Induction of CD4+ TH1 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

Rheumatoid Arthritis: Definition

Rheumatoid arthritis is characterized by a chronic inflammation of the synovial joints and infiltration by blood-derived cells, chiefly memory 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, chiefly 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.

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 DRß chain, in the polymorphic region lining the peptide binding groove. There is recent evidence that the genetically susceptible HLA-DR4 (e.g., DRB1*0401) alleles bind different peptides in their peptide binding groove than the non-susceptible (e.g., DRB1*0402) 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 DRß chain in particular correlates with the genetic linkage of RA.

Amino acid sequences in the β chain HLA-DRB1*0401 molecules dictate susceptibility to RA

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

(2) Extra-Articular

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

(b) Subcutaneous nodules (rheumatoid nodules)

(c) Pulmonary involvement - pleuritis, interstitial pneumonia, rheumatoid nodules

(d) Pericarditis

(e) Ocular disease - keratoconjunctivitis, granulomatous scleritis

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

(3) Associated Syndromes

(a) Sjogren’s syndrome - salivary gland inflammation and keratoconjunctivitis

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

(c) Amyloidosis-type II
Pathogenesis of 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.

Initiating Event in Rheumatoid Arthritis

- RA auto-antigen binds to antigen specific SmIg on B or phagocytic receptors on dendritic cells.
- Internalized and digested into peptides in endosomes.
- Bound to MHC class II molecule (DR4).
- DR4/peptide complex triggers TCR on antigen specific T cells.
- T cell activation.
CD4+ T Cells Differentiate into Distinct Th1 and Th2 Subsets

- **Cytokine Profile**
  - Th1: IL-2, IFN-γ, TNF-α, GM-CSF, LT
  - Th2: IL-4, IL-5, IL-6, IL-10, IL-13

- **Functions**
  - T-macrophage interactions
  - DTH responses
  - Intracellular pathogens
  - T-B cell interactions
  - Antibody responses
  - Extracellular pathogens

T-Macrophage Interactions Induce Synovial Cell Proliferation and Activation

- Synovial Cell Proliferation
  - BONE RESORPTION
  - Synthesis of PGE-2, Collagenase, IL-1

Immunopathophysiology of Rheumatoid Arthritis

- Dendritic cell/APC
- CD4+ TH1
- CD4+ TH0
- B Cell
- Plasma Cell
- Rheumatoid factor (RF)
- Vascular
- Immunopathology

(1) Synthesis of PGE-2, Collagenase, IL-1
(2) Synovial cell destruction

Consequences of CD40L/CD40 interactions on Dendritic cell function

- Activated T cell
- Lymphocytes
- Activated B cell
- Plasmacytoid cell

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

- Activated B cell
- Lymphokines
  - IL-4, IL-5, IL-6, IFN-γ, TGF-β

- Activated T cell
  - IgG
  - IgA
  - IgE

- Plasma Cell
  - IL-4, IL-5, IL-6, IFN-γ, TGF-β
Rheumatoid Factors

(1) Characteristics of RF's
   (a) RF's are autoantibodies with specificity for the Fc region of self-IgG
   (b) Most RF's are IgM but IgG and IgA RF's are also observed

(2) Biologic Occurrence and Disease Associations
   (a) RF's are the major autoantibodies observed in RA
   (b) RF's can be induced in experimental animals by injection of either denatured IgG or by immunization with bacteria.
   (c) High titered 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) RF's 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 titered RF is associated with systemic vasculitis in RA

Mechanisms of action of drugs used to treat RA

(a) Block T-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

(c) Inhibit products of T/macrophages
   NSAIDs, TNF receptor inhibitors, IL-1 receptor inhibitors

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

Figure 3. Cytokine Disequilibrium in Rheumatoid Arthritis
T Cell Activation

New Surface Molecules are Expressed after T cell Activation

Immune Complexes in the RA Joint

Cellular and Immune Interactions in the RA Joint