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# Rheumatoid Arthritis (RA)

**Rheumatoid arthritis (RA)** is a chronic autoimmune disease that causes damage to the joints. RA tends to affect small joints first like those in the hands, feet, and neck. As the condition progresses, symptoms often spread to the larger joints of the arms and legs. The affected joints appear warm, swollen, and red. Patients experience pain and stiffness from the inflammation of the synovial membranes in the joints. This pain and stiffness is often worse in the morning or after a period of rest. Gentle movement can sometimes decrease pain. However, during a flare up of heightened inflammation and symptoms, it is unlikely that movement will help and it will probably hurt worse. A distinguishing feature of RA compared to other types of arthritis is that the pain and stiffness is usually symmetrical (i.e. found on both sides of the body). This is because as an autoimmune disease, it affects the body systemically instead of in one area.

Autoantibodies against citrullinated proteins called **anti-citrullinated protein antibodies (ACPAs)** can be detected in those with RA. These ACPAs bind specific proteins that have undergone a citrullination process that makes them immunogenic. Citrulline is a derivative of the amino acid arginine, so any protein containing arginine is capable, in theory, of becoming citrullinated, which is irreversible. Citrullination is catalyzed by an enzyme called **peptidylarginine deaminase (PAD)** that is normally under tight control to limit its hyperactivation. Calcium and redox conditions are important regulators of PAD activity. Periodontal disease specifically has shown to stimulate an increase in PAD activity. Those with RA have overactive PAD activity which may be due to immune processes and tissue damage. When a protein is citrullinated, its 3-dimensional structure might change enough that a person's immune system will begin to recognize it as foreign and attack it as if it were an immunogen. Citrullinated proteins of the synovial membrane found within moveable joints are often under attack during an RA flare up and lead to the tissue damage frequently observed.

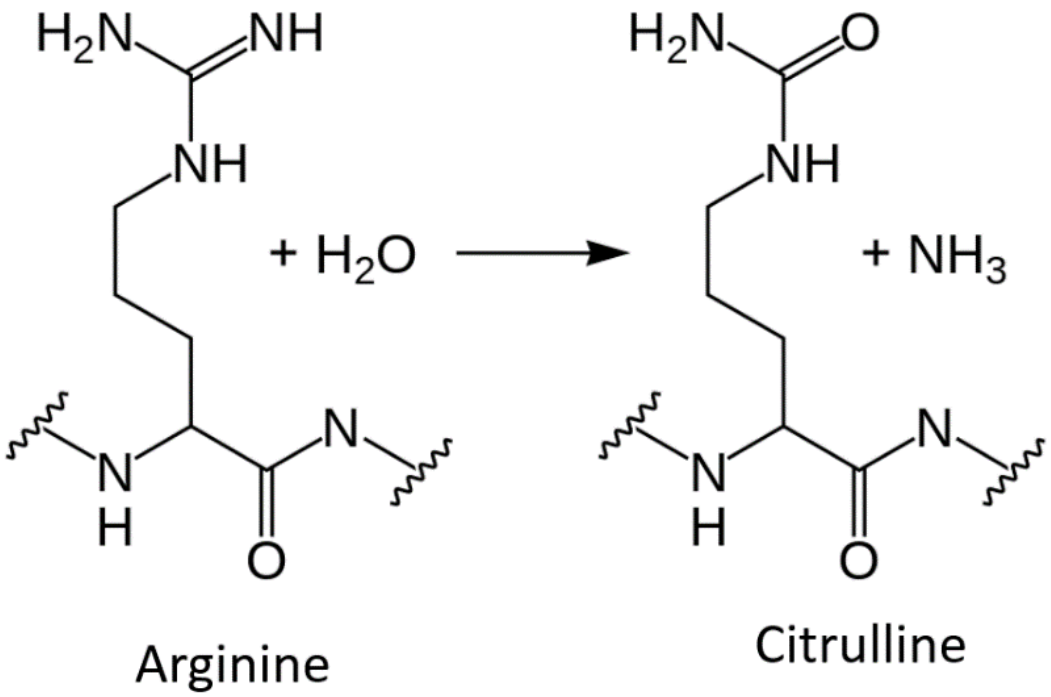



*Image in public domain by Fvasconcellos https://en.wikipedia.org/wiki/Citrullination*

**Action of PAD**

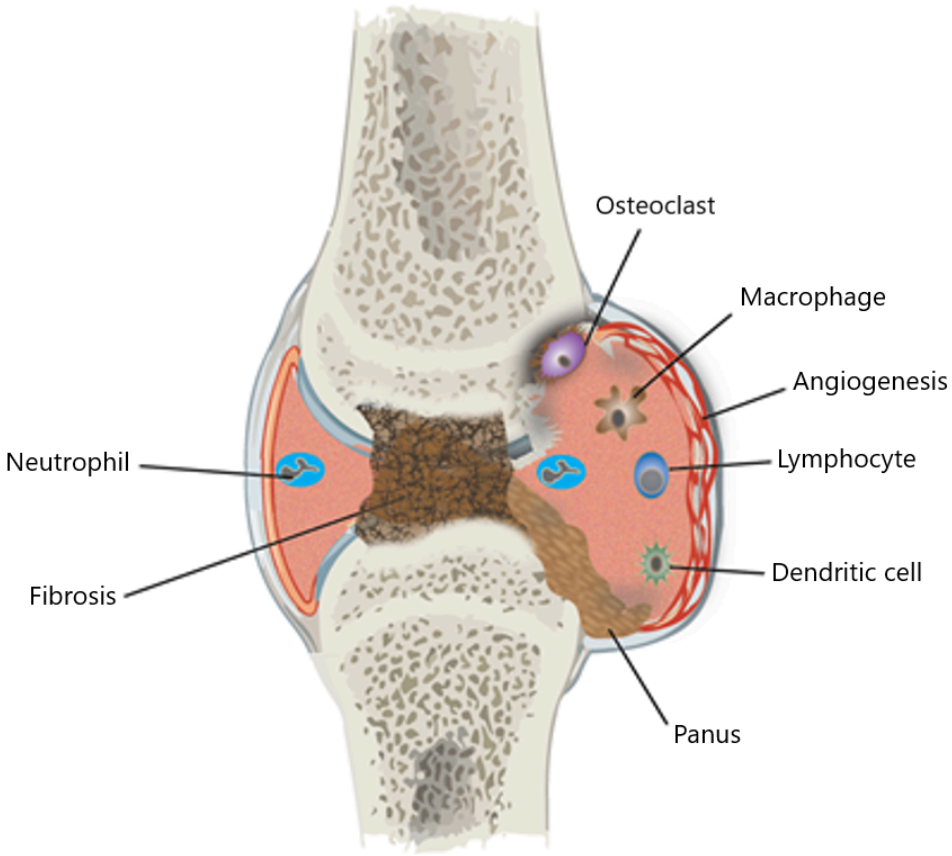
Another autoantibody common in RA is called **rheumatoid factor (RF)**. Not everyone with rheumatoid arthritis has RF, but about 70% do. This autoantibody is an IgM that recognizes and binds the Fc portion of IgG antibodies, thus forming immune complexes that can get deposited in tissues like the synovial fluid of moveable joints. Complement system can then be activated and immune cells recruited to the area. This reaction leads to sustained inflammation and progressive tissue damage. It is not well known what triggers RF production, but it can be found in other chronic inflammatory autoimmune conditions like lupus.

There are three phases of rheumatoid arthritis progression:

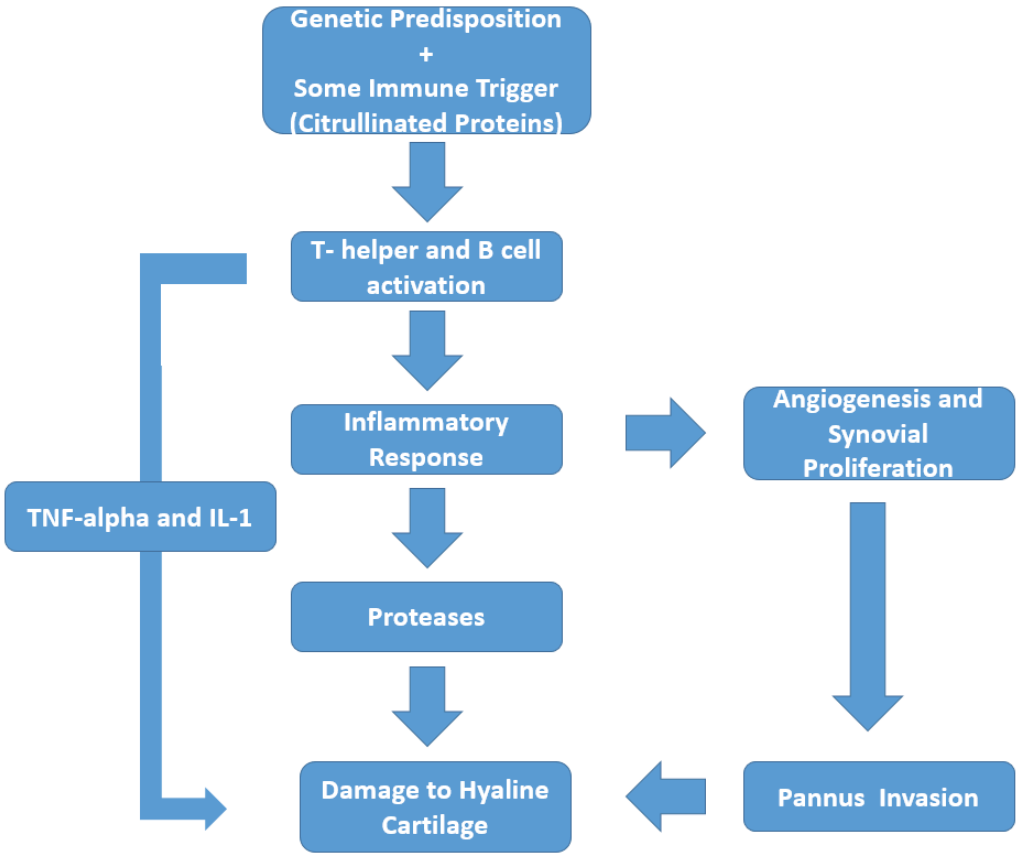
1. **Initiation:** Some type of non-specific tissue damage or antigen expression that leads to citrullination of proteins.
2. **Immune activation:** T-cell and B-cell activation against citrullinated proteins of synovial membranes and possibly IgG antibodies.
3. **Chronic inflammation:** RA is different for nearly every patient and its stages are still under investigation. The disease can wax and wane between inflammatory flare ups and periods of remission. During an acute flare-up, affected joints get hot, red and sore. The involved immune cells release cytokines, three of the most common being IL-1, TNF-alpha, and IL-6. Over time, the chronic inflammation of joints will destroy cartilage and erode bones, leading to increased pain, swelling, and loss of motion. Bone deformities may also present.

Activated immune cells can produce signals that stimulate nearby fibroblasts and blood vessels to expand the connective tissue components of the synovial membrane. This creates a vascular fibrotic lesion called a **pannus** that expands into the joints and destroys hyaline cartilage and bone. In other words, pannus is a thickening and expansion of the fibrous synovium into the joint area due to hyper-stimulated synovial cells. Special immune cells such as T and B lymphocytes, macrophages, lymphocytes, dendritic cells, neutrophils, and others contribute to the composition of pannus formations. Pannus ultimately spreads across the hyaline cartilage that covers the surfaces of the ends of the

bones. As the pannus tissue fills the joint, it will result in joint ankylosis (fusing of joint within a thick, fibrotic, and hardened capsule).




**Elements of a Joint Affected by Rheumatoid Arthritis** *Adapted from: Title: File:907 Synovial Joints.jpg; Author: OpenStax College; Site: https://commons.wikimedia.org/wiki/File:907_Synovial_Joints.jpg; License: This file is licensed under the Creative Commons Attribution 3.0 Unported license.*




**Progression of Rheumatoid Arthritis** *Image by JS S21*

RA can affect other tissues of the body besides the joints:

- The skin may present with **rheumatoid nodules**, which are a type of granulomatous inflammation unique to RA. They are firm lumps that develop under the skin next to affected joints, typically over bony prominences. These are likely due to the deposition of RF immune complexes. About a fourth of patients with RA develop these nodules.
- A fibrotic condition can arise in the lungs as nodules develop there similar to the granulomas in the skin. Again, these are likely due to the deposition of RF immune complexes. Exudative pleural effusions may occur.
- Individuals with RA are more prone to issues with their cardiovascular system including atherosclerosis, pericarditis, endocarditis, and vasculitis. These are consequences of chronic systemic inflammatory processes likely associated with deposition of immune complexes.
- RA may also lead to complications of the eyes. Most common is a condition of dryness that can result in keratitis with associated pain and some loss of vision.
- RA patients have an increased risk of developing **Sjogren's syndrome**, which is a dry mouth secondary to autoimmune destruction of the salivary glands.
- **Felty syndrome** is a triad that includes RA, enlargement of the spleen, and neutropenia. Felty syndrome arises when the systemic and chronic inflammation with RA stimulates growth of the spleen. The enlarged spleen sequesters neutrophils, thus leading to the neutropenia.
- Kidneys, bones, and teeth can also be affected by RA and result in tissue damage secondary to the systemic chronic inflammatory processes.

It is estimated that at least half of a person's risk for getting RA is genetic. The MHC antigen HLA-DR4 is strongly associated with a risk of developing RA. Environmental causes also play a large part. Smoking causes a three-fold increase in the risk of developing RA and silica exposure correlates with an increased risk of RA as well. There is no known infectious agent responsible for triggering RA, but periodontal (gum) disease has a strong correlation with RA risk.

There is no cure for RA. Treatments are applied to manage the symptoms and minimize the damage. Disease modifying anti-rheumatic drugs (DMARDs) are the primary treatment. There are a lot of DMARDs that have been and continue to be used. They fall into the following categories:

- Immunosuppressants
- TNF-alpha inhibitors
- IL-6 inhibitors
- Anti-inflammatory agents including NSAIDs and glucocorticoids (for short-term relief)

Treatment is most effective if it is started early. Regular exercise is helpful to slow the progression as it keeps the joints more stable and helps ward off fatigue. Joints that are severely damaged may be surgically altered to remove the synovial membrane and fuse the joint (called **arthrodesis**). Some joints may be replaced.

## Comparison of OA and RA

| Characteristic: | Osteoarthritis: | Rheumatoid Arthritis: |
|---|---|---|
| **Age of onset:** | >50 years | 30-50 years |
| **Speed of onset:** | Rapid | Slow |
| **Cause:** | Mechanical stress/wear and tear | Autoimmune condition |
| **Joint pattern:** | Asymmetric | Bilateral and symmetric |
| **Pain levels after moving:** | Often better, but not so much in the later stages | Often worse, especially during flare ups, but can bring some relief early in the disease in between flare ups |
| **Morning stiffness:** | Not a common symptom early on, but more common as the disease progresses | Quite common and usually lasts for more than an hour |
| **Affecting the wrist, ankle, or elbow:** | Uncommon | Common |
| **Systemic symptoms:** | Uncommon | Common |
| **Joint swelling/ appearance:** | Hard, without redness and heat | Softer with redness and heat |
| **ESR and CRP tests:** | Normal | Elevated |