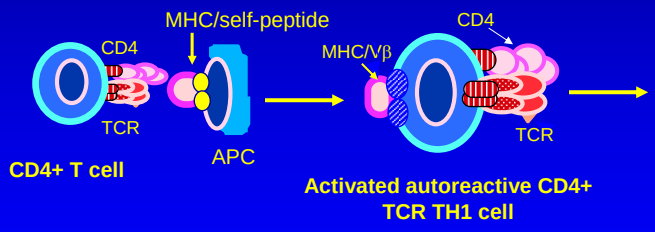
Induction of CD4+ T_H1 mediated autoimmunity:

A paradigm for the pathogenesis of rheumatoid arthritis, multiple sclerosis and type I diabetes



(1) expansion of CD4+, autoreactive TH1 cells specific for autoantigens

(2) migration and infiltration of these self reactive CD4+ TH1 cells into tissues and induction of inflammation and autoimmunity

(3) induction of regulatory cells and cytokines which control the growth and activation of the pathogenic autoreactive CD4+ T cells

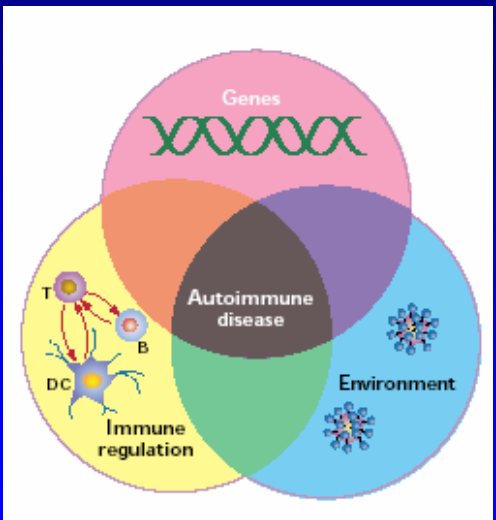
1

Rheumatoid Arthritis: Definition

Rheumatoid arthritis is characterized by a chronic inflammation of the synovial joints and infiltration by blood-derived cells, chiefly T cells, macrophages, and plasma cells, all of which show signs of activation. This leads in most cases to progressive destruction of cartilage and bone, which occurs after invasion of these tissues by the cellular synovial tissue and is believed to be mainly mediated by cytokine induction of destructive enzymes, including matrix metalloproteinases. There is also prominent development of new vessels and evidence of systemic inflammation, for example, upregulated acute phase proteins. In more severe cases there is involvement of vessels and other organs.

2

Requirements in the Development of an Autoimmune Disease



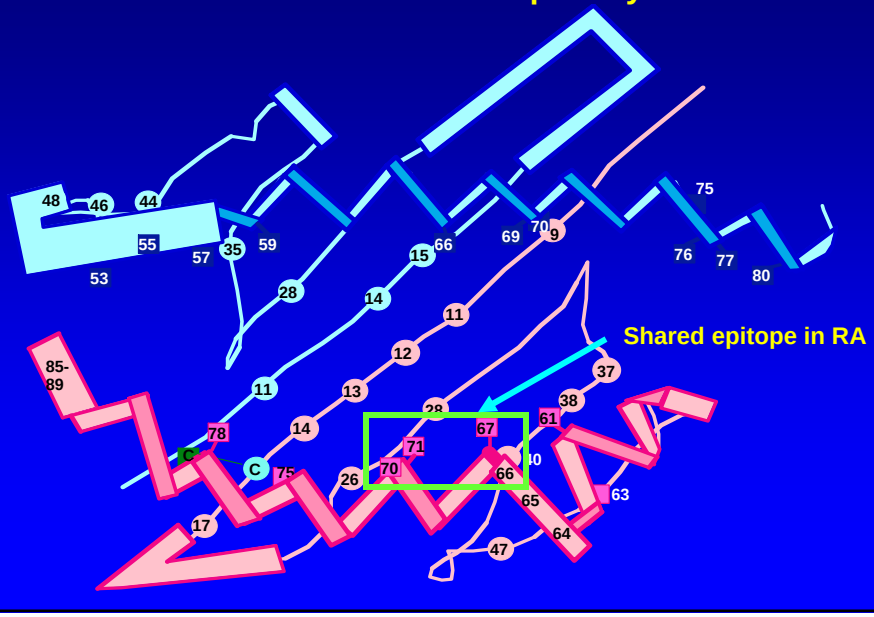
3

Rheumatoid Arthritis: Genetics

Twin and other genetic studies have demonstrated that a major genetic contribution to disease predisposition resides in the MHC class II HLA-DR locus. Females are about 2-3 times more susceptible than males. More than 80% of caucasian rheumatoid patients express DR1 or DR4 subtypes which share an epitope mapping to amino acids 70-74 of the DRβ chain, in the polymorphic region lining the peptide binding groove. There is recent evidence that the genetically susceptible HLA-DR4 (e.g., DR0401) alleles bind different peptides in their peptide binding groove than the non-susceptible (e.g., DR0402) alleles. Susceptible alleles bind a negatively charged amino acid at the p4 pocket of the binding groove. Mutation analysis revealed that position 71 of the DRβ chain in particular correlates with the genetic linkage of RA susceptibility

4

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



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Amino Acids in the Shared Epitope

	67	70	71	74	RA Association
DRB1* 0401	Leu	Gln	Lys+	Ala	++
DRB1* 0404			Arg+		++
DRB1* 0101			Arg+		++
DRB1* 0402	Ile	Asp-	Glu-		None

6

Clinical Manifestations of Rheumatoid Arthritis

(1) Arthritis

(a) Symmetrical involvement of the small joints of the hands and feet, particularly the proximal interphalangeal (PIP), metatarsophalangeal (MTP), and metacarpophalangeal (MCP) joints, but involvement of wrists, ankles, knees, elbows, and hips is also common.

(b) When the disease involves the axial skeleton, it is most frequently in the cervical region.

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Clinical Manifestations of Rheumatoid Arthritis

(2) Extra-Articular

(a) Constitutional -normochromic and normocytic anemia, fever, malaise and weight loss

(b) Subcutaneous nodules (rheumatoid nodules)

(c) Pulmonary involvement-(pleuritis, interstitial pneumonitis, alveolitis and intrapulmonary rheumatoid nodules)

(d) Cardiac involvement-pericarditis

(e) Ocular disease-keratoconjunctivitis, granulomatous scleritis

(e) Other common vasculitic manifestations-skin ulcerations, palpable purpura, ischemic ulceration of GI tract, mononeuritis multiplex

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Extra-Articular manifestations of RA

10

Clinical Manifestations of Rheumatoid Arthritis

(3) Associated Syndromes

(a) Sjögren's syndrome-salivary gland inflammation and keratoconjunctivitis

(b) Felty's syndrome-profound neutropenia, thrombocytopenia and splenomegaly

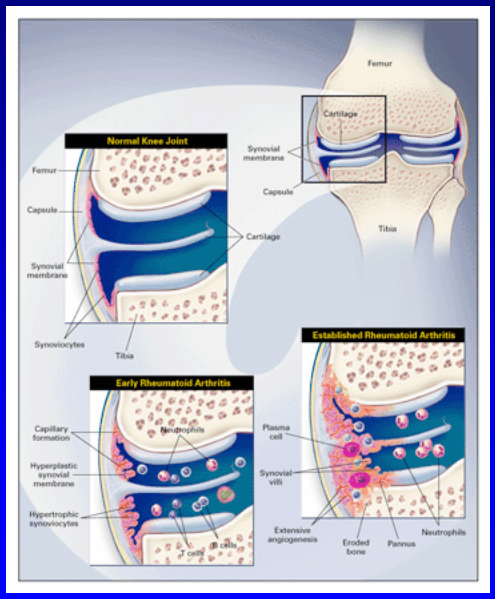
(C) Amyloidosis-type II

11

Clinical Manifestations of Sjögren's syndrome

12

Pathogenesis of Rheumatoid Arthritis.



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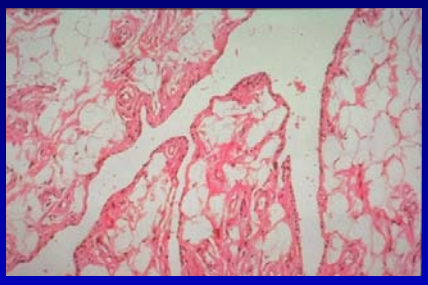
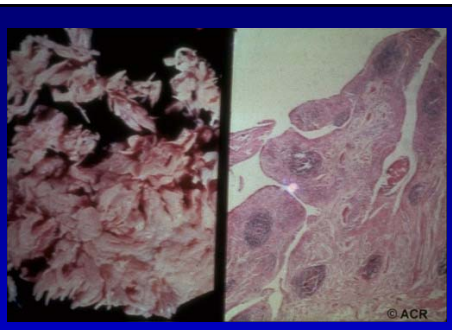
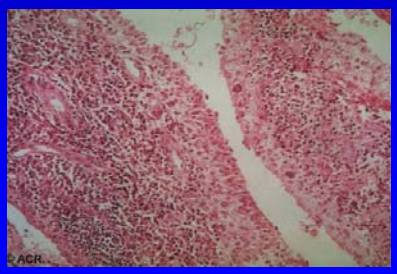


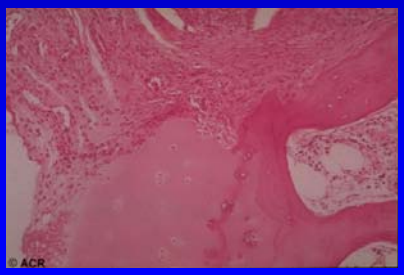
Normal synovium



Villous Synovitis



Rheumatoid Synovium
(Pannus)



Pannus Invading and
Destroying cartilage and Bone

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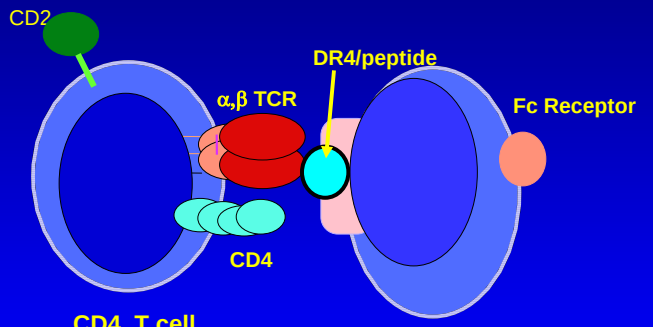
Initiating Event in Rheumatoid Arthritis



CD4 T cell

Macrophage/ dendritic
cell/B cell

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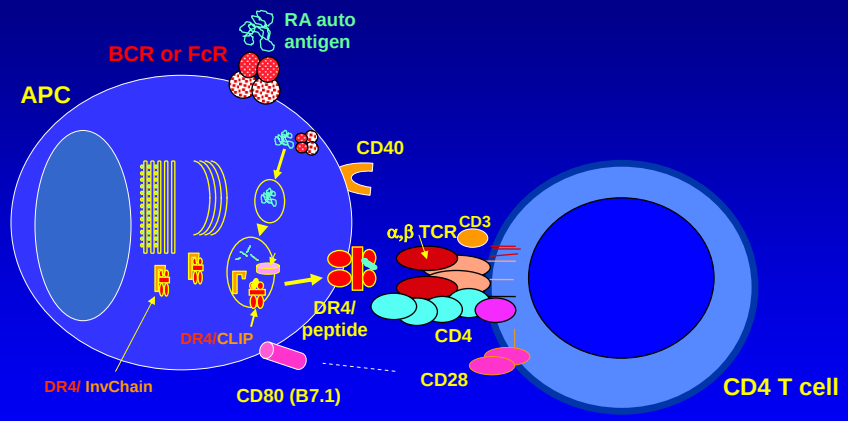
The Initiating Event in Rheumatoid Arthritis



The putative RA inducing protein binds antigen specific SmIg on B or phagocytic receptors on dendritic cells cells and is internalized and digested into peptides in endosomes and bound to the MHC class II molecule (DR4). The DR4/peptide complex triggers the TCR on antigen specific T cells leading to T cell activation.

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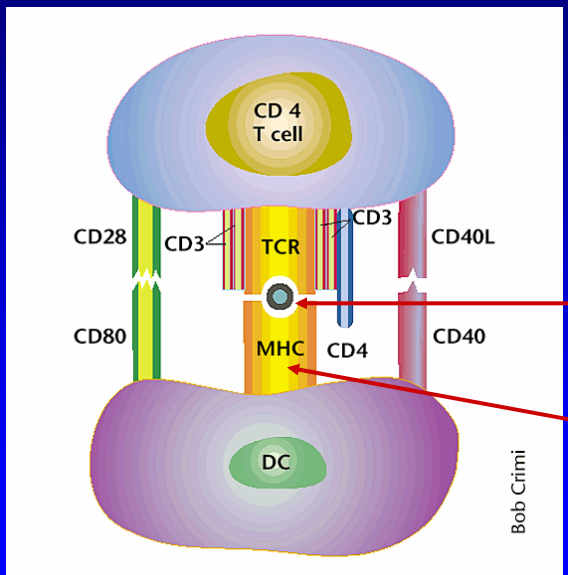

RA auto-antigenic peptide

DR4, DR1

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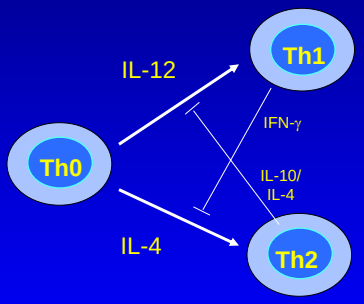
CD4+ T Cells Differentiate into Distinct T_H1 and T_H2 Subsets



	Cytokine Profile	Functions
Th1	IL-2, IFN-γ	T cell-macrophage interactions DTH responses Intracellular pathogens
Th2	IL4, IL-5, IL-6 IL-10, IL-13	T cell-B cell interactions Antibody responses Extracellular pathogens

Negative Feedback Loops

IL-4, IL-10 suppress emergence of T_H1 clones
IFN-γ suppresses emergence of T_H2 clones

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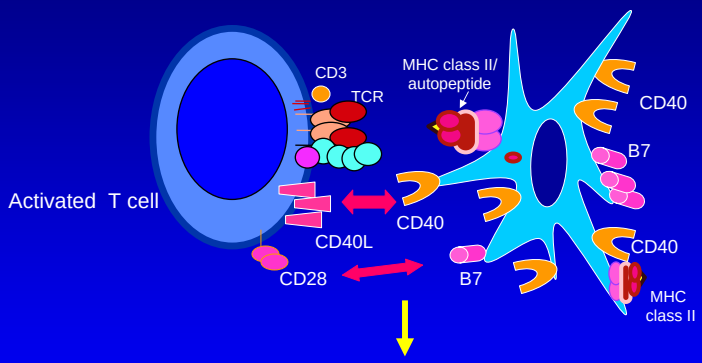
Consequences of CD40L/CD40 interactions on Dendritic cell function



(1) Induction of cytokines (IL-8, IL-12, TNF-α, MIP-1)

(2) Stimulation of B7-1 and B7-2 expression and co-stimulatory function with activation of T cell growth

(3) Augmentation of antigen-presenting function

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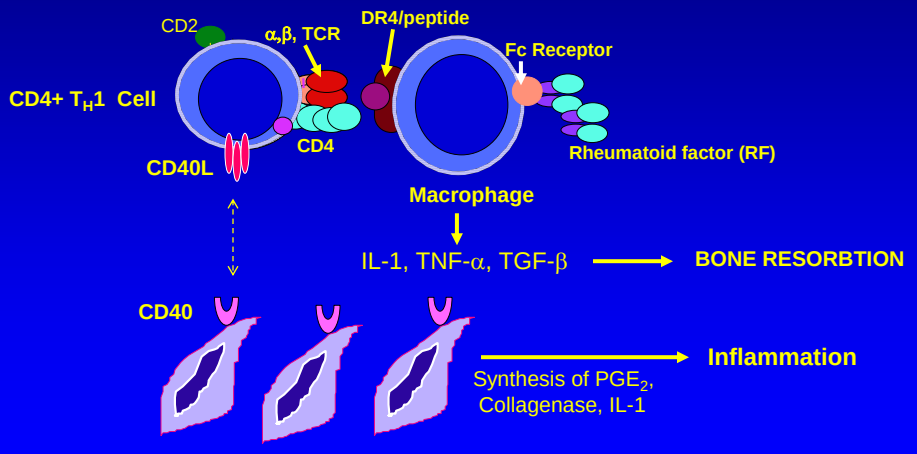
T cell-Macrophage Interactions Induce Synovial Cell Proliferation and Activation



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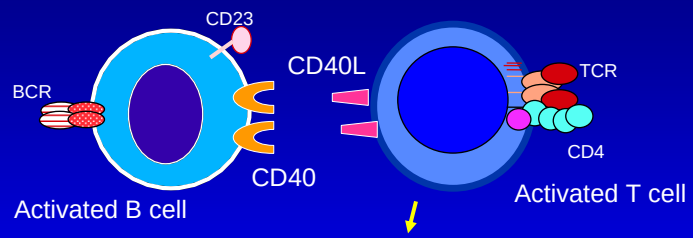
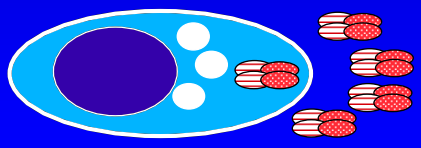
Final Phases of B cell Differentiation are Mediated by Contact T cell signals (CD40L/CD40) and Lymphokines

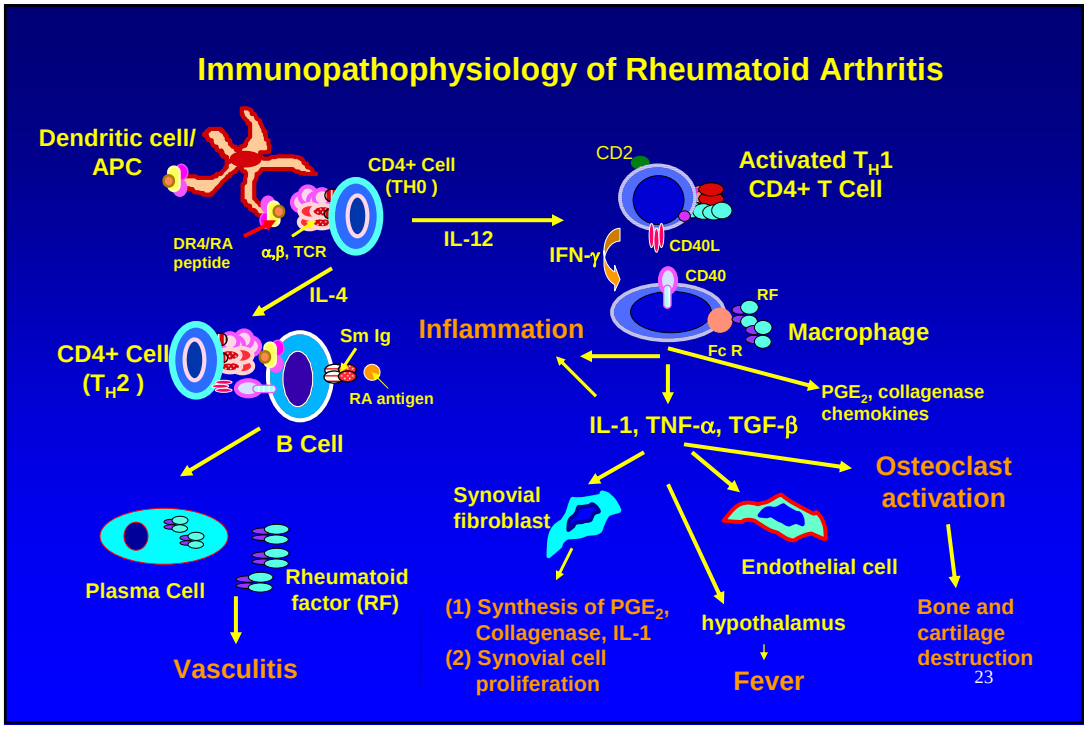


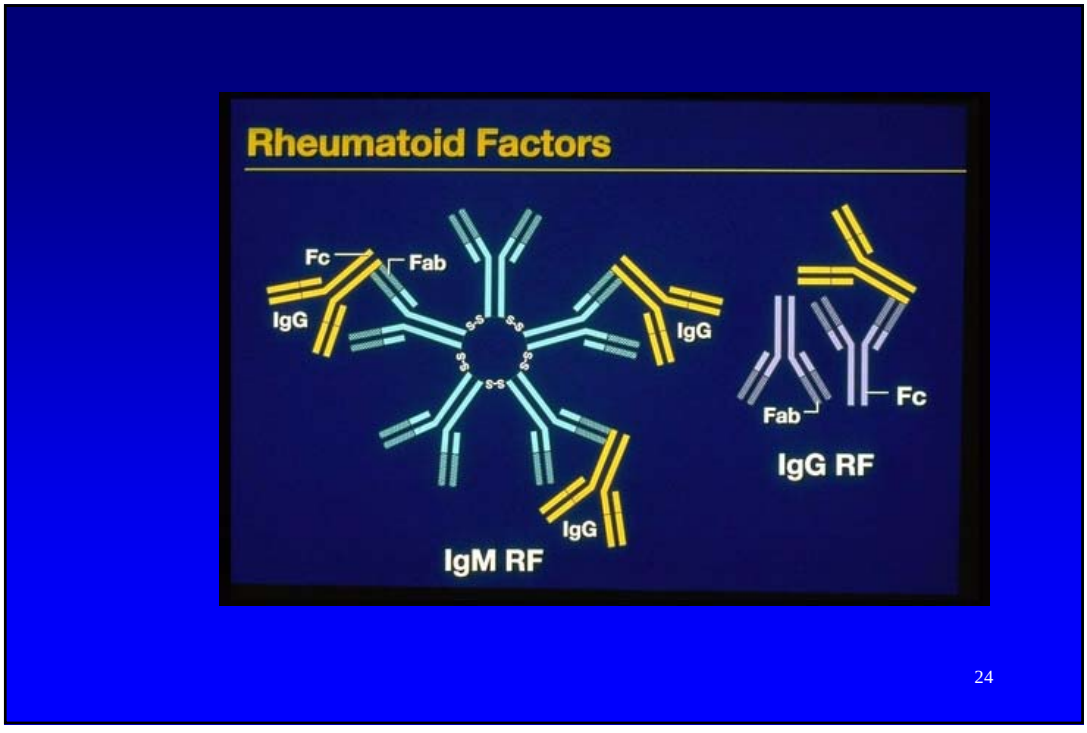


IgG
IgA
IgE

Plasma Cell

22


Immunopathophysiology of Rheumatoid Arthritis
Dendritic cell/ APC
CD4+ Cell (TH0)
DR4/RA peptide
α,β, TCR
IL-12
IL-4
CD2
Activated T_H1 CD4+ T Cell
IFN-γ
CD40L
CD40
RF
Fc R
Macrophage
Inflammation
CD4+ Cell (T_H2)
Sm Ig
RA antigen
B Cell
PGE2, collagenase chemokines
IL-1, TNF-α, TGF-β
Osteoclast activation
Synovial fibroblast
Endothelial cell
Plasma Cell
Rheumatoid factor (RF)
(1) Synthesis of PGE2, Collagenase, IL-1
(2) Synovial cell proliferation
hypothalamus
Bone and cartilage destruction
Vasculitis
Fever
23


Rheumatoid Factors
Fc
Fab
IgG
IgG
IgG
IgM RF
Fab
Fc
IgG RF
24

Rheumatoid Factors

(1) Characteristics of RFs

(a) RFs are autoantibodies with specificity for the Fc region of self-IgG

(b) Most RFs are IgM but IgG and IgA RFs are also observed

(2) Biologic Occurrence and Disease Associations

(a) RFs are the major autoantibodies observed in RA

(b) RFs can be induced in experimental animals by injection of either denatured IgG or by immunization with bacteria.

(c) High titer RF is seen in chronic inflammatory conditions such as rheumatoid arthritis, other rheumatic conditions, TB and SBE

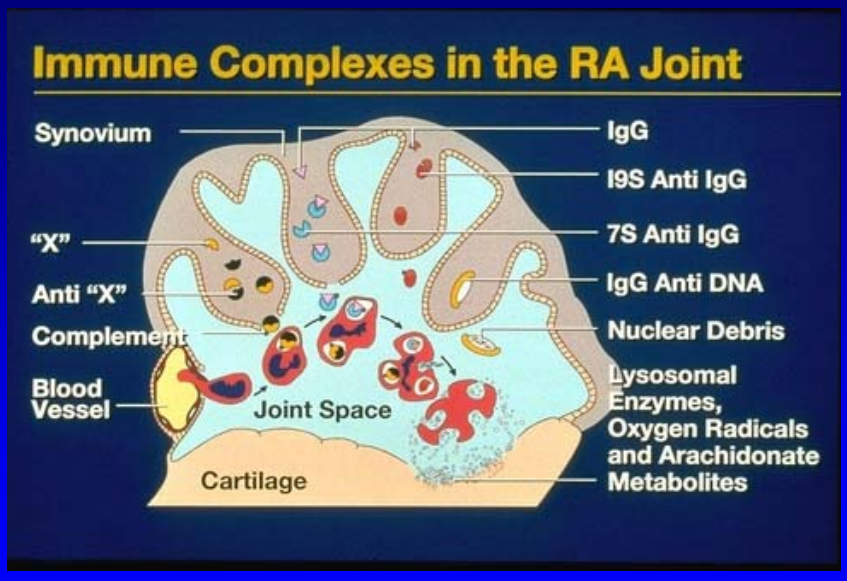
(3) Biologic and Pathologic Functions of RF's

(a) RFs may play a role in augmenting the phagocytosis of opsonized particles and in the clearance of immune complexes.

(b) 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

(c) Rheumatoid factors can bind to Fcγ receptors on macrophages and augment the release of monokines, including IL-1 and and TNF-α

25



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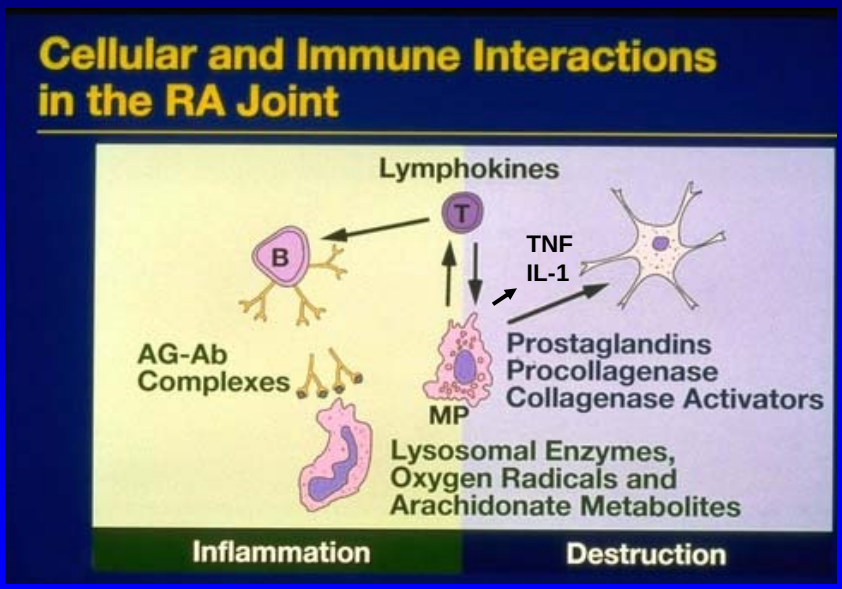
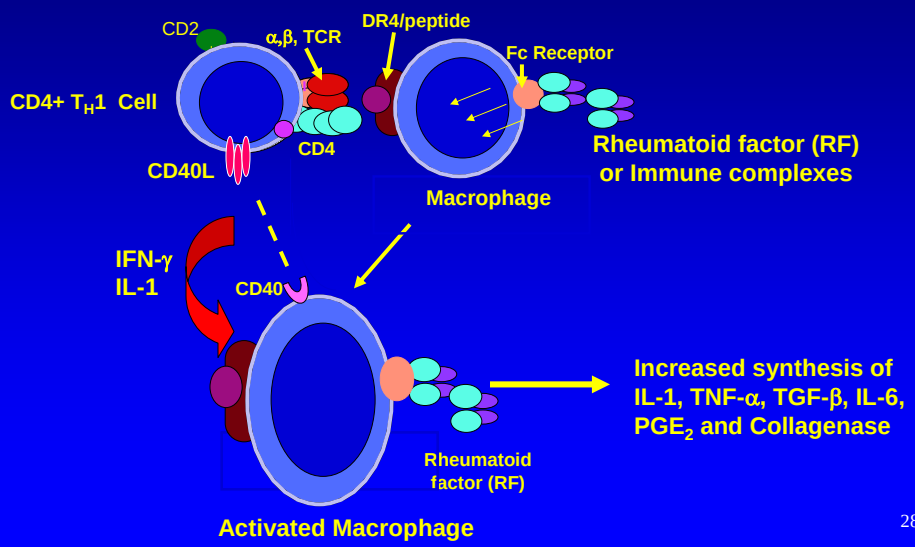

Cellular and Immune Interactions in the RA Joint
Lymphokines
T
B
TNF
IL-1
AG-Ab Complexes
MP
Prostaglandins
Procollagenase
Collagenase Activators
Lysosomal Enzymes,
Oxygen Radicals and
Arachidonate Metabolites
Inflammation
Destruction

27


Rheumatoid Factors and Immune Complexes Augment the Activation of Macrophages
CD2
α,β, TCR
DR4/peptide
Fc Receptor
CD4+ TH1 Cell
CD4
CD40L
Macrophage
Rheumatoid factor (RF) or Immune complexes
IFN-γ
IL-1
CD40
Increased synthesis of IL-1, TNF-α, TGF-β, IL-6, PGE2 and Collagenase
Rheumatoid factor (RF)
Activated Macrophage

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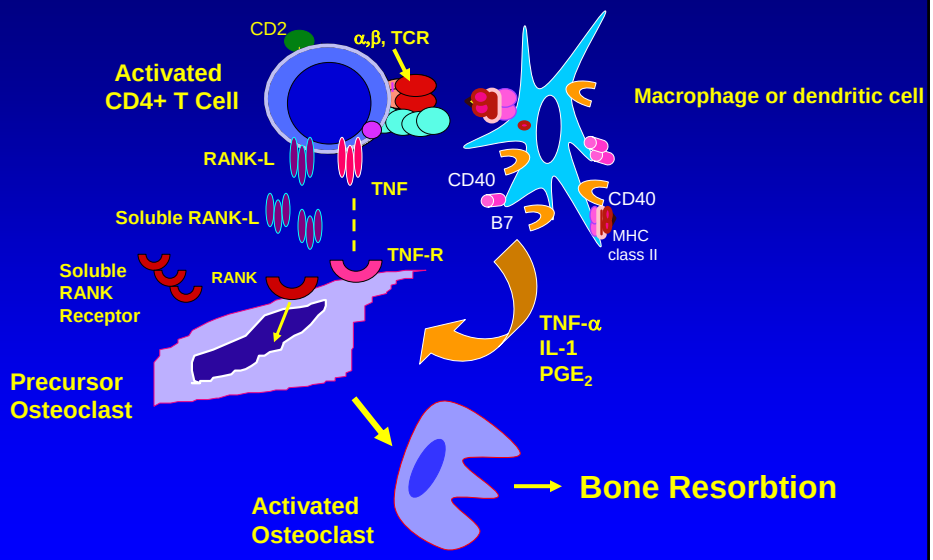
TNF, IL-1 and RANK-L activate osteoclasts to induce bone resorbtion



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Mechanisms of action of drugs used to treat RA

(a) **Block T cell-APC interaction**
antibodies to MHC class II, CD4 or the TCR

(b) Decrease T cell activation
cyclosporine, anti-CD3, anti-CD28, anti-CD80 (B7), anti-CD40L, CTLA-4 agonist

(e) Inhibit products of T cells and macrophages
NSAIDs, TNF receptor inhibitors, IL-1 receptor inhibitors

(c) Prevent T cell, B cell or synovial cell proliferation
Methotrexate, Imuran, Cytoxan

(d) Inhibit T cell or APC function
steroids, gold, penicillamine

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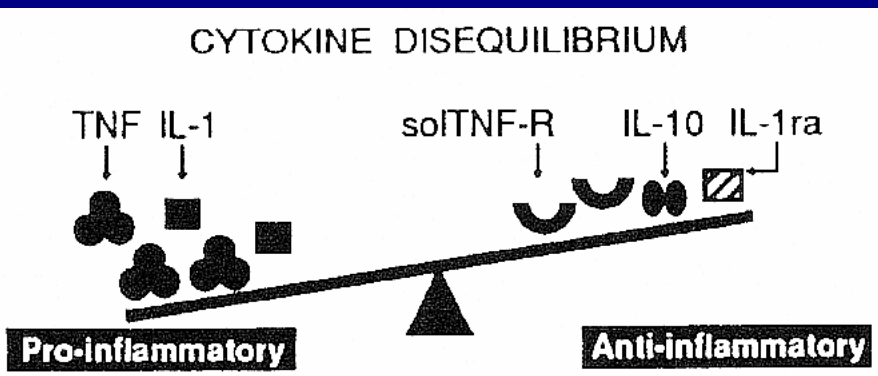

Figure 3. Cytokine Disequilibrium in Rheumatoid Arthritis

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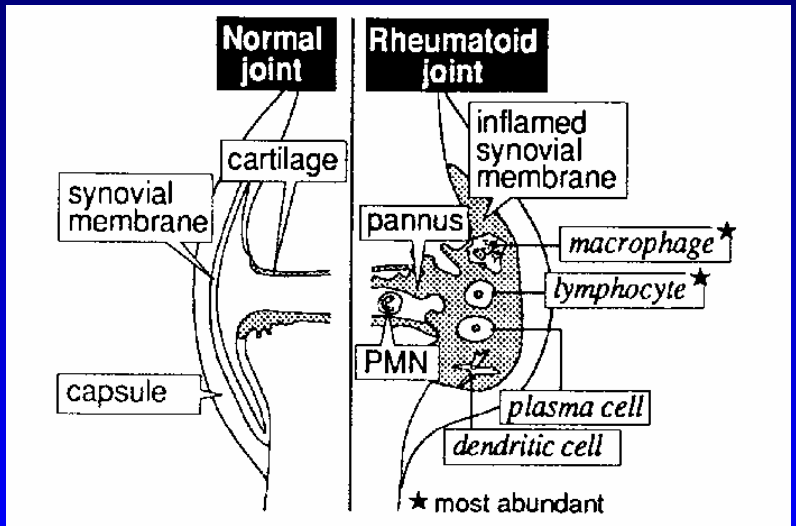

Figure 1. Rheumatoid Joint Indicating Major Cell Types and Sites of Joint Destruction

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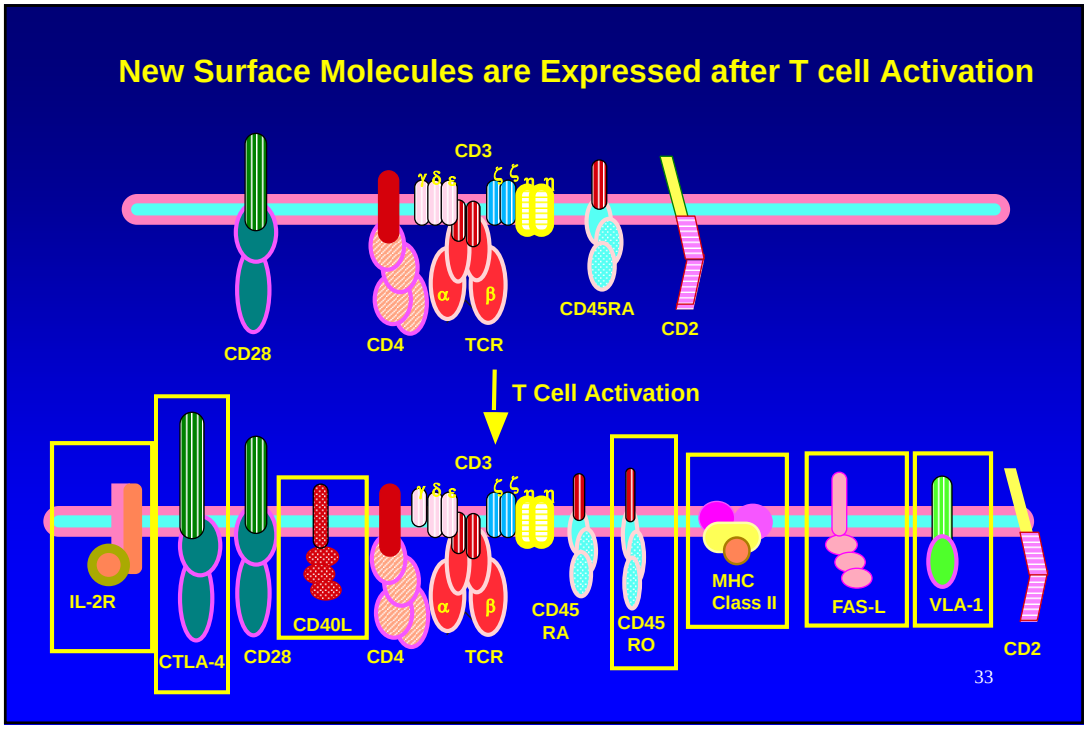
New Surface Molecules are Expressed after T cell Activation
CD3
γ δ ε
ζ ζ η η
CD28
CD4
α
β
TCR
CD45RA
CD2
T Cell Activation
CD3
γ δ ε
ζ ζ η η
IL-2R
CTLA-4
CD28
CD40L
CD4
α
β
TCR
CD45
RA
CD45
RO
MHC
Class II
FAS-L
VLA-1
CD2
33