# Evolving concepts of rheumatoid arthritis

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**Rheumatoid arthritis is the most common inflammatory arthritis and is a major cause of disability. It existed in early Native American populations several thousand years ago but might not have appeared in Europe until the 17th century. Early theories on the pathogenesis of rheumatoid arthritis focused on autoantibodies and immune complexes. T-cell-mediated antigen-specific responses, T-cell-independent cytokine networks, and aggressive tumour-like behaviour of rheumatoid synovium have also been implicated. More recently, the contribution of autoantibodies has returned to the forefront. Based on the pathogenic mechanisms, specific therapeutic interventions can be designed to suppress synovial inflammation and joint destruction in rheumatoid arthritis.**

*"Life can only be lived forwards, but must be understood backwards."* Søren Kierkegaard

Rheumatoid arthritis (RA) is a symmetric polyarticular arthritis that primarily affects the small diarthrodial joints of the hands and feet. In addition to inflammation in the synovium, which is the joint lining, the aggressive front of tissue called pannus invades and destroys local articular structures. The synovium is normally a relatively acellular structure with a delicate intimal lining. In RA, $CD4^+$ T cells, B cells and macrophages infiltrate the synovium and sometimes organize into discrete lymphoid aggregates with germinal centres (Fig. 1). Hyperplasia of the intimal lining results from a marked increase in macrophage-like and fibroblast-like synoviocytes. Locally expressed degradative enzymes, including metalloproteinases, serine proteases and aggrecanases, digest the extracellular matrix and destroy the articular structures. RA occurs in 0.5–1.0% of the adult population worldwide, although the prevalence may have changed substantially in Europe since the Renaissance (see Box 1).

## Era of rheumatoid factor and immune complexes

Prevailing notions on the pathogenesis of RA have evolved since the mid-20th century, when the first concepts of immune hyper-reactivity were considered. The first clue that self-reactivity plays a key role in RA was the identification of 'rheumatoid factor' in the blood of affected patients. Rheumatoid factor was observed originally by Waaler in 1939 and later rediscovered by Rose in 1948 by virtue of its ability to agglutinate sheep red cells that had been coated with rabbit serum. The seminal studies of Kunkel ultimately characterized the unknown factor as an antibody that binds to the Fc portion of immunoglobulins[1]. This observation led to the logical view that RA might be an autoimmune disease caused by self-reactive antibodies. About 80% of patients are 'seropositive' for rheumatoid factor, and its presence predicts a more aggressive, destructive course.

The primary pathogenic potential of rheumatoid factor in RA as an initiator of immune complex-mediated disease was formulated during the 1960s and classically described by Zvaifler in 1973[2]. In this model, immune complexes formed by rheumatoid factors and perhaps other autoantibodies fix complement and release chemotactic factors such as C5a. Inflammatory cells are subsequently recruited to the rheumatoid joint along a chemotactic gradient where they are activated and contribute to local destruction. Neutrophils, in particular, accumulate in synovial fluid where they engulf immune complexes and release proteolytic enzymes.

Considerable data have accumulated to support this hypothesis. Ultrastructural studies of cartilage reveal immune complexes embedded in the superficial layers, thereby providing a solid surface to facilitate neutrophil adherence and activation. The synovium itself is a rich source for the local production of complement proteins and rheumatoid factor[3]. Despite the abundant production of complement in RA, synovial fluid concentrations are low in RA compared with other inflammatory arthropathies owing to intra-articular complement consumption[4]. However, many normal individuals and patients with other chronic inflammatory diseases produce rheumatoid factor, indicating that the mere presence of the autoantibody is insufficient for a phlogistic response. Because many immune-mediated and infectious diseases are marked by the presence of immune complexes, this hypothesis did not necessarily provide an adequate explanation of the unique features of RA.

## Role of T cells in rheumatoid arthritis

Although the immune-complex theory could explain many of the acute inflammatory features of RA, the prominent T-cell infiltrate suggested these cells are key participants. In 1976, Stastny demonstrated that RA lymphocytes proliferate normally in allogeneic mixed-leukocyte reactions when stimulated by normal lymphocytes[5], but the patients had deficient responses when stimulated by cells from other RA patients. These experiments actually demonstrated genetic similarities between RA patients and led to the discovery that specific human leukocyte antigen (HLA)-DR genes, which reside in the major histocompatibility complex (MHC) and participate in antigen presentation, are associated with the disease. The relationship between the MHC and RA is by far the strongest genetic link in RA and has been mapped precisely to the third hypervariable region of DRβ chains,

Box 1
Origins of rheumatoid arthritis

Examination of skeletal remains from antiquity in Europe and North Africa shows various forms of arthritis, including osteoarthritis, ankylosing spondylitis and gout[76]. But characteristic rheumatoid lesions with marginal erosions at the bone–cartilage interface of the small joints are strikingly absent. In contrast, palaeopathological studies of specimens dating back several thousand years show clear evidence of rheumatoid arthritis (RA) in Native American tribes in North America[77]. The prevalence of RA in the same regions today remains extraordinarily high, with over 5% of individuals affected in some groups.

Evidence of RA in Europe first appeared in early 17th century art, especially by the Dutch Masters (see Box 1 Figure below), and Sydenham published the first case report in 1676. Although intermittent case series were subsequently reported, the disease was not fully recognized until it was defined by Garrod in 1859. He named it 'rheumatoid' arthritis to distinguish it from the two well-known forms arthritis, rheumatic fever and gout. By the early 20th century, RA was viewed as separate from osteoarthritis ('arthritis deformans'). In 1957, Charles Short described RA definitively and clearly set it apart as a defined clinical entity distinct from the seronegative spondyloarthropathies, crystal-induced disease, osteoarthritis, systemic lupus erythematosus, and many other conditions.

**Box 1 Figure** Example of RA-like findings in Dutch art. Little evidence of RA-like disease was noted in art or skeletal remains before the 17th century in Europe and Northern Africa. Findings suggestive of RA appear in 17th century Dutch art. Detail from *La Familia de Jordaens en un Jardín* by Jacob Jordaens (c. 1630) is shown. Note swelling of the metacarpal-phalangeal and proximal interphalangeal joints (arrows). (Image courtesy of the Museo del Prado, Madrid.)

especially amino acids 70 through 74 (ref. 6). The susceptibility epitope is glutamine-leucine-arginine-alanine-alanine (QKRAA) or QRRAA. This sequence is found in multiple RA-associated DR genes, including DR4, DR14 and DR1 (for example, DRB*0401, DRB*0404, DRB*0101 and DRB*1402). The susceptibility epitope might also influence severity of disease, as the risk of extra-articular and erosive disease is greater if patients have the gene and is further increased by homozygosity[7].

The location of the susceptibility epitope on the MHC molecule suggests that it might have a role in the ability of HLA-DR to bind and present specific arthritogenic peptides that might cause RA. The precise role of HLA-DR in RA could be more complex, as crystal structures of DR molecules show that the susceptibility epitope residues primarily face away from the antigen-binding groove of DR molecules that determine which peptides are presented to $CD4^+$ T cells[8]. Specific peptides that bind to the DR proteins in RA patients have not been identified[9]. Several alternative roles for the role of the susceptibility epitope have been proposed (see Table 1).

The notion that T cells participate in the aetiology and pathogenesis of RA was a key intellectual breakthrough in our understanding of the disease[10]. Several animal models of arthritis commonly used to investigate the mechanisms of synovitis, such as collagen-induced arthritis or adjuvant arthritis in rodents, are clearly T-cell-dependent and provide a link between pre-clinical and clinical investigation. This evidence is circumstantial, however, and the arthritogenicity of an antigen in mice is no guarantee that it has a role in the human disease. Using *in vitro* proliferation assays with T cells from RA patients, many putative autoantigens have been identified as candidate antigens. Type II collagen, proteoglycans, aggrecan, cartilage link protein, heat shock proteins and many relatively specific joint antigens have been implicated by virtue of the T-cell reactivity[11,12] and antibodies[13,14] in RA, as well as their ability to cause arthritis in appropriately immunized mice[15].

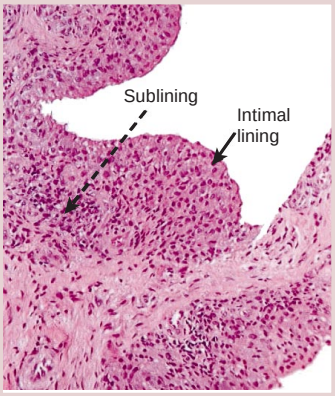


**Figure 1** Synovial histology in rheumatoid arthritis. A photomicrograph (magnification ×200) shows the redundant folds of the synovial lining and intense infiltration with inflammatory cells in RA. The intimal lining layer (solid arrow) is hyperplastic, with multiple layers of cells compared with a normal lining that is one or two cell layers deep. The sublining region (dashed arrow) is marked by accumulation of mononuclear cells such as $CD4^+$ T cells, macrophages and B cells.

## Explaining disease perpetuation using cytokine networks

### Cytokine autocrine and paracrine networks

By the late 1980s, new molecular techniques were available to measure cytokines in RA synovium and synovial fluid, which offered an opportunity to confirm the role of T cells as the driving force in RA. The most striking observation was that T-cell cytokines such as interleukin (IL)-2 and interferon (IFN)-γ were present in relatively low concentrations, whereas macrophage and fibroblast products were abundant[16]. Subsequent studies confirmed the unbalanced cytokine profile and indicated that T-cell lymphokines, although detectable, were present in low amounts compared with other antigen-mediated processes like tuberculous pleuritis, asthma or inflamed tonsils[17]. In contrast, a broad array of macrophage and fibroblast cytokines, including IL-1, IL-6, IL-15, IL-18, tumour-necrosis factor (TNF)-α, granulocyte–macrophage colony-stimulating factor (GM-CSF), various chemokines, and many others, are produced by rheumatoid synovium. Interrupting cytokine networks to treat RA using biological agents, such as anti-TNF-α antibody, was supported by subsequent studies demonstrating efficacy in collagen-induced arthritis in mice[18]. Suppressive cytokines, such as transforming growth factor (TGF)-β and IL-1Ra, as well as anti-inflammatory cytokine signalling mechanisms, such as the suppressor of cytokine signalling-3 (SOCS3), are expressed in RA synovium, but at levels that are inadequate to block synovitis[19].

To explain this apparent paradox, paracrine and autocrine networks involving factors such as IL-1 and TNF-α were proposed in 1990 as mechanisms that perpetuate synovitis in a T-cell-in

Table 1 **Potential role of HLA-DR in RA**[72–75]

| |
|---|
| • Binds to arthritogenic peptides that can be presented to T cells |
| • Shapes the T-cell repertoire and permits escape from tolerance or survival of autoreactive clones |
| • Leads to enhanced T-cell reactivity owing to unique contacts between T-cell receptors and MHC molecules |
| • Serves as a target for autoreactive T cells owing to molecular mimicry with a pathogen (for example, *Escherichia coli* DnaJ or Epstein–Barr virus peptides) |
| • Closely linked to other genes in the MHC that are associated with RA |
| • Fails to bind peptides of an arthritogenic pathogen, leading to an inadequate immune response |

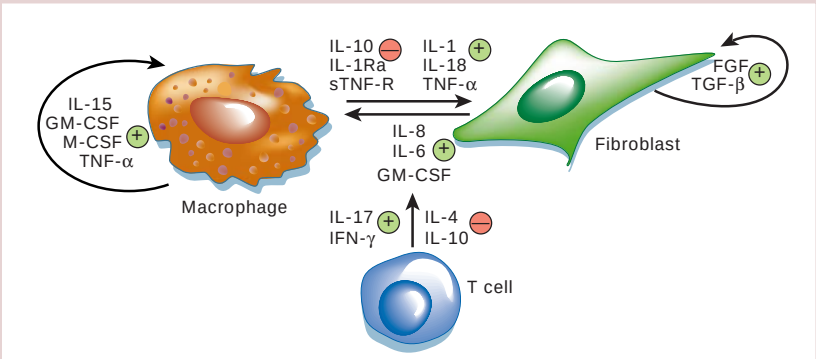


**Figure 2** Cytokine networks in rheumatoid arthritis. Macrophages and fibroblasts are adjacent to one another in the synovial intimal lining and produce cytokines that can activate either themselves or their neighbouring cells. Pro-inflammatory cytokines (+) and anti-inflammatory proteins (–) are indicated. This scenario involving interactions between mesenchymal cells and antigen-presenting cells can participate in many inflammatory reactions and is not necessarily specific to RA. The process is not autonomous because cessation of anti-cytokine therapy leads to flares of disease in RA.

dependent manner[20]. Fibroblast-like synoviocytes and macrophage-like synoviocytes in the intimal lining can produce factors that maintain inflammation by activating cells in the local environs (Fig. 2). Adjacent cells express other cytokines, metalloproteinases, and small molecule mediators such as prostaglandins and nitric oxide. Adhesion molecules are induced on endothelium, and circulating cells expressing the appropriate chemokine receptors and adhesion molecule receptors accumulate in the synovium. This model could explain the accumulation of memory $T_H1$ cells, which express the chemokine receptor CCR5 and the integrin adhesion molecule $\alpha_4\beta_1$, and are the key effector cells in delayed-type hypersensitivity, as well as monocytes and neutrophils without necessarily invoking a specific antigen. The cells accumulate in the joint and might be activated by articular antigens that are unrelated to the aetiologic factors.

Recent therapeutic interventions, including TNF-α and IL-1 inhibitors, strongly support the importance of cytokines in RA. The mechanism of anti-TNF-α action *in vivo* is complex and probably includes suppression of other pro-inflammatory cytokines, decreased synovial cellular infiltration, interference with osteoclast activation, and decreased angiogenesis[21]. Continuous anti-cytokine treatment is required for long-term control and the disease flares when therapy is discontinued. Therefore, a relatively simple view of autonomous cytokine networks cannot explain perpetuation of RA unless additional stimuli that maintain cytokine production are present. The role of TNF-α is also not unique to RA; TNF inhibitors have shown efficacy in Crohn's disease, ankylosing spondylitis, psoriasis and psoriatic arthritis. New factors have been implicated and are also potential therapeutic targets for RA. For instance, IL-18, which is a member of the IL-1 family and can be inhibited by IL-18-binding protein, activates synovial macrophages and biases T cells to differentiate towards the $T_H1$ phenotype[22]. IL-15 is produced by macrophages and can activate T cells to increase TNF-α production by macrophages.

More precise characterization of T-cell products and phenotype requires modification of the cytokine network hypothesis. Careful analysis of infiltrating synovial T lymphocytes has revealed a bias towards $T_H1$-like cells that express CCR5 and CXCR3 chemokine receptors[23]. Small but physiologically relevant amounts of IFN-γ and the $T_H1$ cytokine IL-17 are expressed in RA and could contribute to immune responses, fibroblast activation and bone destruction[24]. Direct cell–cell contact between memory or previously activated T cells and other resident synovial cells can also enhance cytokine and metalloproteinase production[25]. Therefore, chronic antigen-dependent and -independent T-cell activation could operate within the rheumatoid synovium.

### Role of cytokines in bone destruction

Studies using anti-TNF agents clearly show that they can slow or prevent the progression of bone and cartilage damage in RA[26]. This activity probably involves suppression of osteoclasts in joint lesions[27]. Other cytokines regulating matrix degradation have also been implicated in animal models of arthritis, most notably IL-1 and IL-17[28]. Perhaps the most exciting development in the pathogenesis of bone erosions in RA relates to the discovery of osteoclast-mediated bone resorption that is regulated by RANKL, the RANK (receptor activator of nuclear factor (NF)-κB) ligand. RANKL is expressed by a variety of cell types involved in RA, including T cells and synoviocytes. These cells, in the presence of cytokines like TNF-α and M-CSF, contribute to osteoclast maturation and activation. The soluble decoy receptor to RANKL, osteoprotegerin (OPG), and RANKL are increased in RA, but normalize after treatment with TNF inhibitors[29].

The role of RANKL in inflammatory joint disease has been confirmed in several animal models. For instance, T-cell activation leads to a RANKL-mediated increase in osteoclasts and bone loss in rat adjuvant arthritis[30]. OPG administration to the arthritic animals blocks bone destruction even though it has little effect on inflammation. RANKL-knockout mice also have diminished bone erosion in arthritis models[31]. In most cases, cartilage protection afforded by blocking RANK/RANKL system is minimal.

### Mechanisms of cytokine gene expression and new therapeutic targets

Understanding the intracellular targets that regulate cytokines in RA can potentially lead to new therapeutic interventions. For instance, NF-κB is activated in the synovium of patients with RA[32] and regulates genes that contribute to inflammation, including TNF-α, IL-6, IL-8, inducible nitric oxidase synthase (iNOS) and cyclooxygenase-2 (COX-2). After stimulation of innate immunity or exposure to pro-inflammatory cytokines, the IκB kinase (IKK) signal complex is activated in synoviocytes, leading to phosphorylation of IκB[33]. IKKβ is both necessary and sufficient for induction of IL-6, IL-8 and intercellular adhesion molecule-1 (ICAM-1) gene expression. Targeting NF-κB is an effective therapeutic strategy in many animal models of arthritis. For instance, rat adjuvant-induced arthritis is suppressed by intra-articular gene therapy with dominant negative IKKβ adenoviral construct[34], while decoy oligonucleotides block streptococcal cell-wall arthritis[35].

The mitogen-activated protein (MAP) kinases are also key regulators of cytokine and metalloproteinase production and could also be targeted in RA. All three kinase families — extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 — are expressed in rheumatoid synovial tissue[36]. All are constitutively expressed by cultured synoviocytes, and exposure to pro-inflammatory cytokines induces rapid phosphorylation. Upstream kinases that activate the MAP kinases, such as MKK3, MKK4, MKK6 and MKK7, are also activated in RA synovium and can form signalling complexes that integrate external environmental stresses to generate an appropriate cellular response.

The MAP kinases have attracted considerable attention as potential therapeutic targets in RA. Pre-clinical studies show that p38 inhibitors are effective in murine collagen-induced arthritis, rat adjuvant-induced arthritis, and many other models[37]. A selective JNK inhibitor, SP600125, is mildly anti-inflammatory in the rat

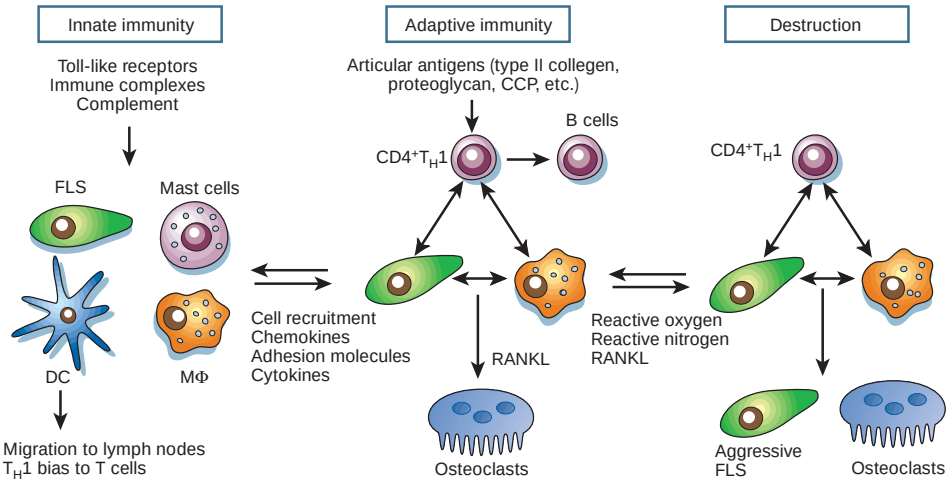


**Figure 3** A proposed model implicating multiple pathogenic mechanisms in RA. According to this model, a step-wise progression can begin with the activation of innate immunity by stimulating dendritic cells, macrophages, fibroblasts and mast cells. After immune cells migrate into the synovium, an opportunity for adaptive immune responses arises in individuals with the appropriate genetic background. While antigen presentation can occur in the synovium, extra-articular sites can also participate if dendritic cells migrate to lymph nodes and bias T cells to a $T_H1$ phenotype. In the destructive phase of disease, osteoclast activation mediates abundant bone resorption under the influence of RANKL, while synoviocytes can invade cartilage. These processes are not necessarily mutually exclusive. Activation of innate and adaptive immunity can also occur in a parallel fashion (denoted by bidirectional arrows), perhaps contributing to the patterns of disease flares and remissions. DC, dendritic cell; CCP, cyclic citrullinated peptide; FLS, fibroblast-like synoviocyte; Mϕ, macrophage.

adjuvant-induced arthritis, but provides striking protection against bone and cartilage destruction[38]. Of the JNK isoforms, JNK2 is particularly important in arthritis because it is the dominant isoform expressed in synoviocytes. In JNK2-knockout mice, passive collagen-induced arthritis causes less cartilage damage compared with wild-type animals although clinical arthritis is still severe[39].

The transcription factor activator protein-1 (AP-1) also regulates many genes that participate in RA, including TNF-α and metalloproteinases. High levels of AP-1 binding activity are detected in nuclear extracts of RA synovial tissue compared with osteoarthritis. Its components c-Jun and c-Fos are highly expressed in RA synovium, especially in the nuclei of cells in the intimal lining layer[40]. Pro-inflammatory cytokines can activate AP-1 activity in synoviocytes and leads to massive release of metalloproteinases. AP-1 decoy oligonucleotides suppress collagen-induced arthritis and inhibit IL-1, IL-6, TNF-α, matrix metalloproteinase (MMP)-3 and MMP-9 production by synovial tissue[41].

One concern with therapy directed at any of these key regulatory pathways is that they also participate in many normal cellular functions. The risks of toxicity or impaired host defence are significant potential problems because alterations in innate immunity or adaptive responses can be suppressed.

## Rheumatoid arthritis as a locally invasive tumour

Autoimmune and inflammatory mechanisms account for many features of RA. However, relentless progression of joint destruction in the relative absence of synovitis contributed to a parallel line of reasoning in the 1990s that viewed aggressive characteristics of RA synovium as reminiscent of neoplastic tissue. For instance, RA synoviocytes can grow under anchorage-independent conditions and have defective contact inhibition. Examination of X-linked genes demonstrates oligoclonality in the synoviocyte population from RA, but not osteoarthritis, synovium[42]. Permanent changes in synoviocyte function are also apparent in the severe combined immunodeficiency (SCID) mouse model where RA, but not osteoarthritis, synoviocytes invade into cartilage explants[43]. Synovial dedifferentiation has also been described, including overexpression of embryonic genes such as *wnt5A* that can enhance IL-15 expression in rheumatoid synoviocytes[44]. As in neoplastic disease, angiogenesis feeds the expanding synovium[45].

The molecular mechanisms responsible for altered synoviocyte function in RA could include somatic mutations in key genes. The presence of mutations in genes like the p53 tumour suppressor, although controversial, has been identified in RA synovial tissue and synoviocytes[46–48]. Microsatellite instability, another indicator of DNA damage, also occurs in RA synovial tissue, and may be related to decreased expression of DNA mismatch repair enzymes such as hMSH6[49]. Some of the p53 mutations identified in RA are dominant negative and are unable to regulate IL-6 or *bax* gene expression. Microdissection of RA synovium localizes islands of p53 mutant cells to the intimal lining, with higher expression of IL-6 than wild-type regions[50]. DNA damage in RA and resultant mutations in regulatory genes likely results from exposure to persistent oxidative stress in a hostile environment. The mutations, therefore, are the result of RA rather than the cause and potentially alter the natural history of RA. However, the ultimate impact of relatively small numbers of abnormal cells on disease progression is uncertain.

## Return of immune complexes and autoantibodies

The recent fortuitous discovery of a spontaneous arthritis model in mice that produce antibodies directed against a ubiquitous antigen, glucose-6-phosphoisomerase (GPI), contributed to resurgent interest in autoantibodies and immune complexes[51]. The murine arthritis can be transferred using serum from affected mice. Elegant molecular studies using knockout mice demonstrate an absolute requirement for FcγR (especially FcγRIII) and components of the alternative complement cascade (for example, Factor B) as well as complement proteins C3 and C5[52]. Although the model is, in part, dependent on TNF-α, IL-1 plays a pivotal role.

Although anti-GPI antibodies are present in many patients, they are neither specific nor sensitive for RA[53]. The ability of ubiquitous antigens like GPI to induce synovial inflammation is probably related to their adherence to the cartilage surfaces. The presentation of immobilized antigen–antibody complexes on cartilage provides an exceptionally good substrate for complement fixation, similar to rheumatoid factor embedded in rheumatoid cartilage. A similar situation occurs in

murine passive collagen-induced arthritis, where anti-type II collagen antibody binds to collagen arrayed on the surface of articular cartilage.

Many autoantibody systems that could participate in inflammatory joint disease are now recognized in RA, including rheumatoid factor, type II collagen, immunoglobulin heavy gene binding protein (BiP), heat shock proteins and hnRNP-33 (RA33)[54]. Some, like anti-collagen antibody and rheumatoid factor, are produced by rheumatoid synovial B cells. The mere presence of the autoantibodies in serum is not specific for RA; instead, patterns of antigen immunoreactivity could be pathogenic in humans (a form of autoantibody 'signature'). Antibodies directed against proteins containing citrulline, which is derived from post-translational modification of arginine by peptidylarginine deiminase, might be more specific for RA[55].

Careful analysis of the B-cell repertoire in rheumatoid synovial tissue suggests a local antigen-driven immune response. Most B cells isolated from germinal centres in RA synovium have unmutated *VH* genes, suggesting that they have recently migrated into the tissue and are activated at the site of disease[56]. Shared mutations containing identical sequences throughout the variable domain occur in RA synovial B cells, and a limited number of *VH* and *DH* gene segments are utilized[57]. The subsequent gene rearrangements and mutations implicate synovial autoimmunity directed against articular antigens.

Innate immunity also participates in antibody-mediated arthritis, and mast cells are required for the disease onset of some models[58]. Toll-like receptors (TLRs) can also participate. For instance, administration of a small dose of endotoxin, which activates TLR4, during the pre-clinical phase of collagen-induced arthritis can markedly exacerbate joint inflammation and destruction[59]. CpG oligonucleotides can engage TLR9 and either cause arthritis directly in rodents or enhance disease in adjuvant-induced arthritis[60].

## From bench to bedside

The advent of TNF inhibitors[61,62] illustrates the success of applied translational research in RA, based on characterization of cytokine networks and studies suggesting that TNF-α production might serve as an autologous stimulus for other cytokines in RA synovium[63]. Although perhaps 40% of patients have dramatic responses, the remainder have some evidence of persistent synovitis or minimal clinical benefit. IL-1Ra, a natural IL-1 antagonist, has also been approved for use in the United States. The response rates are less than for TNF inhibitors, perhaps because IL-1Ra is a competitive antagonist that must be present in large excess. Numerous additional cytokine-directed agents, such as anti-IL-6 receptor antibody, are also in clinical development, with preliminary response rates similar to TNF antagonists. Inhibition of IL-18 and IL-15 represents additional attractive approaches that could block $T_H1$ differentiation, inflammatory mediator production, or TNF-α expression. Based on the $T_H1$ bias of T cells in the synovium, treatment with $T_H2$ cytokines (IL-4, IL-10 and IL-13) was tested in many animal models of arthritis and showed considerable promise[64]. But so far, administration of IL-10, which serves as a prototypic $T_H2$ cytokine, has met with only limited success[65].

Our understanding of the signal transduction pathways implicated in RA has led to drug development programmes targeting MAP kinase and NF-κB inhibitors. In addition, biological agents like CTLA4-Ig, designed to interfere with co-stimulatory molecules and antigen presentation, have been impressive and raise the possibility that modulation of T-cell function will have therapeutic utility in RA. Adhesion molecule inhibitors (for example, $\alpha_4/\beta_1$ integrin) or chemokine receptor antagonists (for example, CCR1 or CCR5) could block cell ingress into affected synovial tissue. OPG might prevent or heal bone erosions by blocking the differentiation and activation of osteoclasts. The extracellular matrix could also be protected by inhibiting metalloproteinases (for example, MMP13 or collagenase-3), aggrecanases or cathepsins (for example, cathepsin K). Clinical studies with broad-spectrum metalloproteinase inhibitors have demonstrated limited effect on joint destruction and have been complicated by some toxicity. The tumour-like properties of synovium suggest that approaches normally reserved for oncologic diseases might be useful in RA, including induction of apoptosis (for example, Fas ligation)[66] and anti-angiogenesis agents.

Finally, the role of autoantibodies raises the possibility that B-cell-specific therapy might be useful in RA. Rituximab, which targets CD20, seems to be effective in RA, especially in combination with cyclophosphamide, methotrexate and/or corticosteroids[67]. The mechanism of action is still uncertain and might involve inhibition of B-cell cytokines or antigen presentation, because changes in the amount of rheumatoid factor and autoantibody do not necessarily correlate with clinical responses. Other cytokines that are important in B-cell differentiation, like BLyS, are also potential targets[68]. The use of soluble receptors to BLyS and related proteins is effective in collagen-induced arthritis. Inhibition of autoantibody production through these mechanisms or blockade of innate immunity, such as with C5a antagonists, have also attracted interest[69].

## Updated model incorporating 50 years of theories

The various hypotheses that have attempted to explain RA over the last half century might be re-interpreted in order to appreciate the complexity of the disease and the multiple mechanisms of synovial inflammation. A multi-stage model might help integrate these concepts, although it is important to note that significant temporal overlap can occur (see Fig. 3)[70]. Activation of innate immunity probably occurs early in RA and can serve as a key pathogenic mechanism that initiates synovial inflammation. TLR agonists, including proteoglycans and bacterial DNA, have been detected in rheumatoid synovium[71]. Engagement of Fc receptors by autoantibodies, like rheumatoid factor and anti-cyclic citrullinated peptide antibodies, represents an alternative mechanism. Synovial dendritic cells activated by TLR ligands can migrate to lymph nodes where primed T cells can be biased towards the $T_H1$ phenotype and, through chemokine receptors like CCR5, home to inflamed synovial tissue. Production of cytokines and expression of adhesion molecules after activation of innate immunity in the joint can permit the continued ingress of immune cells. This early stage might occur commonly in humans but is typically self-limited.

In the appropriate conditions, such as the presence of the correct HLA-DR alleles or perhaps cytokine promoter polymorphisms, lymphocytes could accumulate into the transiently inflamed synovium. Under these circumstances, the loss of tolerance related to the effects of HLA-DR background or the T-cell repertoire might contribute to autoreactivity to newly exposed articular antigens. Ultimately, long-standing disease could lead to a destructive phase that some investigators believe can run an independent course.

This hypothesis does not presuppose a specific 'rheumatoid antigen'. Instead, a variety of antigens can be targets and lead to both T-cell activation and B-cell maturation. Hence, the progression of disease might require a combination of stochastic events (activation of innate immunity), pre-determined events (genetic background), and adaptive immune responses directed against autologous antigens. It is also possible that recurrent activation of innate immunity or overlap with other elements of this model could participate to varying degrees during the course of disease and contribute to patterns of flare and remission.

Although significant therapeutic advances have greatly improved the lives of patients with RA, the problem is hardly solved. Persistent disease and the accumulated disability caused by decades of inflammatory synovitis remains a major clinical problem. By targeting the intracellular signalling pathways, cytokines, and other mediators of the phases of RA, the residual disease could be controlled. Perhaps with appropriate therapy the impact of RA will fade to the halcyon days of pre-Renaissance Europe when the disease was essentially unknown. □

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