Rheumatoid Arthritis

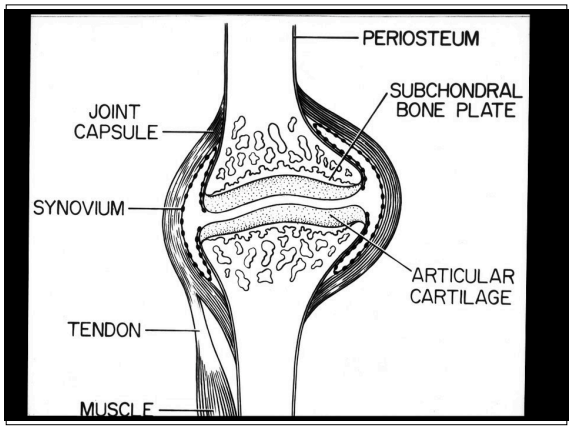
Chronic inflammatory disease
Autoimmune disease

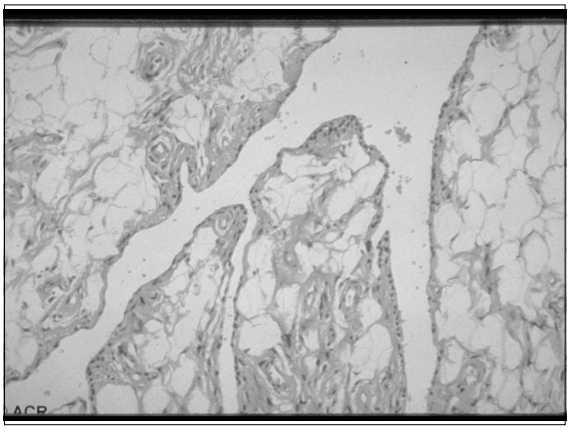
Autoimmunity
Reactivity to self-antigens
—immune dysregulation

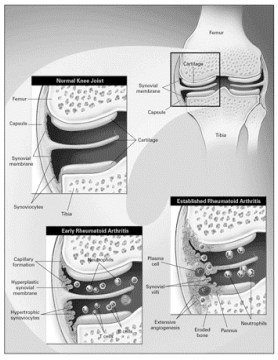
Autoimmune Disease
Autoreactivity leading to
tissue inflammation and damage
occurring in absence of ongoing infection

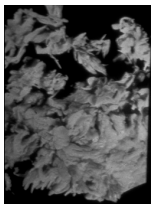
Epidemiology

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

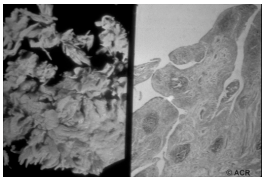


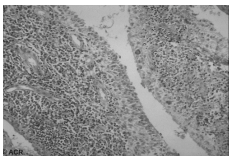


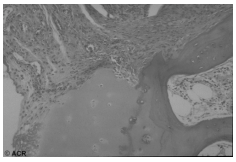




Pannus



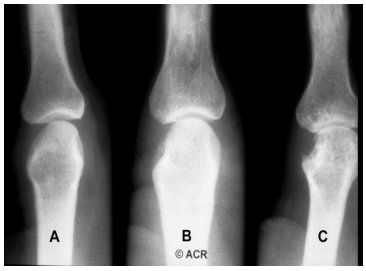




PIP swelling

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

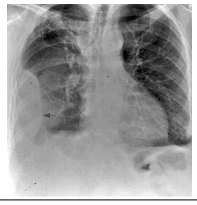
Vasculitis

Extraarticular manefestations

Rheumatoid nodules

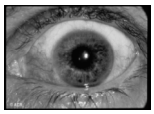
Extra-articular manifestations

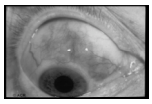
- Pulmonary manifestations
  - Pulmonary nodules
  - Pleuritis
  - Interstitial lung disease
  - Interstitial alveolitis



Extra-articular manifestations

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





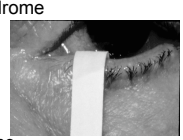
Extra-articular manifestations

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

Clinical Manifestations

Associated syndromes

Sjogren's Syndrome



Felty's Syndrome

Seropositive Rheumatoid Arthritis
Splenomegaly
Granulocytopenia

Pathogenesis

Genetic factors Environmental factors

Immune dysregulation

Autoimmune disease

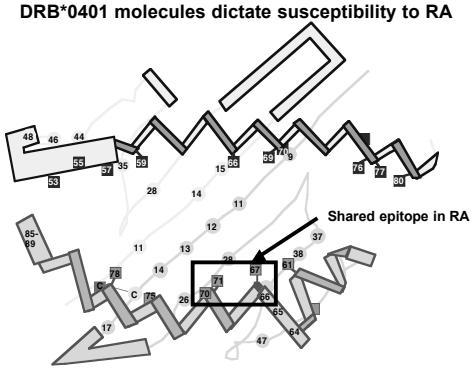
Genetic factors

- 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

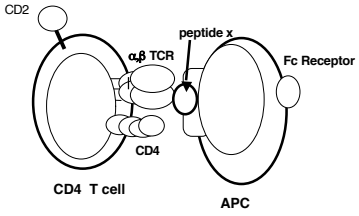
Associated alleles	67	68	69	70	71	72	73	74
DRB1*0401	Leu			Glu	Lys			Ala
DRB1*0404	Leu			Glu	Arg			Ala
DRB1*0101	Leu			Glu	Arg			Ala
Non-associated allele								
DRB1*1402	Ile			Asp	Glu			

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

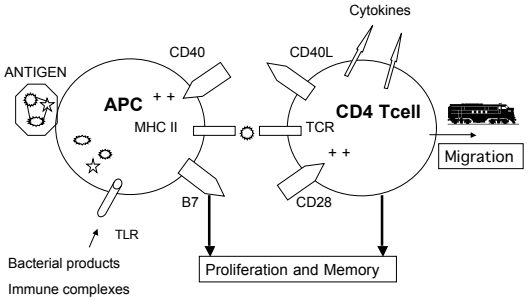


Pathogenesis

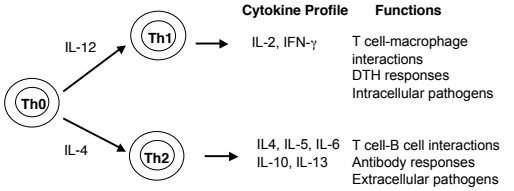
Initiating Event in Rheumatoid Arthritis



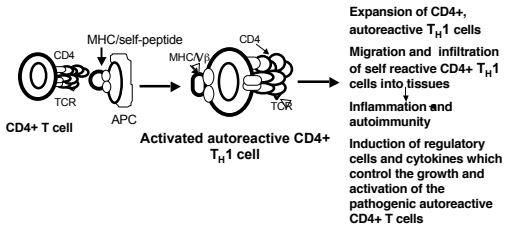
Antigen Recognition and Costimulation



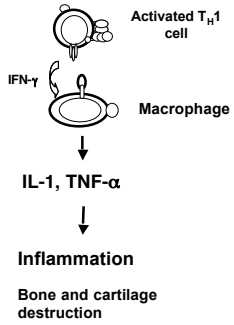
CD4+ T Cells Differentiate into Distinct T_H1 and T_H2 Subsets



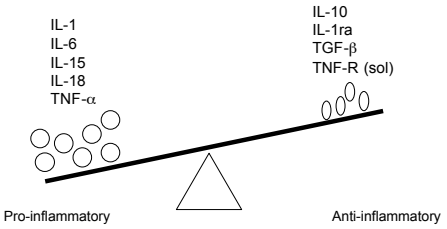
Consequences of CD4+ T_H1 mediated autoimmunity:

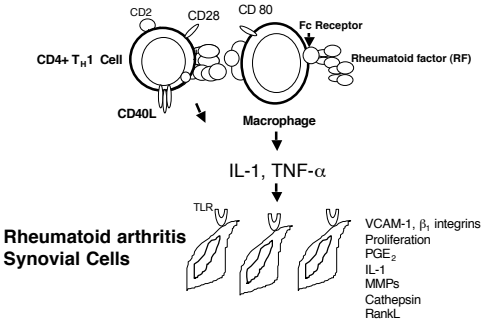


Immunopathophysiology of Rheumatoid Arthritis



Inflammatory cytokine disequilibrium in Rheumatoid arthritis





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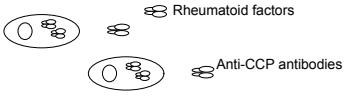
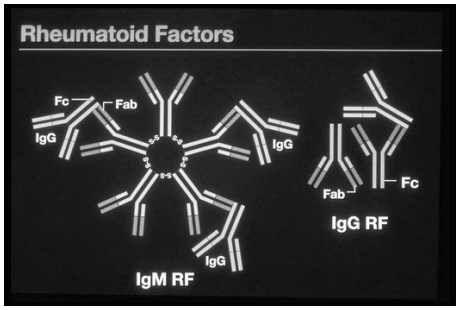


B cells in Rheumatoid Arthritis

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

CCP = cyclic citrullinated peptide



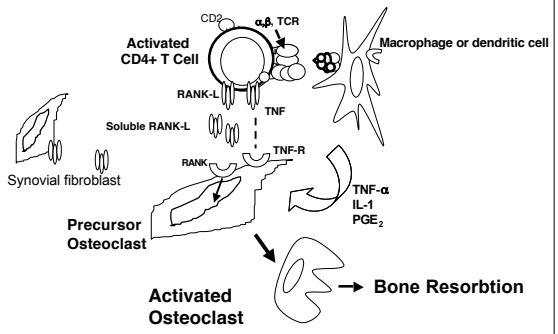
Rheumatoid factor

- 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

BONE RESORPTION IN RHEUMATOID ARTHRITIS
TNF, IL-1 and RANK-L



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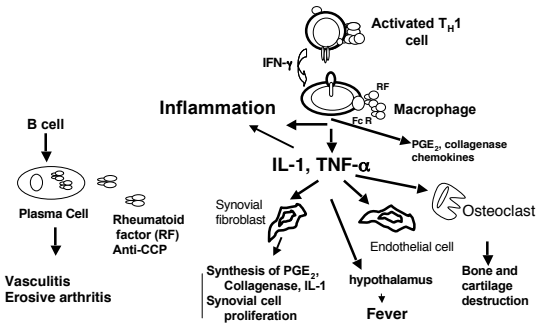


Treatment of Rheumatoid Arthritis

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

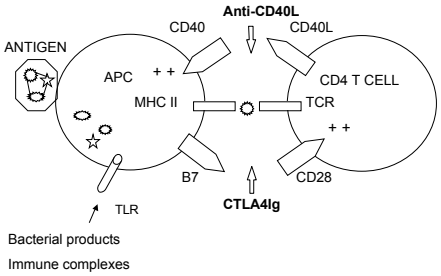
Decrease T cell activation
Cyclosporin

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