Mechanisms of unresponsiveness: Peripheral tolerance in B cells (II): Anergy

**Acute antigens**
- BCR
- CD40
- NFκB
- Ca^2+
- Growth genes

**Chronic antigens**
- BCR
- CD40
- TLR4
- LPS
- NFκB
- Inhibitory genes

The two-signal requirement for T cell activation

**Signal 1**
- TCR
- Costimulatory receptor (CD28)
- T cell activation

**Signal 2**
- Antigen recognized by APC
- APC: MHC presented microbial antigen

**TCR**
- Activated APC: increased expression of costimulators, secretion of cytokines
- T cell proliferation
- And differentiation

Role of co-stimulation in T cell activation

**Antigen recognition**
- Resting APC: (costimulator-deficient)

**Activation of APC initiates immune response**
- Activated APC: increased expression of costimulators, secretion of cytokines

**T cell response**
- No response
- T cell proliferation
- And differentiation

The role of co-stimulation in T cell activation

Regulation of T cell homeostasis during immune responses

**Immunosurveillance:** Tumors which Evolve in Lymphocyte Deficient Hosts are Rejected in WT Mice

<table>
<thead>
<tr>
<th>Tumor Incidence</th>
<th>WT origin</th>
<th>RAG/-/- origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAG-/-</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Host: RAG/-/-  WT

Tumor (Sarcoma) Incidence is Increased in MCA-treated Lymphocyte Deficient Mice
Immune Surveillance: Tumor Cell Expression of IFNγ Receptor is Required for Lymphocyte-Mediated Tumor Rejection

Immune Recognition

Cross-Priming: Induction of Anti-tumor T cell response

Effectors Mechanisms

CD8 CTL Can Recognize Class I –peptide Complex and Induce Tumor Lysis and Apoptosis

Effectors Mechanisms

Macrophages are Cell-Mediated Effectors

Tumor Evasion: Two Separate Problems

- Tumor antigens are not recognized by immune response-poorly immunogenic (Immunologically ignorant).
- Tumors are resistant to or inhibit immune cytotoxic responses.(active suppression—either dampen “priming” or avoid/inhibit/resist effector cell function).
Strategies for induction of anti-tumor Immune Responses
- Passive -
  - Adoptive transfer of T cells: Antigenic specific T cell clones requires HLA-restricted "customized" therapy or cytokine-enhanced antigen-non-specific T cells (LAK cells). Has worked for EBV lymphoproliferative disorders.
  - Monoclonal and engineered antibodies:
    1. Humanized/chimeric mAbs: Herceptin (anti-HER2), Rituxan (anti-CD20), anti-idiotype (custom therapy), anti-EGFR (Erbitux), CAMPATH (anti-CD52), anti-VEGF (targets neovascularature, Avastin).
    2. Immune conjugates ("smart bombs") mAb-toxin (Mylotarg: anti-CD33 calicheamicin), mAb-chemo, mAb-isotope (anti-CD20 Zevalin and Bexxar).

Model of Innate Recognition and Initiation of the Adaptive Antitumor Immune Response

Monoclonal Antibody Therapeutics in Cancer
Rituxan (anti-CD20)
- High response rate in B cell lymphoma (>70%).
- Synergy with chemotherapy or XRT.
- Recognizes B cell marker regulating B cell activation.
- Induces growth arrest/apoptosis in vitro.

Herceptin (anti-HER2)
- Lower response rate in breast cancer (15%).
- Synergy with chemo (60%) or XRT.
- Recognizes EGF-like receptor regulating cellular proliferation (ERBB2).
- Induces growth arrest/apoptosis in vitro.

Functions of Th1 and Th2 cells

<table>
<thead>
<tr>
<th>Type</th>
<th>Function</th>
<th>Helpful</th>
<th>Harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th1</td>
<td>Activates macrophages, dendritic cells</td>
<td>Tb, fungi and other intracellular bacteria</td>
<td>MS, systemic lupus, RA, thyroiditis</td>
</tr>
<tr>
<td>Th2</td>
<td>B cell help</td>
<td>Clearance of antigens/toxins</td>
<td>Allergy, Autoantibody</td>
</tr>
<tr>
<td>Th0</td>
<td>Down-regulate Th1</td>
<td>Down-regulation</td>
<td>MS, Autoimmune</td>
</tr>
</tbody>
</table>

Immunopathology of MS

Oligodendrocytes

Naked axon (plaque)

CD4+ T cells and Myelin binding MHC class II + oligodendrocyte

Perivascular infiltrate of CD4+ T cells and APCs

Immunopathophysiology of Diabetes

β cell death

? Antibody mediated injury

β cell survival
### Pathophysiology of Scleroderma

- **CD4+ T Cell**
- **Activated CD4+ T Cell**
- **B Cell**
- **Plasma Cell**
- **Dermal Fibroblast**
- **MHC class II**
- **DR/peptide**
- **IL-1, TNF, TGF-β**
- **IL-2, IL-4, IL-5, IL-6**
- **Fibroblast proliferation**
- **PGE2, collagen**
- **Anti-ic 70, Ro, La and RFs**

### SLE pathogenesis

- **CD4+ T cell Driving force Autoactive to self peptides**
- **Autoactive B cells**
- **IgG autoantibody Production**
- **Autoantibody-mediated Disease**
- **Genetic susceptibility:** Complex polygenic
- **Genes Involved:** MHC class II, Complement deficiency, Multiple non-MHC (unknown), X-chromosomal (unknown)

### Two major mechanisms of antibody-mediated tissue injury operating in SLE

<table>
<thead>
<tr>
<th>Type of antibody induced injury</th>
<th>Mechanism of injury</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune complex formation and deposition</td>
<td>Ag/Ab complexes deposit in vessel walls, causing inflammation by activation of complement cascade and activation of Fc receptors on phagocytes, mesangial cells, NK cells</td>
<td>Glomerulonephritis, Dermatitis, Granulitis, periarteritis, pericarditis, Others vascular</td>
</tr>
<tr>
<td>Direct binding to antigen of cells</td>
<td>Antibody binds to and kills cells by activating the complement attack pathway, or interacting with Fc receptors on phagocytes or NK cells</td>
<td>Hemolytic anemia, Thrombotic thrombocytopenia, Leukopenia, Splenic anemia</td>
</tr>
</tbody>
</table>

### Serum Sickness develops after injection of soluble foreign antigens

- **Disease:** Vasculitis, Glomerulitis, Arthritis, Pleuritis, Pericarditis, Dermatitis

### Why do SLE patients make autoantibodies?

1. **Anti-self immunity:** Abrogation of self tolerance
   - SLE might be the result of insufficient elimination of autoreactive T cell clones in the thymus or periphery. This might result in such autoreactive T cells being released into the peripheral circulation and causing the autoimmune features of the disease.

2. **Hidden antigens**
   - The nuclear and cytoplasmic antigens that are associated with autoimmunity are not commonly exposed to the immune system. If such antigens (e.g., DNA, for example) are liberated during cellular turnover, they may incite an immune response. Thereafter, further release of such antigens might form the nidus for IC.

3. **Cross reactivity**
   - SLE might be a disease caused by an unknown pathogen such as a virus or a bacterium. The interaction of pathogen derived peptides with a susceptible HLA haplotype may elicit "autoimmune" diseases by activating pathogenic T cells. Such a pathogen has not been identified in SLE, but no feature of the disease suggests that this could not be the etiology.

4. **Abnormal regulation:** Failure of suppression
   - SLE might arise as a consequence of abnormalities in regulatory CD4+ or CD8+ T cells.
Evidence that T cells are important in the development of SLE

- The pathogenic anti-DNA antibodies in SLE are high affinity IgG molecules. Because it is known that class switching to IgG as well as somatic mutation and affinity maturation requires T cells, we infer that anti-DNA antibody-producing B cells are expanded in SLE by a process that mimics the normal CD4+ T cell-dependent responses, involving common mechanisms of somatic mutation, affinity maturation, and IgM to IgG class switching.

- The MHC class II restriction and the known association of DR2 and DR3 with susceptibility to SLE also strongly point to a predominant role of CD4+ T cells in the induction of autoimmunity in SLE.

- Finally, animal models of SLE are effectively treated with molecules which block key functions of CD4+ T cells.

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 Factors and Immune Complexes Augment the Activation of Macrophages

- TNF, IL-1 and RANK-L activate osteoclasts to induce bone resorption
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
(e) **Inhibit products of T/macrophages**
   - NSAIDs, TNF receptor inhibitors, IL-1 receptor inhibitors
(c) **Prevent T cell, B cell or synovial cell proliferation**
   - Methotrexate, immuran, cytoxan
(d) **Inhibit T cell or APC function**
   - Steroids, gold, penicillamine

Spondylitis Diseases

- Ankylosing spondylitis
- Reiter’s syndrome / reactive arthritis
- Psoriatic arthritis
- Undifferentiated spondyloarthritis
- Enteropathic arthritis (ulcerative colitis, regional enteritis)

Spondyloarthritis Diseases

2. Genetic:– Susceptibility to develop disease is associated with inheritance of certain MHC class I alleles, notably HLA-B27

3. Pathogenesis:– CD8 T cells are centrally implicated while CD4 T cells or B cells are not essential as shown by MHC class I HLA associations, plus:
   - Occur at increased prevalence in those with advanced AIDS
   - No Autoantibodies “Seronegative”
   - CD8 T cells activated, clonally expanded and sometimes show antigen drive in sites of inflammation

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Reiter’s syndrome- Reactive arthritis -Mechanism

Activation

Disruption of “tolerance” of autoreactive CD8 T cells likely occurs through a combination of mechanisms:

- Molecular mimicry - Older theory… T cell clones involved in attack on microorganisms expand and initiate attack on cells expressing target proteins that contain peptides that mimic the amino acid sequence found in the microorganisms
- Provision of co-stimulatory signals by activated dendritic cells and macrophages in initial immune response to infection disrupts anergic or unreactive state of T cells
- CD8 T cells express NK and other receptors that foster the activation of these cells by “danger” signals recognized by innate immune system receptors
CD8 T-cell Activation & Clonal Expansion

Angiogenesis

Lining & Infiltrating Monocyte / Macrophage Activation

Rx Methotrexate

Inflammation, Destruction & Fibrosis

Rx TNF-α Blockers

CD4 and CD8 T Cell Recruitment

Synoviocyte Proliferation and Alteration in Gene Expression

Fibroblast Activation

Periosteal new bone formation

CD8 T-cell Self Antigenic Peptide Recognition

MHC class I Molecule

Synovial or Endon Fibroblasts

Cognitive Recognition

Monocyte / Macrophage Activation

Lining & Infiltrating Monocyte / Macrophage Activation

Rx Methotrexate

Inflammation, Destruction & Fibrosis

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CD4 and CD8 T Cell Recruitment

Synoviocyte Proliferation and Alteration in Gene Expression

Fibroblast Activation

Periosteal new bone formation