Induction of CD4+ T_{H1} mediated autoimmunity:
A paradigm for the pathogenesis of rheumatoid arthritis, multiple sclerosis and type I diabetes

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

Shared epitope in RA

<table>
<thead>
<tr>
<th>Amino Acids in the Shared Epitope</th>
<th>DRB1*0401</th>
<th>DRB1*0404</th>
<th>DRB1*0101</th>
<th>DRB1*0402</th>
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<tbody>
<tr>
<td>67 70 71 74 RA Association</td>
<td>Leu Gln Lys+ Ala ++</td>
<td>Arg+ ++</td>
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</table>
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.
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
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

Clinical Manifestations of Sjögren’s syndrome
Pathogenesis of Rheumatoid Arthritis.
Normal synovium

Rheumatoid Synovium (Pannus)

Villous Synovitis

Pannus Invading and Destroying cartilage and Bone

Initiating Event in Rheumatoid Arthritis

CD2

αβ TCR

DR4/peptide

Fc Receptor

CD4 T cell

Macrophage/ dendritic cell/B cell
The Initiating Event in Rheumatoid Arthritis

The putative RA inducing protein binds antigen specific SmIg on B or phagocytic receptors on dendritic 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.
CD4+ T Cells Differentiate into Distinct Th1 and Th2 Subsets

Cytokine Profile

- **Th1**: IL-2, IFN-γ
- **Th2**: IL-4, IL-5, IL-6, IL-10, IL-13

Functions

- Th1: T cell-macrophage interactions, DTH responses, Intracellular pathogens
- Th2: T cell-B cell interactions, Antibody responses, Extracellular pathogens

Negative Feedback Loops

- IL-4, IL-10 suppress emergence of Th1 clones
- IFN-γ suppresses emergence of Th2 clones

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
T cell-Macrophage Interactions Induce Synovial Cell Proliferation and Activation

- CD4+ T<sub>H1</sub> Cell
- CD40L
- Macrophage
- DR4/peptide
- Fc Receptor
- Rheumatoid factor (RF)
- IL-1, TNF-α, TGF-β

- BONE RESORPTION
- Inflammation
- Synovial Cell Proliferation

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

- Activated B cell
- CD23
- BCR
- CD40L
- CD40
- CD4
- Activated T cell
- IL-4, IL-5, IL-6, IFN-γ, TGF-β

- Plasma Cell
- IgG
- IgA
- IgE
Immunopathophysiology of Rheumatoid Arthritis

Activated TH1 CD4+ T Cell

CD4+ Cell (TH0)

DR4/RA peptide

αβ, TCR

IL-4

CD4+ Cell (TH2)

Sm Ig

RA antigen

IL-12

Activated TH1 CD4+ T Cell

IFN-γ

IL-1, TNF-α, TGF-β

Macrophage

PGE2, collagenase chemokines

Osteoclast activation

Endothelial cell

Fever

Bone and cartilage destruction

Dendritic cell/ APC

αβ, TCR

IL-4

CD4+ Cell

Sm Ig

RA antigen

Plasma Cell

Rheumatoid factor (RF)

Vasculitis

Synovial fibroblast

Synovial cell proliferation

(1) Synthesis of PGE2, Collagenase, IL-1

(2) Synovial cell proliferation

Rheumatoid Factors

IgM RF

IgG RF

Fc

Fab

IgG

IgG

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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
Increased synthesis of IL-1, TNF-α, TGF-β, IL-6, PGE₂ and Collagenase

Rheumatoid Factors and Immune Complexes Augment the Activation of Macrophages

Rheumatoid factor (RF) or Immune complexes

Activated Macrophage

Increased synthesis of IL-1, TNF-α, TGF-β, IL-6, PGE₂ and Collagenase
TNF, IL-1 and RANK-L activate osteoclasts to induce bone resorption

Activated CD4+ T Cell

RANK-L

Soluble RANK-L

RANK

Precursor Osteoclast

Activated Osteoclast

Bone Resorption

Macrophage or dendritic cell

Activated CD4+ T Cell

αβ, TCR

TNF

CD40

B7

MHC class II

RANK

RANK-L

TNF-α

IL-1

TNFα, IL-1 and RANK-L activate osteoclasts to induce bone resorption

Activated CD4+ T Cell

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MHC class II

RANK

RANK-L

TNF-α

IL-1

PGE2

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
Figure 3. Cytokine Disequilibrium in Rheumatoid Arthritis

Figure 1. Rheumatoid Joint Indicating Major Cell Types and Sites of Joint Destruction
New Surface Molecules are Expressed after T cell Activation

- CD3
- CD28
- CD4
- CD45RA
- CD2
- TCR
- αβ
- IL-2R
- MHC Class II
- CD40L
- FAS-L
- VLA-1
- CTLA-4
- CD25