Rheumatoid Arthritis

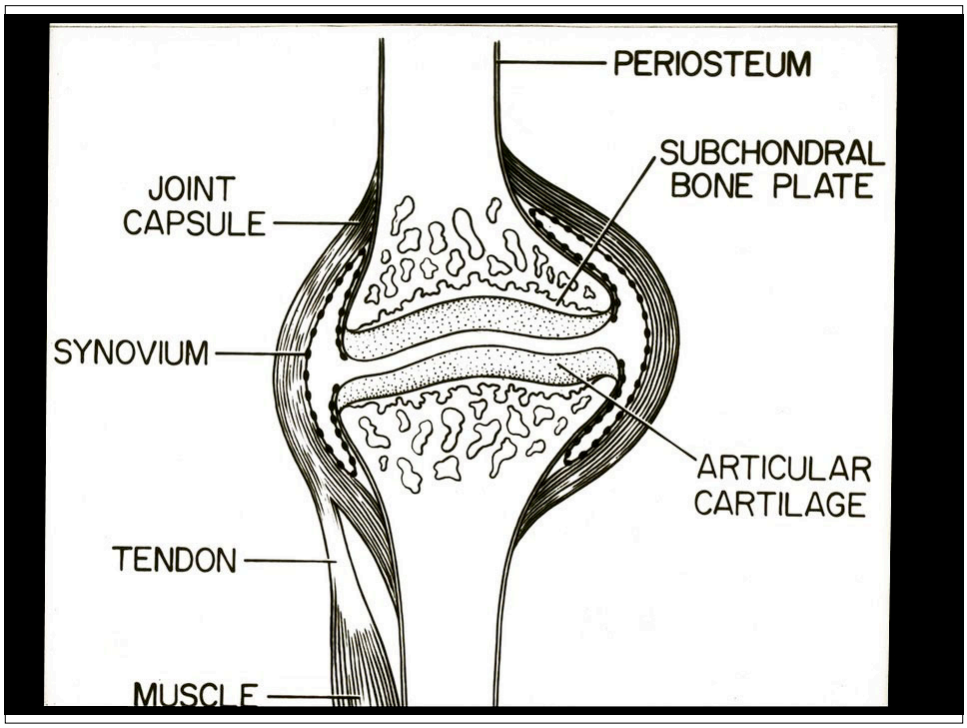
Chronic inflammatory disease
Autoimmune disease

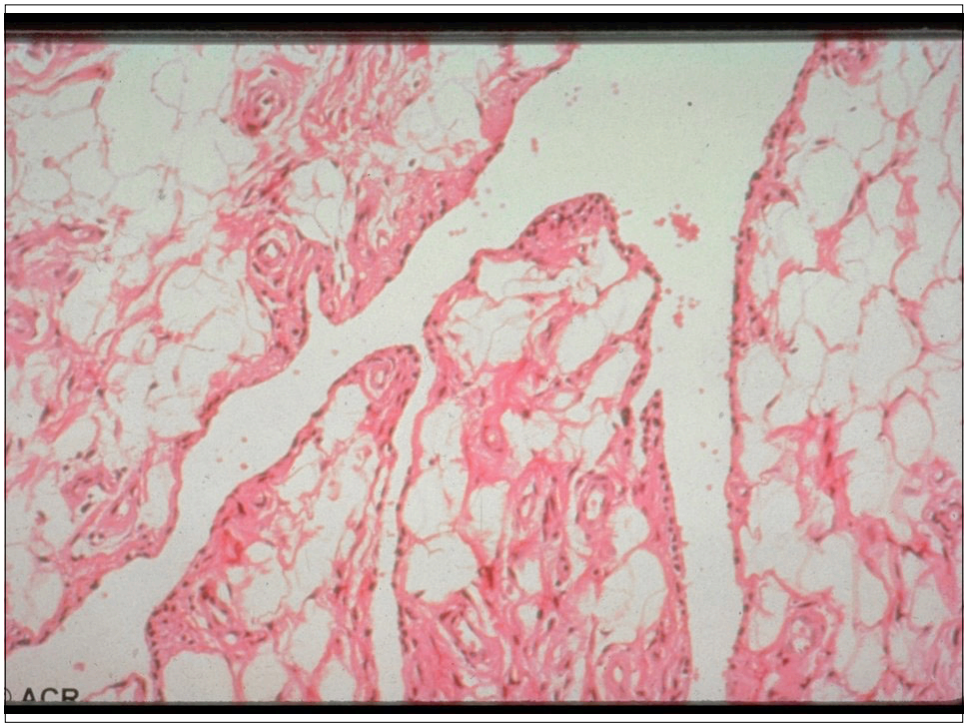
Autoimmunity
- Reactivity to self-antigens
- —immune dysregulation

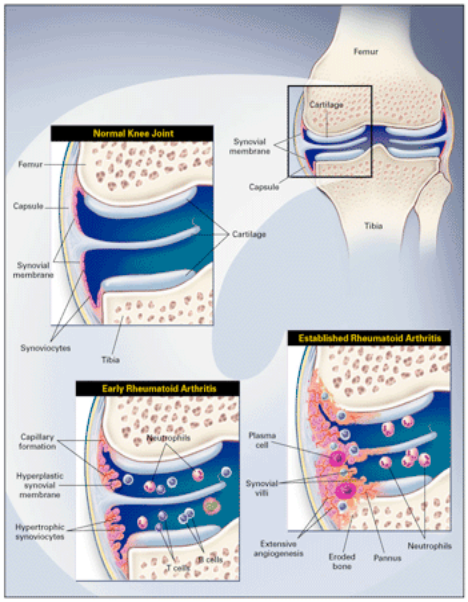
Autoimmune Disease
- Autoreactivity leading to
- tissue inflammation and damage
- occurring in absence of ongoing infection

Epidemiology

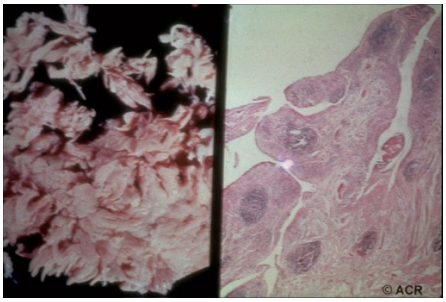
- Wordwide– Overall 1% prevalence
- Female:Male 2-3 : 1
- Age of onset 30’s-50’s

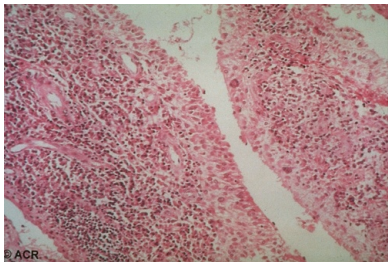

PERIOSTEUM
SUBCHONDRAL BONE PLATE
JOINT CAPSULE
SYNOVIUM
ARTICULAR CARTILAGE
TENDON
MUSCLE

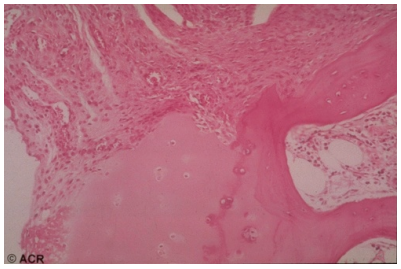



Normal Knee Joint
Femur
Capsule
Synovial membrane
Cartilage
Synoviocytes
Tibia
Femur
Cartilage
Synovial membrane
Capsule
Tibia
Early Rheumatoid Arthritis
Capillary formation
Neutrophils
Hyperplastic synovial membrane
Hypertrophic synoviocytes
T cells
B cells
Established Rheumatoid Arthritis
Plasma cell
Synovial villi
Extensive angiogenesis
Eroded bone
Pannus
Neutrophils

Pannus



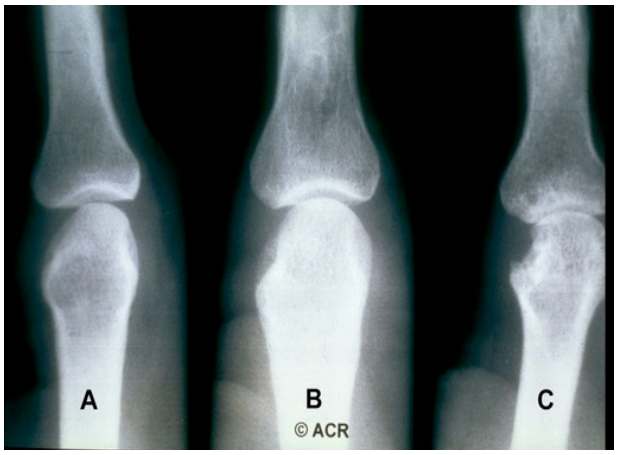




PIP swelling

Ulnar deviation, MCP swelling
left wrist swelling

Bouteniere's and swan neck
deformities



Bony erosion

Clinical Manifestations

Arthritis

Inflammatory

Symmetric

Pattern:

- small joints of the hands and feet
  wrists ankles
- knees
- elbows
- hips
- cervical spine

Clinical Manifestations

Extra-articular

Constitutional symptoms

Rheumatoid nodules

Pulmonary involvement

Ocular involvement

Cardiac involvement

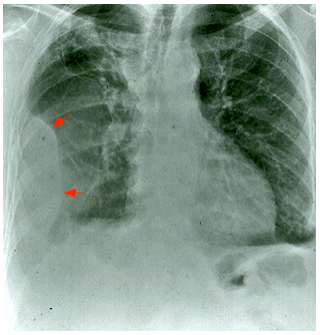
Vasculitis

Extraarticular manefestations

Rheumatoid nodules

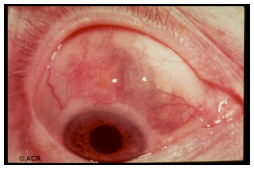
Extra-articular manifestations

- Pulmonary manifestations
  - Pulmonary nodules
  - Pleuritis
  - Interstitial lung disease
  - Interstitial alveolitis



Extra-articular manifestations

- Ophthalmologic manifestations
  - Dry eyes/Sjogren's syndrome
  - Inflammatory eye disease
    - Episcleritis
    - Scleritis
    - Uveitis
    - Corneal melt



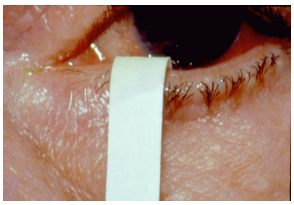
Extra-articular manifestations

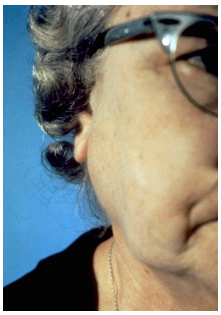
- Cardiac involvement
  - Pericarditis
- Vasculitis
  - Skin ulcerations
  - Palpable purpura
  - Mononeuritis multiplex

Clinical Manifestations

<u>Associated syndromes</u>

Sjogren's Syndrome

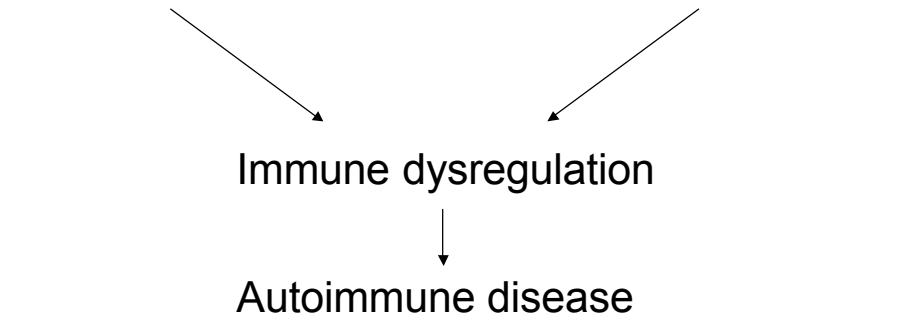




Felty's Syndrome

Seropositive Rheumatoid Arthritis
Splenomegaly
Granulocytopenia

Pathogenesis



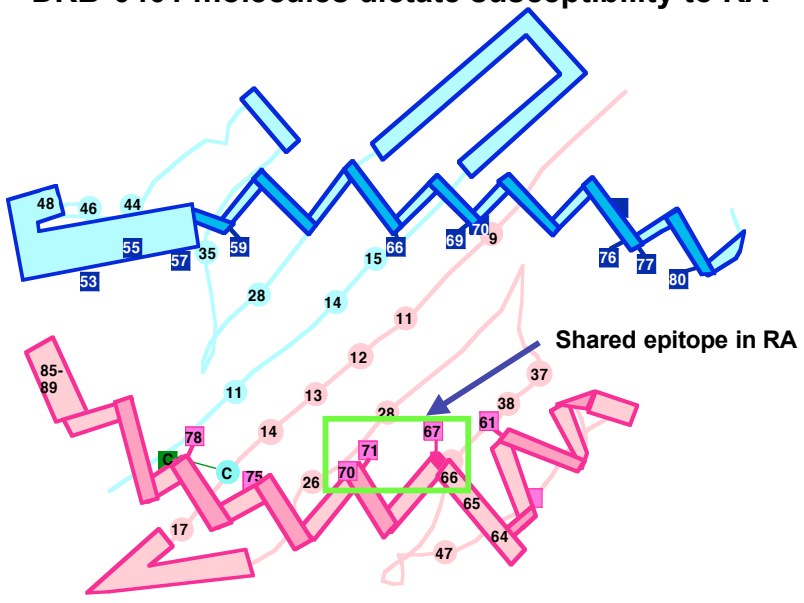
Genetic factors

- HLA shared epitope
- Peptidylarginine deiminase (PADI4) (J)
  Forms citrulline from Arg residues in proteins
- PTPN22 (EU)
  Hematopoietic-specific protein tyrosine phosphatase gene
- MHC2TA promotor
  MHC Class II transactivator, a major transcription factor for MHC Class II and other genes
- FCRL3 (J)
  Fc receptor-like 3
- CTLA4 (Asian)
- IL5R, IL2, IL4, IL1RA, IFN-γ, IL10 p, MBL, PD-1, PDCD-1

HLA DRB1 Alleles Associated with RA

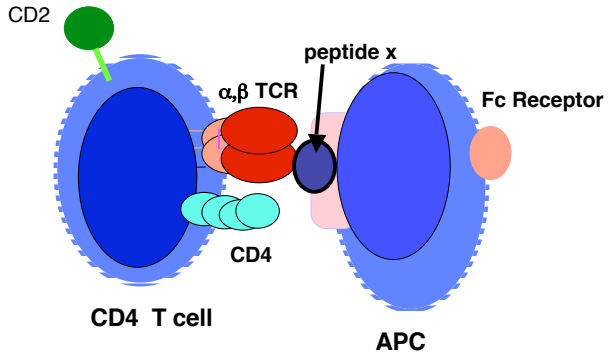
Associated alleles	67	68	69	70	71	72	73	74
DRB1*0401	Leu			Glu	Lys			Ala
DRB1*0404	Leu			Glu	Arg			Ala
DRB1*0101	Leu			Glu	Arg			Ala
Non-associated allele								
DRB1*1402	Ile			Asp	Glu			

Amino acid sequences in the β chain HLA-DRB*0401 molecules dictate susceptibility to RA

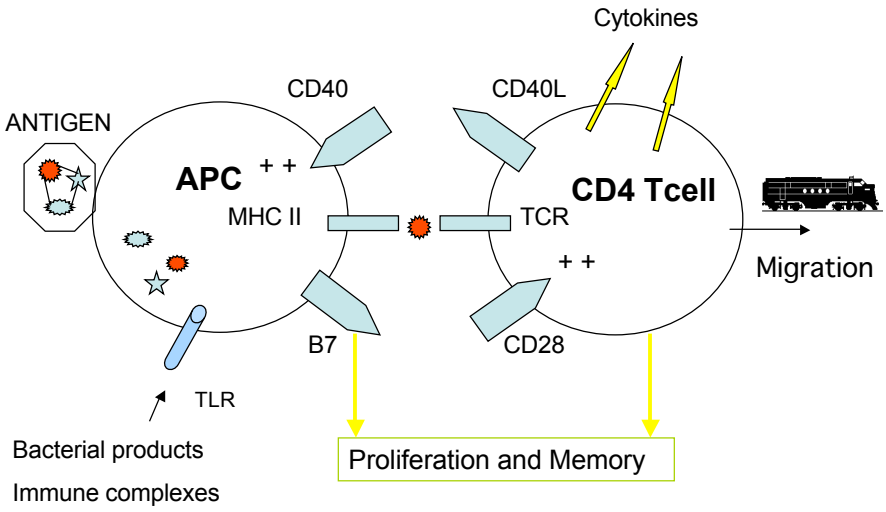


Pathogenesis

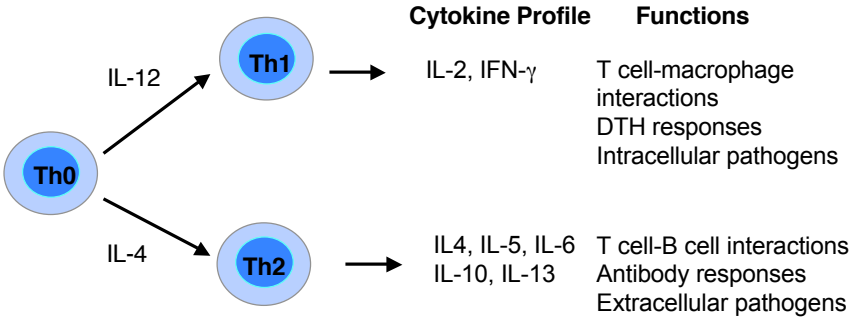
Initiating Event in Rheumatoid Arthritis



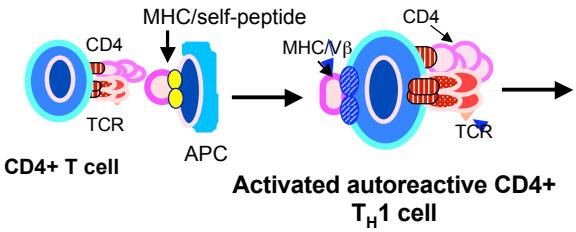
Antigen Recognition and Costimulation



CD4+ T Cells Differentiate into Distinct T_H1 and T_H2 Subsets



Consequences of CD4+ T_H1 mediated autoimmunity:



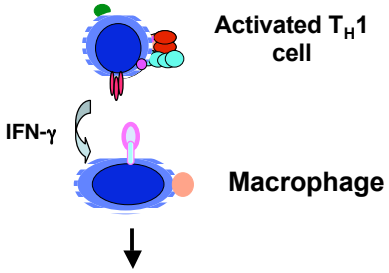
Expansion of CD4+, autoreactive T_H1 cells

Migration and infiltration of self reactive CD4+ T_H1 cells into tissues

Inflammation and autoimmunity

Induction of regulatory cells and cytokines which control the growth and activation of the pathogenic autoreactive CD4+ T cells

Immunopathophysiology of Rheumatoid Arthritis

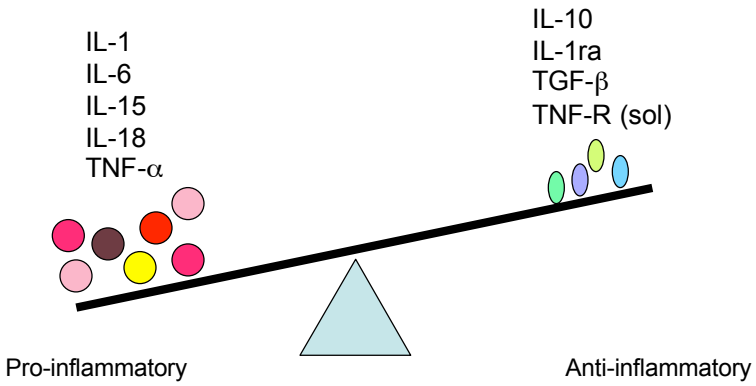


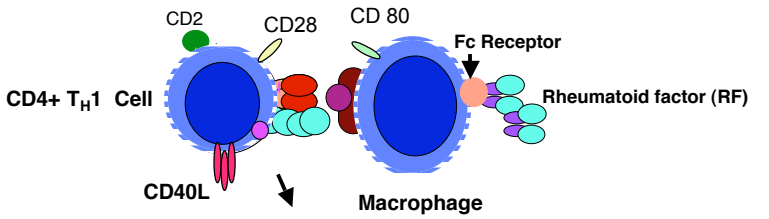
IL-1, TNF-α

Inflammation

Bone and cartilage destruction

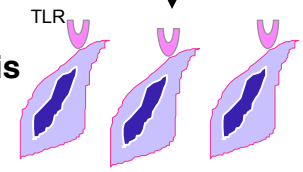
Inflammatory cytokine disequilibrium in Rheumatoid arthritis





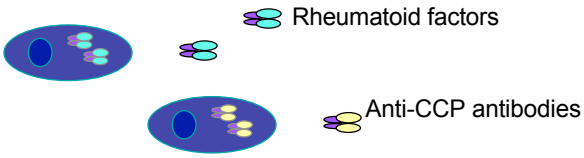
IL-1, TNF-α

Rheumatoid arthritis Synovial Cells



VCAM-1, β_1 integrins
Proliferation
PGE_2
IL-1
MMPs
Cathepsin
RankL

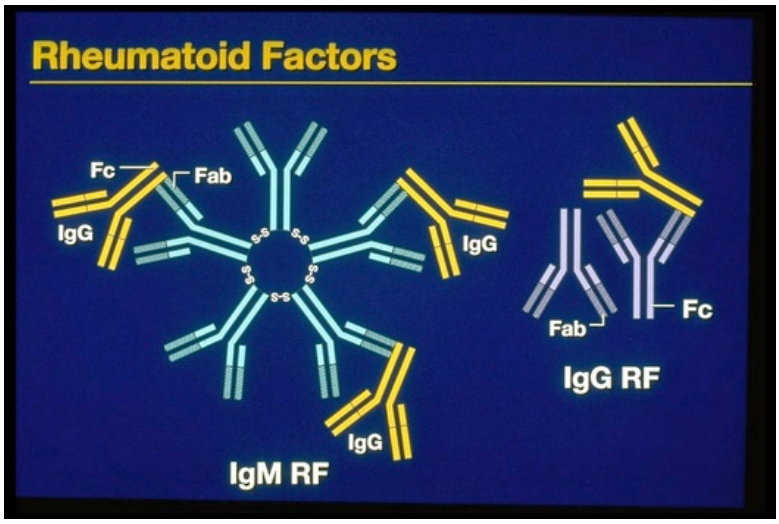
Immunopathophysiology of Rheumatoid Arthritis



B cells in Rheumatoid Arthritis

Auto-antibody production
Lymphoid architecture
T cell IFN-γ production

CCP = cyclic citrullinated peptide

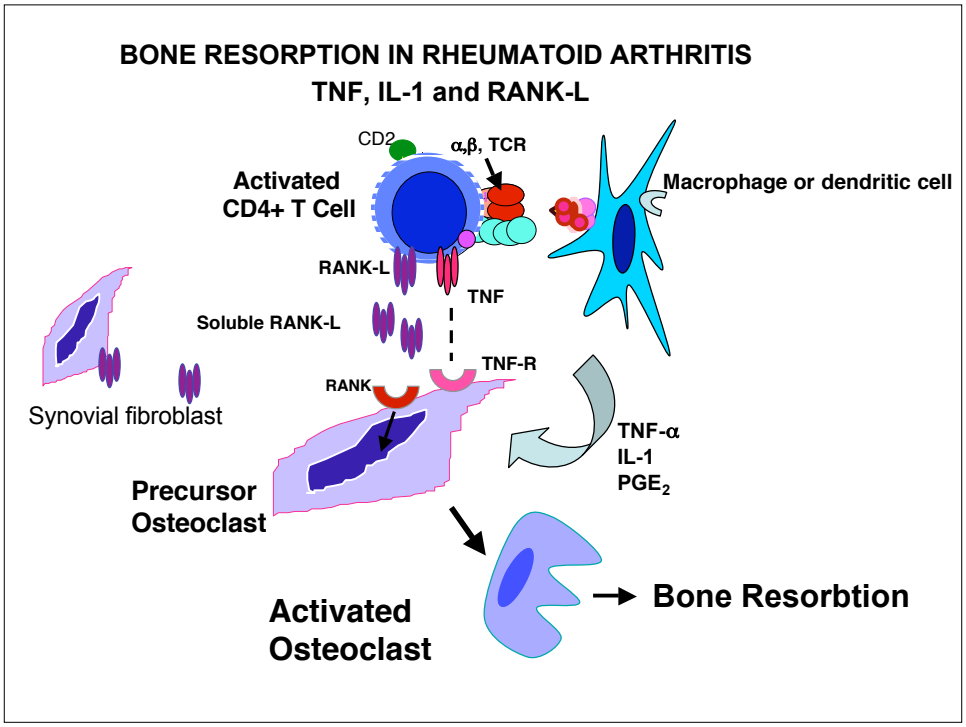


Rheumatoid factor

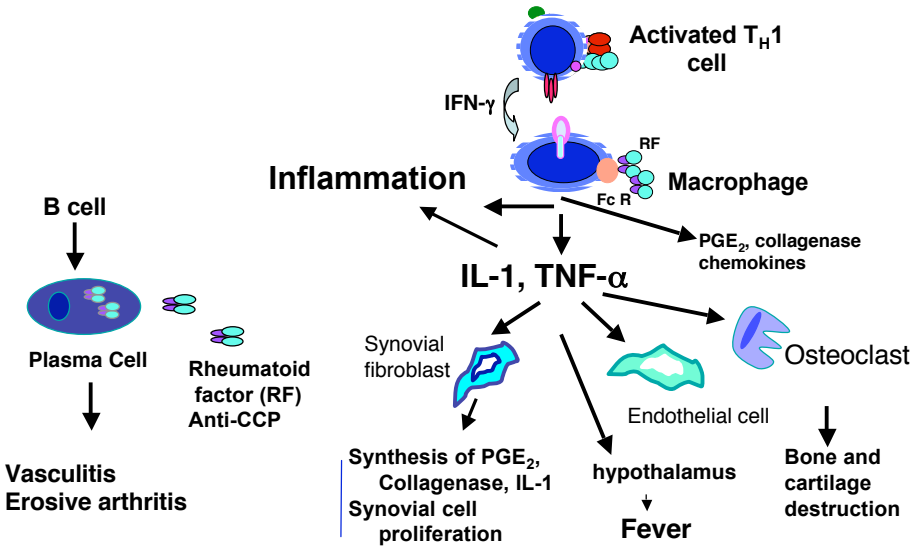
- Recognizes Fc portion of IgG
- Typically IgM, but may be IgG, IgA, IgE
- 80% of RA patients
- Not specific for RA, seen in other rheumatic conditions as well as chronic inflammatory conditions (TB, SBE)
- Biologic and Pathologic Functions of RF's
  - Augment phagocytosis of opsonized particles
  - Immune complex clearance
  - RF bound to IgG or to immune complexes can precipitate in vessel walls and induce vasculitis. High titer RF is associated with systemic vasculitis in RA
  - Rheumatoid factors bind to Fcγ receptors on macrophages and augment the release of cytokines, including IL-1 and TNF-α

Anti-CCP

- Recognizes citrullinated proteins
- Precedes development of RA by years
- 80% sensitivity, 98% specificity in RA
- Modulation of erosive arthritis in animal models



Immunopathophysiology of Rheumatoid Arthritis



Treatment of Rheumatoid Arthritis

Inhibit products of T cells and macrophages
NSAIDs, TNF inhibition, IL-1 receptor inhibitors

Prevent T cell, B cell or synovial cell proliferation
Methotrexate, Azathioprine, Leuflunomide

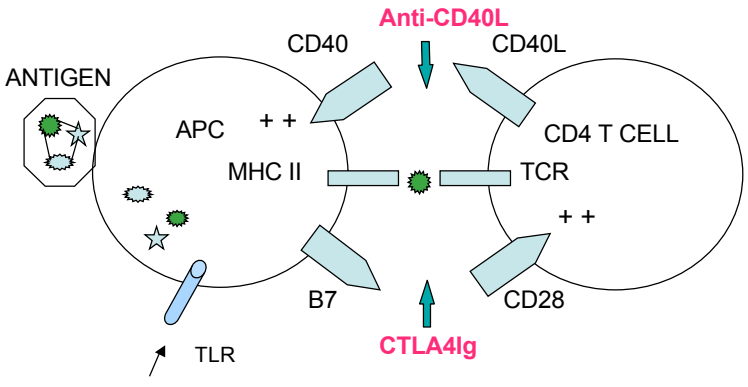
Decrease T cell activation
Cyclosporin

Inhibit T cell or APC function
Corticosteroids, gold, penicillamine

Potential Treatment of Rheumatoid Arthritis

- **Block T cell activation**

Blockade of T cell activation by costimulation antagonists



Potential Treatments of Rheumatoid Arthritis

- **Block T cell activation**
  Anti-CD40L, CTLA4-Ig
- **B cell depletion**
  Anti-CD20 antibody--Rituximab