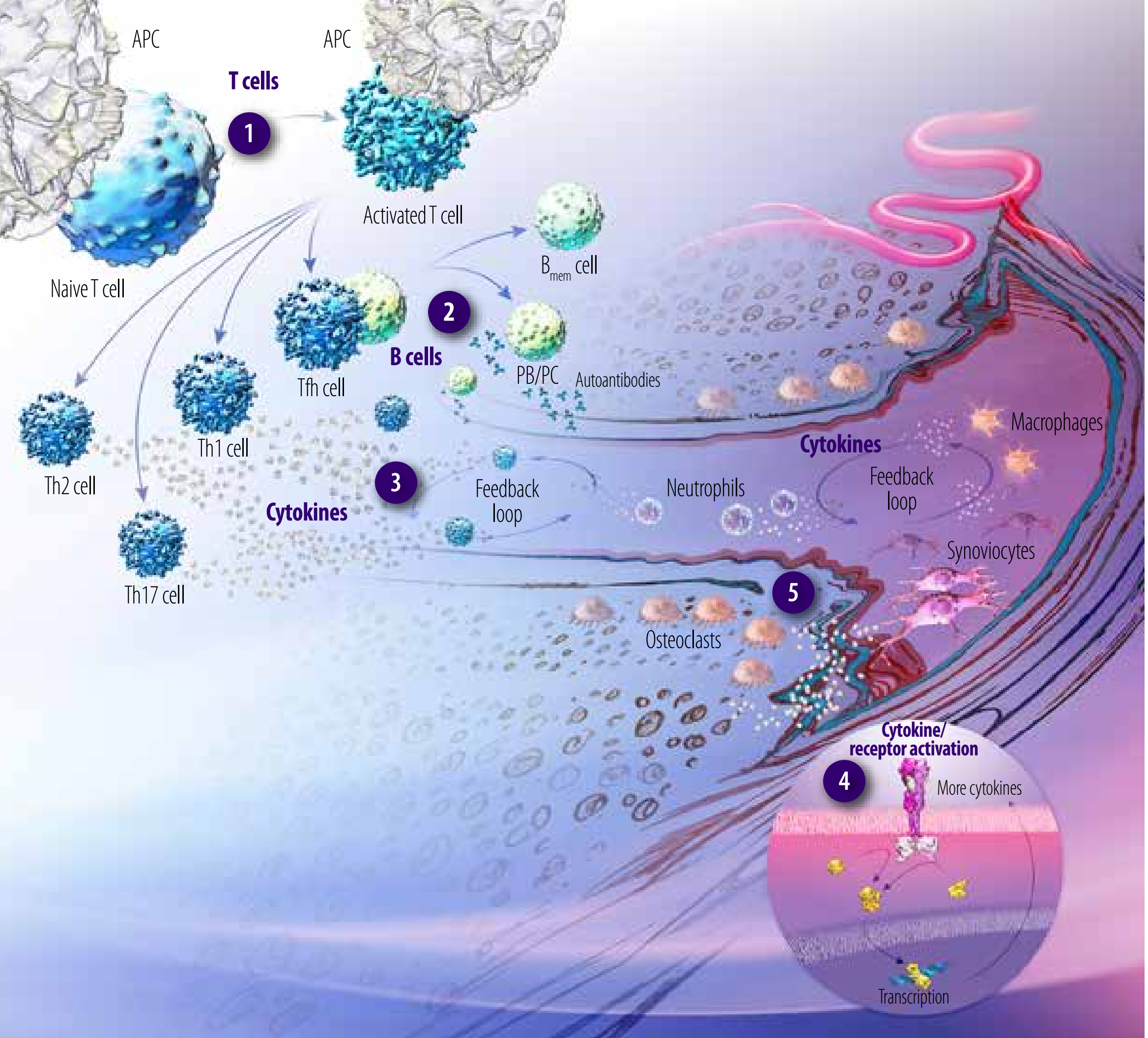

Pathways in Rheumatoid Arthritis

1. T cell Activation, Proliferation and Differentiation
2. B cell Activation and Antibody/ Autoantibody Production
3. Pro-inflammatory Cytokine Production
4. Cytokine/Receptor Interactions Trigger Intracellular Signaling Cascades Leading to Inflammation
5. Cartilage and Bone Destruction

AMGEN®

Inflammation

Pathways in Rheumatoid Arthritis

RA is a chronic inflammatory autoimmune disease with articular, extra-articular and systemic effects. RA affects the synovial joints (most often those of the hands, feet and knees). The synovium of the affected joint is characterized by hyperplasia, increased vascularity and infiltration of multiple cytokine producing cells. The pathobiology of RA is complex, involving multiple cell types (eg. T cells, B cells, macrophages, synoviocytes, osteoclasts) and a complex network of interactions with various immune modulators (including pro-inflammatory cytokines TNF, IL-6).

1 T cell Activation, Proliferation and Differentiation
T cell activation requires a dual signal: 1) antigen-presentation to Antigen-presenting cells (APCs) such as dendritic cells, macrophages and activated B cells and 2) engagement of additional cell surface receptors on the APC (eg. CD20/86 via CD28). Activated T cells in turn proliferate and differentiate into various effector T cell subpopulations including Th1, Th17 and Th2, Tfh cells.

2 B cell Activation and Antibody/Autoantibody Production
B cells become activated through interactions with T cells and through cytokines which enhance their proliferation and differentiation into antibody-forming plasma cells (PB/PC) and memory B cells.

3 Pro-inflammatory Cytokine Production
T and B cells activation result in increased production of cytokines and chemokines leading to a feedback loop for additional T cell, macrophage and B cell interactions. Synoviocytes, macrophages and neutrophils also produce cytokines (eg. TNF-α, IL-1 and IL-6) which drive feedback loops resulting in increased cytokine synthesis.

4 Cytokine/Receptor Interactions Trigger Intracellular Signaling Cascades Leading to Inflammation
TNF and IL-6 play dominant roles in the pathobiology of RA. However, other cytokines (including IL-1 and IL-17) also have an impact on the disease process. Cytokine/Receptor interactions trigger intracellular signaling cascades (involving diverse intracellular mediators such as Janus kinases) that activate genes associated with inflammatory responses including additional cytokines, upregulation of adhesion molecules, activation of osteoclasts, induction of prostaglandins, nitric oxide, matrix metalloproteinases (MMPs) and acute phase response.

5 Cartilage and Bone Destruction
Synoviocytes, together with neutrophils and chondrocytes contribute to the destruction of cartilage and bone by secreting MMPs. The principal cause of bone erosion is the pannus which is found at the interface with cartilage and bone. The pannus is rich in osteoclasts which are the primary mediators of bone destruction.

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