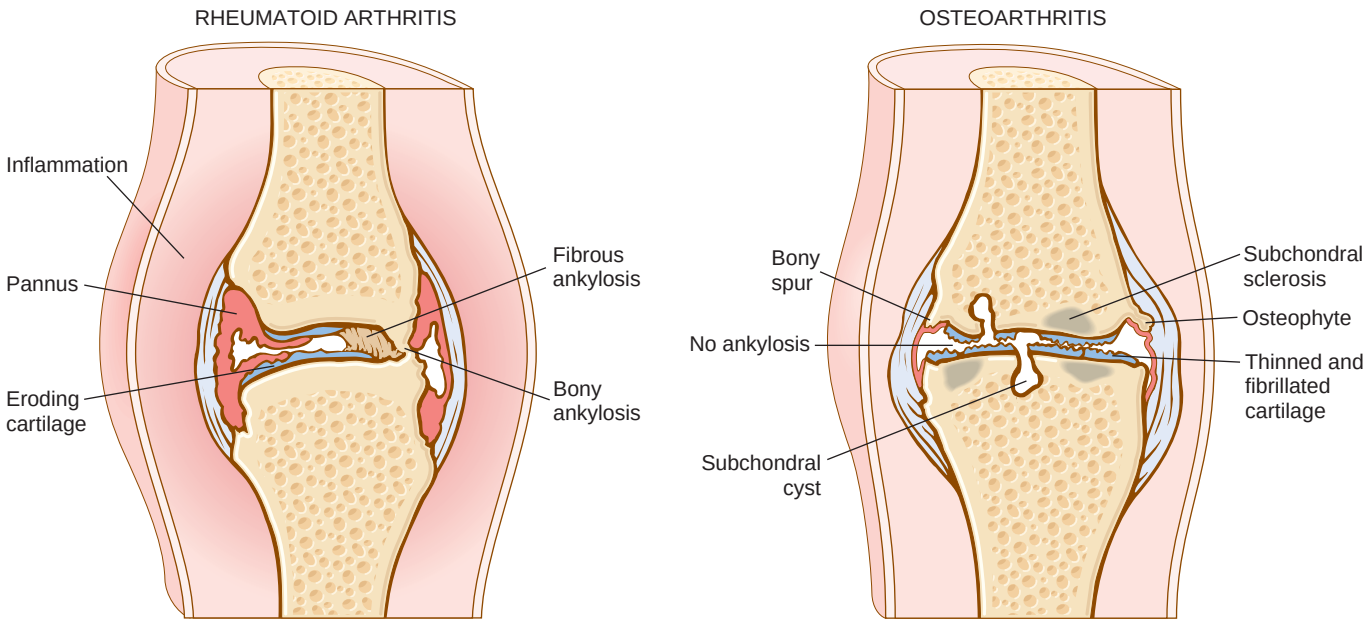


**Figure 26-41** Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.

Of these, TNF has been most firmly implicated in the pathogenesis of RA and TNF antagonists have proved to be remarkable effective therapies for the disease (see later).

**The synovium of RA contains germinal centers with secondary follicles and abundant plasma cells which produce antibodies, some of which are against self-antigens.** Many of the autoantibodies produced in lymphoid organs and in the synovium are specific for *citrullinated peptides* (CCPs) in which arginine residues are post-translationally converted to citrulline. In RA, antigen-antibody complexes containing citrullinated fibrinogen, type II collagen, α-enolase and vimentin deposit in the joints. Antibodies against these peptides are diagnostic markers for the disease and may mediate joint injury. Evidence suggests that the raised levels of anti-CCP antibodies in combination with a T-cell response to the citrullinated proteins contribute to the disease becoming chronic. Additionally, about 80% of patients have serum IgM or IgA autoantibodies that bind to the $F_c$ portions of their own IgG. These autoantibodies are called *rheumatoid factor* and may also deposit in joints as immune complexes although they are not uniformly present in all patients with RA and can be found in patients without the disease, so the link to pathogenesis is questionable.

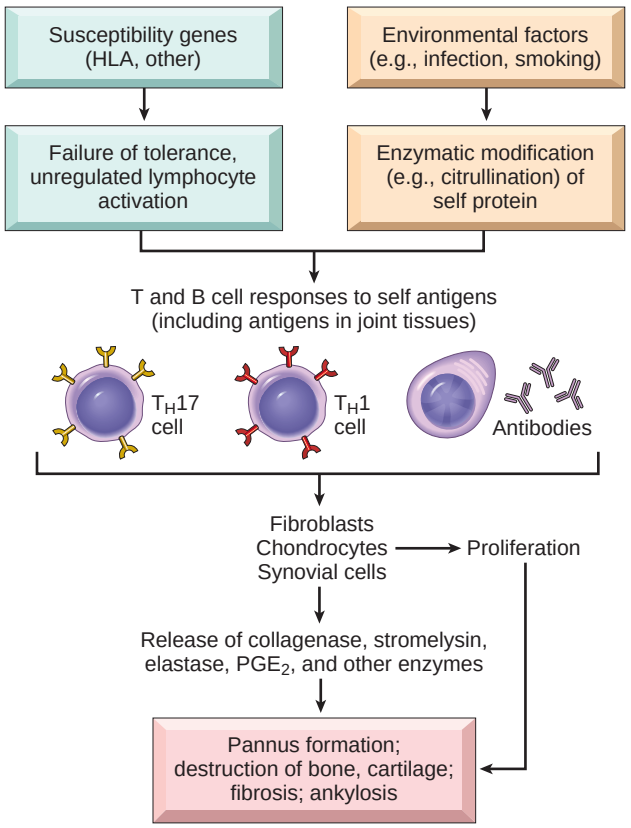


**Figure 26-42** Major processes involved in the pathogenesis of rheumatoid arthritis.

It is estimated that 50% of the risk of developing RA is related to inherited genetic susceptibility. Specific *HLA-DRB1* alleles are linked to rheumatoid arthritis, and these alleles share a common sequence of amino acids in a polymorphic region of the β chain, which is designated the *shared epitope*. The shared epitope is located in the antigen-binding cleft of the DR molecule. This location is presumably the specific binding site of the arthritogen(s) that initiates the inflammatory synovitis. Linkage and genome wide association studies have also implicated the *PTPN22* gene. *PTPN22* encodes a protein tyrosine phosphatase that is postulated to inhibit T-cell activation.

The environmental arthritogen whose antigens initiate RA by activating T or B cells remains uncertain. CCPs are produced during inflammation, so insults such as infection and smoking may promote citrullination of self-proteins, creating new epitopes that trigger autoimmune reactions. The robust immune reaction to these autoantigens suggests that they may be important arthritogenic agents.