

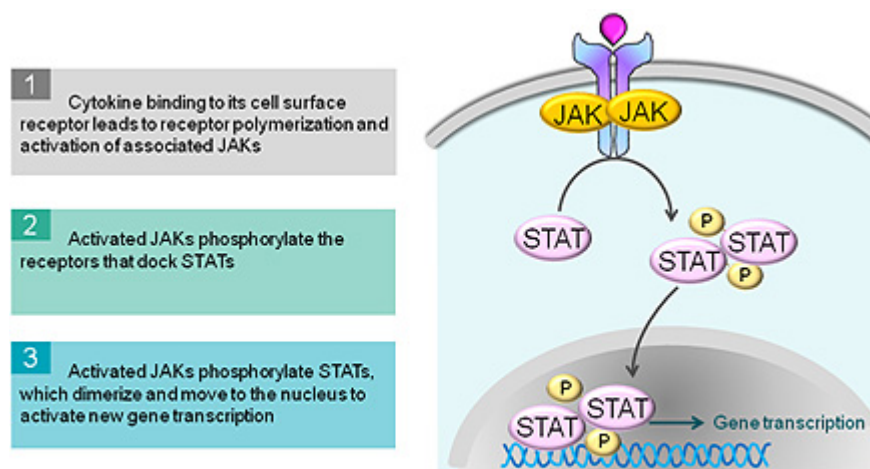
## Issue 1: Pathophysiology of RA

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by a proliferating synovitis leading to cartilage and bone destruction, and resulting in joint deformities and increasing functional limitations. [1] The condition is an autoimmune disease whose exact etiology is not known, although genetic predisposition is known to be a contributory factor. The HLA-DRB1 and PTPN22 genes play a role, other genes are also involved but genetic factors only account for about one third of RA cases. [2] Smoking is the only known environmental trigger. [3]

### Preclinical phase

Several cell types and cytokines are involved in RA, and upregulation of cytokines, cytokine-related factors, and chemokines can pre-date the development of clinical symptoms. [4] Anti-citrullinated protein antibodies (ACPAs), which include include perinuclear factor (APF), antikeratin antibodies (AKA), anti-Sa antibodies, and anticyclic citrullinated peptide antibodies (anti-CCP), are sensitive and specific serological markers of RA, offering predictive value for a diagnosis of RA, [5, 6] and may be early predictors of the efficacy of anti-TNF therapy. [7] Anti-CCP antibodies and rheumatoid factor (RF) may predate the onset of RA by several years, [8] and anti-CCP testing is a superior option for RA diagnosis and monitoring. [9-11] Anti-mutated citrullinated vimentin (anti-MCV) testing has similar diagnostic performance to anti-CCP. [9] Determination of anti-Sa can help in identifying a subset of arthritis patients with a more severe course and who are negative for anti-CCP and anti-MCV. [12]

### Clinical phase



JAK=Janus kinase, P=phosphate, STAT=signal transducer and activator of transcription.  
 Shuai K, Liu B. *Nat Rev Immunol* 2003;3(11):900-911.

The clinical phase of RA is characterized by joint inflammation. Several cell types and cytokines are involved in the rheumatoid joint, with synovial macrophages playing an important role. The macrophages are activated by Th1 cytokines, including interferon-gamma (IFN-g), interleukin 12 (IL-12), and IL-18, which are released following activation of T cells by antigen-presenting cells. Macrophages may also be activated by direct contact with T cells, or by immune complexes or bacterial products in the synovial

### Inside this issue:

- Preclinical phase
- Clinical phase
- New Directions
- References

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### New Directions (Continued)

Syk is a key signalling molecule in B cells and a variety of cells expressing Fc-activating receptors. Syk activation is important in TNF $\alpha$ -induced cytokine and metalloproteinase production in RA fibroblast-like synoviocytes. [19] The MAPKs, i.e., p38, extracellular signal-related kinase (ERK) and c-Jun N-terminal kinase (JNK), stimulate gene transcription and are involved in activation of synovial cells in RA. [20]

An excess of proinflammatory cytokines in RA ultimately leads to chronic inflammation with proliferation of synovial cells and pannus formation, triggering cartilage thinning mediated by the release of matrix metalloproteinases from synovial fibroblasts together with chondrocyte-mediated destruction and failure of repair mechanisms. Activation of osteoclasts results in destruction of bone. [13] While TNF $\alpha$  drives many of the changes involving chondrocytes and osteoclasts, IL-6 contributes to systemic effects. [21] Many of the extra-articular manifestations (e.g., cardiovascular disease, anemia, osteoporosis and ocular involvement) of RA are associated with increased disease activity and with markers of inflammation, such as high levels of rheumatoid factor (RF) and C-reactive protein (CRP). [22, 23]

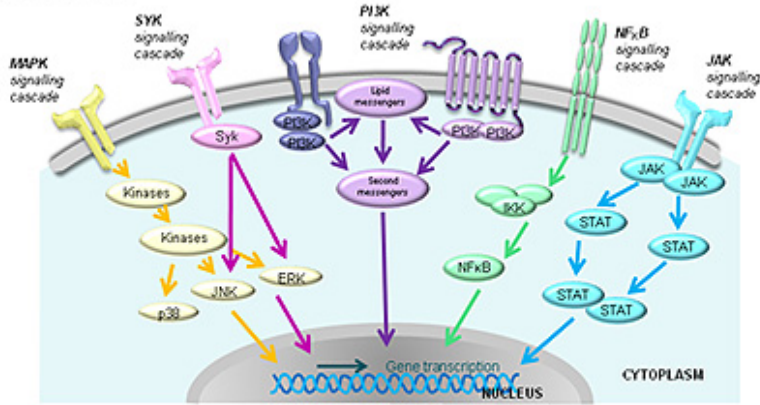
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fluid. Once activated, macrophages release multiple cytokines and other inflammatory mediators. [13] Key cytokines involved in the pathogenesis of RA include several interleukins, tumor necrosis factor (TNF), transforming growth factor- $\beta$  (TGF- $\beta$ ), and interferons (IFN $\alpha$  and IFN $\beta$ ). [14, 15] Each cytokine may have multiple pleiotropic actions, but in patients with RA, the balance swings in favour of the proinflammatory cytokines. [13]

## New Directions

The binding of a subset of cytokines to a cell surface receptor activates intracellular enzymes that transmit signals by phosphorylation, i.e., the protein kinases – janus kinase (JAK), spleen tyrosine kinase (Syk), and p38 mitogen-activated protein kinases (MAPK). The JAKs are involved in transmitting signals to the nucleus to initiate gene transcription and production of cytokines and other immune mediators. Several pro-inflammatory cytokines (IL-6, IL-7, IL-10, IL-12, IL-15, IL-21, IL-23, IFN $\alpha$  and IFN $\beta$ ) utilize the JAK pathways. [16] Overactivation of JAK signalling is a key feature in RA, which results in a disruption of the balance between pro- and anti-inflammatory cytokines, and contributes to a cycle of inflammation, with recruitment of more immune cells and overproduction of pro-inflammatory cytokines. [17, 18]

- Many cytokine receptors lack intrinsic kinase activity, instead relying on associated tyrosine kinases, such as JAKs, to transmit signals from the extracellular environment to the nucleus<sup>1,2</sup>



ERK=extracellular signal related kinases; IKK=inhibitor of kappaB kinase; JAK=Janus kinase; JNK=Jun N-terminal kinase; MAPK=mitogen-activated protein kinase; NF- $\kappa$ B=nuclear factor kappa B; PI3K=Phosphoinositide 3-kinase; STAT=signal transducer and activator of transcription; Syk=Spleen tyrosine kinase.  
Adapted from Mavers M, et al. *Curr Rheum Rep.* 2009;11:378-395 and Rommel C, et al. *Nat Rev Immunol.* 2007;7:191-201.

[ [More on right column](#) ]

↑ TOP OF PAGE

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## References

[View References](#)

## In the next issue

Coming up in the next Rheumatoid Arthritis Newsletter, the topic of **Current Therapies** will be covered.