Rheumatoid arthritis

RA is a common disease affecting 1–2% of the adult population and is twice as common in women as men. It is most common between the ages of 25 and 55 years, and the most frequent presentation is an insidious, symmetrical polyarthritis, although the disease can begin abruptly.

Here, a group of auto-antibodies against the host IgG antibodies are produced called **RA factor**. It is an IgM antibody directed against the Fcregion of IgG Anticitrullinated peptide antibodies (**ACPA**) are also produced.

Aetiology

There is an association between possession of HLA-DR4 and -DR1 and rheumatoid factor-positive RA. This association becomes stronger with increasing severity of disease, and the presence of extra-articular manifestations

Type of immune response

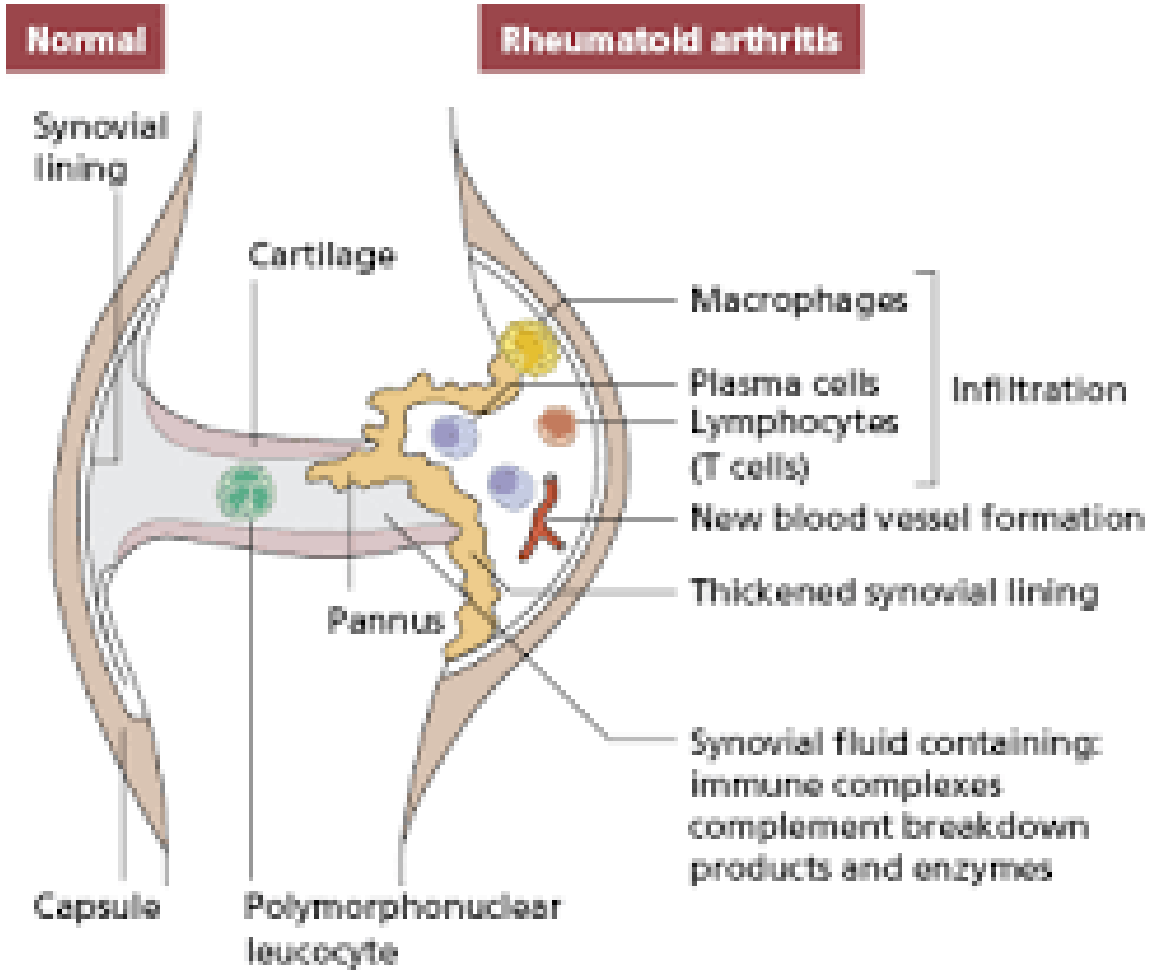
Autoantibodies bind to circulating IgG, forming IgM-IgG complexes that are deposited in the joints and can activate the complement cascade

Morphological evidence for immunological activity

The joint changes in RA are produced by the dysregulated and invasive growth of the synovial cells developing into what is referred to as a ***pannus*** that overlays and destroys cartilage and bone. The synovial membrane that surrounds and maintains the joint space is invaded by large numbers of T cells, mostly CD4, in various stages of activation, usually associated with dendritic cells and macrophages plasma cells are frequently observed

Pathology

The earliest pathological change in RA appears to be an **infiltrate of neutrophils and mononuclear cells around small blood vessels** in the loose connective tissue beneath the synovium. As the disease progresses, large numbers of T cells, macrophages, B cells and plasma cells accumulate in this tissue, and the synovium becomes markedly thickened due to **fibroblast proliferation** and macrophage migration. The surface area increases and becomes folded into villi. New vessel formation (**angiogenesis**) occurs and some blood vessels develop into structures specialized for lymphocyte migration


Normal
Rheumatoid arthritis
Synovial lining
Cartilage
Macrophages
Plasma cells
Lymphocytes (T cells)
Infiltration
New blood vessel formation
Thickened synovial lining
Pannus
Synovial fluid containing: immune complexes complement breakdown products and enzymes
Capsule
Polymorphonuclear leucocyte

IgG autosensitization and immune complex formation

Autoantibodies to the IgG Fc region, known as ***rheumatoid factors***, are a feature of the disease. The majority of patients with rheumatoid arthritis have IgG or IgM rheumatoid factors.

The production of tissue damage

The immune complexes can be stabilized by the multivalent Fcγ-binding molecules IgM rheumatoid factor and C1q, and when present in the joint space they may provoke an influx of neutrophils leading to the release of reactive oxygen intermediates (ROIs) and lysosomal enzymes. These include neutral proteases and collagenase that can ***damage the articular cartilage*** by breaking down proteoglycans and collagen fibrils.

More damage results if the complexes are adherent to the cartilage, as the neutrophil binds but is unable to internalize them (“frustrated phagocytosis”); as a result, the lysosomal hydrolases are released extracellularly into the space between the cell and the cartilage.

Laboratory findings

- Anemia of moderate degree
- ESR ↑ a useful parameter for assessing response to therapy
- C-reactive protein ↑
- RF **(usually IgM)**
- CIC ↑ , complements ↑
- **ANA**
- **Anti-CCP (cyclic citrullinated peptide)**

Serology

A relatively new test for rheumatoid arthritis measures levels of **antibodies that bind citrulline modified proteins** (anti- CCP) is now widely available. It is specific for rheumatoid disease as it is elevated in patients with RA or in those about to develop RA and not in other forms of arthritis.

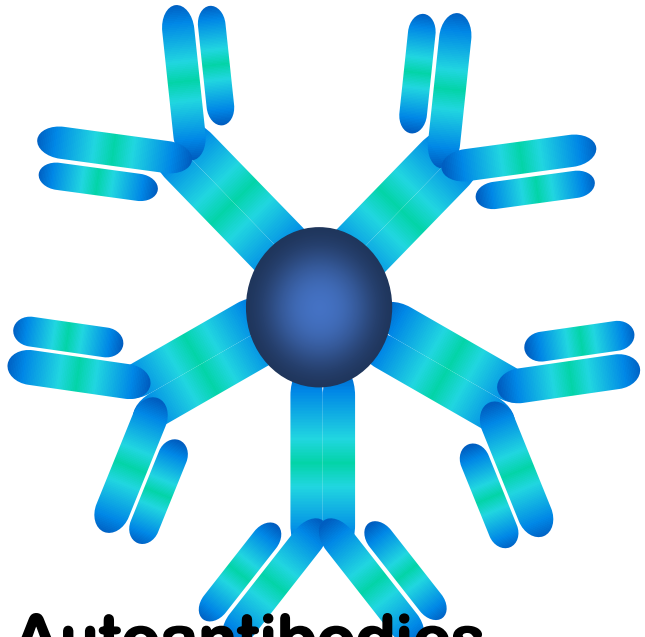
Other serological tests are of little value in RA. Antinuclear antibody (ANA) is present in 40%, but is usually of low titre and often of IgM class; such ANAs are found in many other conditions.

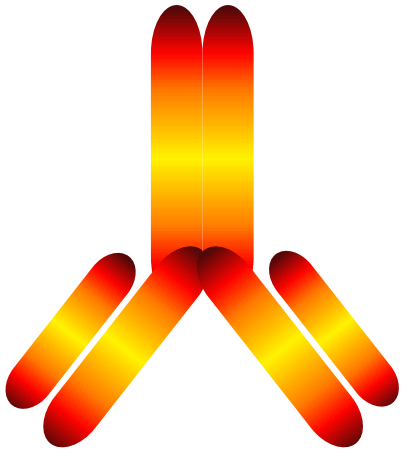
Rheumatoid Factor

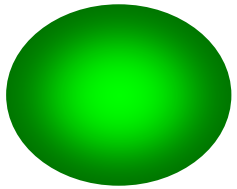
- Antibodies to Fc portion of IgG
- 75-80% of Patients have during course of disease
- Useful for prognosis

Rheumatoid Factor

- **IgG Molecule**
- **Fc Portion**







Antigen Binding Groove

Autoantibodies (IgM) directed against the Fc Fragment of IgG

An Antibody to an Antibody

Their Role in RA is not understood