibility to RA and is associated with RA in 83% of Caucasian patients in the United Kingdom.[2–4] This sequence is located in the α-helix forming the wall of the peptide-binding groove, and is likely to be involved in antigen binding and subsequent interaction with T-cell receptors. Possible molecular mechanisms accounting for susceptibility to RA include permissive binding of specific peptides, such as those on autoantigens or on environmental antigens, initiation of disease by specific binding of superantigens to HLA molecules, or modulation of the T-cell repertoire by selection or tolerance.

Autoantibodies

Rheumatoid factors (RF) are autoantibodies directed against the Fc portion of IgG. They are found in 75–80% of RA patients at some time during the course of their disease. 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 serologic criterion widely used in the diagnosis of RA. It has little predictive value in the general population although the presence of RF, particularly at high levels, may antedate the clinical development of RA.[5] There is now compelling evidence that in a particular genetic context, smoking is a potential trigger for rheumatoid arthritis. Furthermore, when these two factors occur together, they are associated with an autoantibody response directed against highly citrullinated peptides that may considerably antedate the onset of clinical features of RA (Figure 1). Citrulline is derived from the amino acid arginine after peptide translation under the influence of the enzyme peptidyl arginine deiminase (PADI4). Genetic variants of this enzyme are associated with RA. Individuals carrying double alleles for the shared epitope, and who smoke, are at approximately 16-fold increased risk of seropositive rheumatoid arthritis, compared with non-smokers without the shared epitope genes.[6,7] Identification of the true citrullinated target RA antigen(s) is of importance for understanding aetiopathogenesis. Proposed candidates include citrullinated fibrinogen, citrullinated vimentin, citrullinated α-enolase and citrullinated type II collagen. Many patients have detectable autoantibody reactivity to several of these.[8–13] Testing for

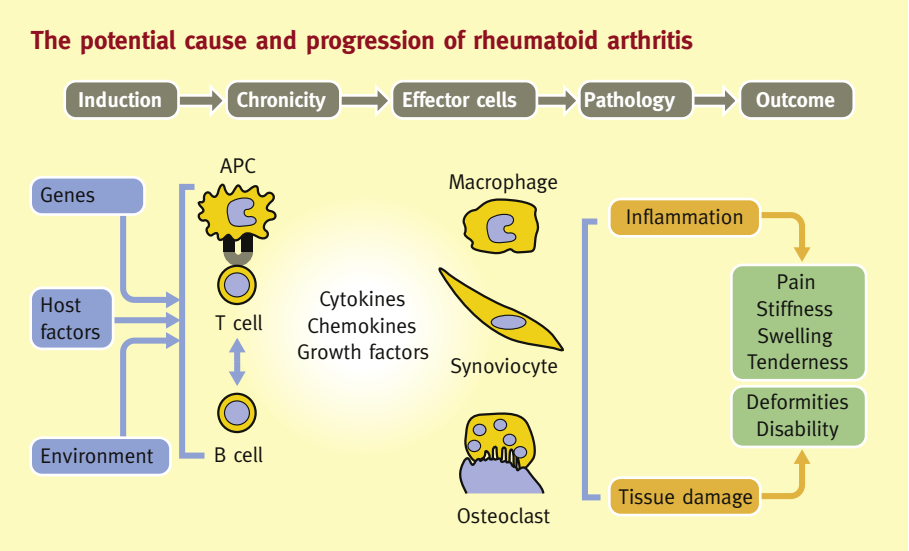

Figure 1 The potential cause and progression of RA. In genetically susceptible individuals, host and environment factors may result in activation of pathogenic T cells and a subsequent cascade of inflammatory events which fail to switch off. An example includes the increased occurrence of auto-antibodies to certain citrullinated peptides in genetically susceptible individuals who smoke. Cytokines are involved in co-ordinating the immune response, and recruitment and activation of effector cells that result not only in inflammation, but also local tissue damage in the RA joint.

anti-citrullinated peptide antibodies (ACPA) has become common in the evaluation of patients for RA. Since ACPA is now recognized as a component of the new criteria for diagnosis of RA,[14] measurement of IgM RF might be considered to be redundant. However, several studies have demonstrated that a small proportion of patients who will be categorized as RA may be positive for RF alone in the early stages of presentation, such that the specificity and sensitivity of a diagnosis if RA is improved by measuring both RF and ACPA. Moreover, high-titre RF appears to be a better predictor of severe disease course, showing more striking correlations with extra-articular manifestations such as interstitial lung disease and vasculitis than appears to be the case for ACPA.

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, all of which show signs of activation.[15] Angiogenesis is a feature from the earliest stages of disease development. The synovial tissue becomes markedly hyperplastic and locally invasive at the interface of cartilage and bone, with progressive destruction of these tissues in the majority of cases. This invasive tissue is termed 'pannus' and 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.

Presentation of self-antigen to T cells is thought to be central to the pathogenesis of RA. Various cell types are capable of antigen-presenting cell function. Dendritic cells in particular have attracted much interest in recent years, because of their potent ability to present antigen and, in particular, their unique capacity to activate naïve T cells.[16] T cells are abundant in active RA, comprising 20–50% of cells in the inflamed synovium. Activated T cells contribute to the regulation of osteoclast activation and

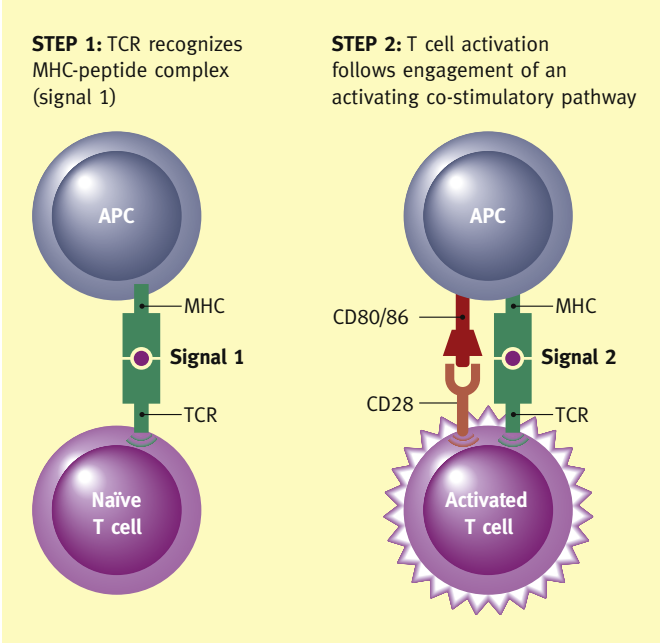

Figure 2 The T-cell receptor (TCR) binds to and recognizes components of both the MHC and peptide to elicit signal one. There are many different variants of both the T-cell receptor and MHC molecules. However, this is insufficient to activate the T cell. Activation follows engagement of a co-stimulatory 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.