Induction of CD4+ T<sub>h</sub>1 mediated autoimmunity: A paradigm for the pathogenesis of rheumatoid arthritis, multiple sclerosis and type 1 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.

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 DR<sub>β</sub> 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 DR<sub>β</sub> 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

<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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<tr>
<td>DRB1* 0401</td>
<td>Leu</td>
<td>Gin</td>
<td>Lys+</td>
<td>Ala</td>
<td>++</td>
</tr>
<tr>
<td>DRB1* 0404</td>
<td>Arg+</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>DRB1* 0101</td>
<td>Arg+</td>
<td></td>
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</tr>
<tr>
<td>DRB1* 0402</td>
<td>Ile</td>
<td>Asp</td>
<td>Glu-</td>
<td></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 pneumonitis, asbestosis and extrapulmonary rheumatoid nodules
(d) Cardiac involvement - pericarditis
(e) Ocular disease - keratoconjunctivitis, granulomatous scleritis
(e) Other common vasculitic manifestations - skin ulcerations, palpebral pustules, ischemic ulceration of GI tract, mononeuritis multiplex

Clinical Manifestations of Sjögren’s syndrome

(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
Pathogenesis of Rheumatoid Arthritis.

The Initiating Event in Rheumatoid Arthritis

Normal synovium
Villous Synovitis
Rheumatoid Synovium (Pannus)
Pannus Invading and Destroying cartilage and Bone
CD4+ T Cells Differentiate into Distinct Th1 and Th2 Subsets

Cytokine Profile
- Th1: IL-12, IFN-γ
- Th2: IL-4, IL-5, IL-6, IL-10, IL-13

Functions
- Th1-macrophage interactions
- DTH responses
- Intracellular pathogens
- 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

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

Immunopathophysiology of Rheumatoid Arthritis

Rheumatoid factors (RF)
- Synthesis of PGE2, collagenase, IL-1
- Vascular, synovial cell proliferation
- Fever

Synovial fibroblast
- Synthesis of PGE2, collagenase, IL-1
- Bone and cartilage destruction

Activated T cell
- CD40L
- CD40
- α,β, TCR
- IL-1, TNF-α, TGF-β
- PGE2, collagenase, chemokines

Activated B cell
- Synthesis of IgG, IgA, IgE
- CD40
- CD23
- B7
- IFN-γ

BONE RESORPTION

Synovial Cell Proliferation

Rheumatoid factor (RF)
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

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
(c) Inhibit products of T cells and macrophages
NSAIDs, TNF receptor inhibitors, IL-1 receptor inhibitors
(d) Prevent T cell, B cell or synovial cell proliferation
Methotrexate, Imuran, Cytoxan
(e) Inhibit T cell or APC function
steroids, gold, penicillamine
New Surface Molecules are Expressed after T cell Activation

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

Figure 3. Cytokine Disequilibrium in Rheumatoid Arthritis