Tolerance and Autoimmunity

Lecture 19    April 20, 2009    Dr. Raveche

Pathways: Deletion/Anergy

Central v.s. Peripheral Tolerance

Factors Involved in Induction of Tolerance

Define mechanisms that lead to Autoimmunity
Autoimmunity - Tolerance

Tolerance - Autoimmunity
Tolerance means the inability to make a positive immune response to a specific antigen.

Tolerance is not global unresponsiveness to all antigens (i.e., immunodeficient patient or patient receiving immunosuppressive drugs).

Tolerance is usually achieved by prior exposure to specific antigens.

Normally we are tolerant to self antigens.
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Effect of response to antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal response</td>
</tr>
<tr>
<td>Infectious agent</td>
<td>Protective immunity</td>
</tr>
<tr>
<td>Innocuous substance</td>
<td>Allergy</td>
</tr>
<tr>
<td>Grafted organ</td>
<td>Rejection</td>
</tr>
<tr>
<td>Self organ</td>
<td>Autoimmunity</td>
</tr>
<tr>
<td>Tumor</td>
<td>Tumor immunity</td>
</tr>
</tbody>
</table>

Fig 1.32 © 2001 Garland Science
Central tolerance

Newly emerged (immature) clones of lymphocytes

Lymphoid precursor

Self antigen present in generative lymphoid organ

Maturation of clones not specific for self antigens present in generative organs

Central tolerance: deletion of lymphocytes specific for self antigens present in generative organs

Figure 16-1a
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
Central Tolerance is Maintained by Clonal Deletion--removal of antigen reactive cells

Main mechanism is apoptosis: programmed cell death

Consequence of immature self-reactive lymphocytes recognizing self-antigen
Peripheral tolerance

Mature lymphocytes

Foreign antigen

Immune response to foreign antigens

Self antigen

Apoptosis

Anergy

Peripheral tolerance: deletion or anergy of lymphocytes that recognize self antigens in peripheral tissues

Figure 16-1b
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
Figure 16-2

Mature lymphocyte

- Tolerogenic antigen
  - Apoptosis

- Immunogenic antigen
  - Anergy
  - Functional unresponsiveness
  - Proliferation

Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
B cells reactivate RAG and undergo 2nd V rearrangement

Transgenic mouse expresses HEL as self antigen

Transgenic mouse expresses anti-HEL on B cells

F1 mouse expresses HEL as self antigen and possesses B cells specific for HEL

Bone marrow

B cells specific for HEL are negatively selected in marrow; most B cells autoreactive with HEL are deleted, some undergo receptor editing

Anergic B cells with downregulated mIg

B cells not autoreactive with HEL are released

Central T

Receptor editing

Deletion

Figure 16-3a
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company
Normal mice do not have detectable numbers of B cells reactive to hen egg lysozyme (naïve B cells have different BCRs with no exposure to Ag, no clonality)

2. Single transgenic >90% of anti-HEL transgenic mice have mIgM reactive with HEL (no Ag injection required these are naïve B cells)

3. Double transgenic: All B (except those that undergo receptor editing) react to HEL, however HEL Ag is also present in periphery— anergy occurs by downregulation of membrane IgM expression
Immature B cells that encounter Ag in bone marrow undergo apoptosis \textit{UNLESS}

- RAG genes are reactivated
- Additional light chain VJ recombination
- New light chain produced
- Different Ig receptor which does not react with Ag present in bone marrow
<table>
<thead>
<tr>
<th>Experimental group</th>
<th>HEL level</th>
<th>Membrane anti-HEL</th>
<th>Anti-HEL PFC/spleen</th>
<th>Anti-HEL serum titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HEL single transgenics</td>
<td>None</td>
<td>+</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Anti-HEL/HEL double transgenics (group 1)</td>
<td>$10^{-9}$ M</td>
<td>+</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Experimental animals were immunized with hen egg-white lysozyme (HEL). Several days later, hemolytic plaque assays for the number of plasma cells secreting anti-HEL antibody were performed and the serum anti-HEL titers were determined. PFC = plaque-forming cells.

**SOURCE:** Adapted from C. C. Goodnow, 1992, *Annual Review of Immunology* 10:489.
T Cells Undergo Peripheral Tolerance of CD4+T due to:

Regulatory T cells: mediated by cytokines

Clonal Anergy

Activation Induced Cell Death:
  Passive: no survival Stimuli
  Active: FasL (privileged site)
Thymic Selection deletes HEL reactive T cells (HEL now self-antigen)

Transgenic mouse expresses HEL as self antigen

Syngeneic anti-HEL B cells introduced to periphery

Anti-HEL B cells encounter HEL in periphery

Activation and proliferation

Anergy due to lack of T-cell help

Figure 16-3b
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company
Figure 16-4
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company

Thymus

Thymocyte

Low affinity for self antigen

High affinity for self antigen

Intermediate affinity for self antigen

Apoptosis

Up-regulation of Foxp3

T cell

T_reg cells suppress reaction to self antigens

T_reg cell

T_reg CD4+, CD25+, FOXP3+
Regulatory T cells

CD4⁺, CD25⁺(bright)

Treg: Develop in thymus
express CTLA-4
express FoxP3 (transcription factor)
PRODUCE: IL-10 AND TGF

Tr1: Suppress Th1 (are antigen specific)
Usually IL-10 cytokine mediated (TGF-β too)
Ag in periphery

Th3: Suppression Usually TGF beta cytokine mediated
Mechanisms of homeostasis in immune responses (T cells)

- T cell activation
- Activated T cells express CTLA-4
- Activated T cells are deprived of antigen and other stimuli
- Functional inactivation
- Apoptosis
- Surviving memory cells

From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 10-14
B7 Costimulatory Pathways

- B7-2 on APC (constitutive), B7-1 appears later
- Receptors…
  - CD28 (low affinity-constitutive on T cells, surface expression
  - CTLA-4 CD152 (high affinity cytoplasmic and upon stimulation becomes surface

**CD28 mediates:**

- T cell proliferation
- Induction of bcl-xl
- Increase in CD40L (CD154
- Differentiation of CD8+CTL
- Cytokine production

**CTLA-4 (CD152**

- Induces apoptosis
- KO mice have LPD
T Cells Undergo Peripheral Tolerance of CD4+T due to:

**Activation-Induced Cell Death**

Apoptosis: Activation of cysteine proteases, caspases

Not Necrosis

Triggered by ligand binding to receptors (Fas, TNFR)

Characterized by DNA cleavage

- Nuclear fragmentation
- Plasma membrane blebbing
- Phagocytosis of apoptotic bodies

Prevented by inhibitors of caspases (FLIP)

Activation of Bcl family
Factors Involved in Tolerance

Tolerance is easier to achieve in newborns

Nature of antigen- soluble antigens are better tolerogens

Route of antigen administration--oral good for tolerance

Dose of antigen

Inefficient antigen presentation leads to T cell tolerance
### Neonatal tolerance to allografts

<table>
<thead>
<tr>
<th>Neonate</th>
<th>Adult</th>
<th>Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Strain A mouse</td>
<td>6 weeks</td>
<td>7–14 days</td>
</tr>
<tr>
<td></td>
<td>Skin graft from</td>
<td></td>
</tr>
<tr>
<td></td>
<td>strain B</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong> Inject leukocytes</td>
<td>6 weeks</td>
<td>7–14 days</td>
</tr>
<tr>
<td></td>
<td>from strain B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin graft from</td>
<td></td>
</tr>
<tr>
<td></td>
<td>strain B</td>
<td></td>
</tr>
<tr>
<td><strong>C</strong> Inject leukocytes</td>
<td>6 weeks</td>
<td>7–14 days</td>
</tr>
<tr>
<td></td>
<td>from strain B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin graft from</td>
<td></td>
</tr>
<tr>
<td></td>
<td>strain C</td>
<td></td>
</tr>
</tbody>
</table>

From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 10-2
Immunologically privileged sites

- Brain
- Eye
- Testis
- Uterus (fetus)
- Hamster cheek pouch
Autoimmunity

Describe Mechanisms responsible for autoimmune damage

Name autoimmune diseases and major self-antigen

Autoimmunity is a breakdown in tolerance
Immune hyperactivity, self recognition
Normally, tolerant to self antigens
Autoimmune Diseases can be Systemic or Organ-Specific

a. Weakly stimulating self-antigen

- Resting T cell
- T cell
- Maintenance
- Lymphoproliferative disorders
- B cell
- Antibody-mediated systemic autoimmunity

b. Stimulating self-antigen
b Stimulating self-antigen

- Immature dendritic cell
- Resting T cell
- Mature dendritic cell

- Deletion or anergy
- Tolerance
- Organ-specific autoimmunity (multi-organ)
- Defective deletion

---

c Foreign antigen

- Resting T cell
- Mature dendritic cell

- Weak cross-reactivity with self
- Transient organ-specific autoimmunity
- Strong cross-reactivity with self
- Organ-specific autoimmunity
- Immunity
Overall Mechanism

• Autoimmune diseases results from breakdown of self-tolerance in B cells, or T cells, or both.

• Genetic, hormonal and environmental factors or infectious agents may contribute to the development of autoimmune diseases.

• Damage may be due to immune complexes, circulating autoantibodies, and/or autoreactive T

• Once initiated, autoimmune reactions may injure tissues and cause the release and alteration of other tissue antigens resulting in activation of lymphocytes specific for these other antigens.
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Disruption of cell or tissue barrier</th>
<th>Infection of antigen-presenting cell</th>
<th>Binding of pathogen to self protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
<td>Release of sequestered self antigen; activation of nontolerized cells</td>
<td>Release of inflammatory mediators, notably IFN-α</td>
<td>Pathogen acts as carrier to allow anti-self response</td>
</tr>
<tr>
<td>Example</td>
<td>Sympathetic ophthalmia</td>
<td>? SLE</td>
<td>? Interstitial nephritis ? SLE</td>
</tr>
</tbody>
</table>

![Diagram](image-url)
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Molecular mimicry</th>
<th>Superantigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
<td>Production of cross-reactive antibodies or T cells</td>
<td>Polyclonal activation of autoreactive T cells</td>
</tr>
<tr>
<td>Example</td>
<td>Rheumatic fever? Diabetes? Multiple sclerosis</td>
<td>? Rheumatoid arthritis</td>
</tr>
</tbody>
</table>

Figure 13-26 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)
<table>
<thead>
<tr>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG antibody</td>
<td>IgG antibody</td>
<td></td>
</tr>
<tr>
<td>Cell- or matrix-associated antigen</td>
<td>Cell-surface receptors</td>
<td>Soluble antigen</td>
</tr>
<tr>
<td>Complement, FcR⁺ cells (phagocytes, NK cells)</td>
<td>Antibody alters signaling</td>
<td>Complement Phagocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrophage activation</td>
</tr>
</tbody>
</table>

- **Type II**
  - IgG antibody
  - Cell- or matrix-associated antigen
  - Complement, FcR⁺ cells (phagocytes, NK cells)

- **Type III**
  - IgG antibody
  - Cell-surface receptors
  - Antibody alters signaling

- **Type IV**
  - Soluble antigen
  - Complement Phagocytes
  - Macrophage activation

**Diagrams**
- Type II: IgG antibody + complement → immune complex + complement → agonist + antagonist
- Type III: Immune complex + complement
- Type IV: TH₁

**Examples**
- Some drug allergies (e.g., penicillin), transfusion reaction, autoimmune hemolytic anemia
- Graves' disease (agonist), Myasthenia gravis (antagonist)
- Serum sickness, Systemic lupus erythematosus
- Contact dermatitis, graft rejection, rheumatoid arthritis
a Hashimoto's thyroiditis

- Autoactive B cell
- CD4 T cell
- CD8 T cell
- Plasma cell
- Thyroid cell
- Necrosis/apoptosis
- Thyroid cell death
- Hypothyroidism

b Graves' disease

- Autoactive B cell
- CD4 T cell
- TSH-reactive B cell
- CTL
- TSHR
- TSI
- Thyroid cell
- Thyroid cell survival
- Hyperthyroidism
STIMULATING AUTO-ANTIBODIES (Graves’ disease)

- Pituitary gland
- Auto-antibody to receptor
- TSH receptor
- TSH
- Stimulates hormone synthesis
- Thyroid cell
- Regulated production of thyroid hormones
- Unregulated overproduction of thyroid hormones

Figure 16-8
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
Normal thyroid follicle lined with
Thyroid follicle in Hashimoto’s thyroiditis with lymphocytic infiltration.
Type III hypersensitivity

Mechanisms of Ab deposition

Effector mechanisms of tissue injury

Abbas 18-1B
<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen involved</th>
<th>Clinicopathologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, nucleoproteins, others</td>
<td>Nephritis, arthritis, vasculitis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Hepatitis B virus surface antigen</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td>Streptococcal cell wall antigen(s); may be &quot;planted&quot; in glomerular basement membrane</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Various proteins</td>
<td>Arthritis, vasculitis, nephritis</td>
</tr>
</tbody>
</table>
Possible Causes of Immune Complex Deposition

- Size of complex - small complexes are not always phagocytosed & can be deposited in vessels.
- Charge - cationic antigens bind to negatively charged components of the basement membranes of blood vessels and kidney glomeruli.
- Sites of high hydrostatic pressure (kidney).
- Following activation of inflammatory cells and mast cells - cytokines & vasoactive mediators are released leading to increased adhesion of leukocytes to endothelium, increased vascular permeability and enlarged interendothelial spaces allowing deposition of complexes.
Pathologic features of antibody-mediated glomerulonephritis

(A) Anti-basement membrane antibody-mediated glomerulonephritis
(B) Immune complex-mediated glomerulonephritis

Goodpasture’s Systemic Lupus Erythematosus (SLE)
<table>
<thead>
<tr>
<th>Candidate activity</th>
<th>Role</th>
<th>Deficiency in SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen clearance</td>
<td>Binding and clearance of autoantigens and immune complexes</td>
<td>Complement proteins: C1q, C1r, and C1s, C4&gt;&gt;C2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum IgM</td>
</tr>
<tr>
<td></td>
<td>Masking or digestion of DNA and chromatin</td>
<td>Serum amyloid P component</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNase 1</td>
</tr>
<tr>
<td>Tolerance induction</td>
<td>Threshold for lymphocyte activation</td>
<td>Lyn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SHP-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FcγRIIB</td>
</tr>
<tr>
<td></td>
<td>Deletion of autoreactive lymphocytes</td>
<td>Fas and Fas ligand</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell-cycle inhibitor p21</td>
</tr>
<tr>
<td>Organ-specific manifestations</td>
<td>Renal disease</td>
<td>FcγRIIB polymorphism</td>
</tr>
<tr>
<td>of autoimmunity</td>
<td></td>
<td>FcγRIII polymorphism</td>
</tr>
</tbody>
</table>
### Associations of HLA serotype with susceptibility to autoimmune disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA allele</th>
<th>Relative risk</th>
<th>Sex ratio (♀ : ♂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>87.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>B27</td>
<td>10</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>DR2</td>
<td>15.9</td>
<td>~1</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>DR2</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>DR3</td>
<td>3.7</td>
<td>4–5</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>DR3</td>
<td>2.5</td>
<td>~1</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DR3</td>
<td>5.8</td>
<td>10–20</td>
</tr>
<tr>
<td>Type I insulin-dependent diabetes mellitus</td>
<td>DR3/DR4</td>
<td>~25</td>
<td>~1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>DR4</td>
<td>4.2</td>
<td>3</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>DR4</td>
<td>14.4</td>
<td>~1</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>DR5</td>
<td>3.2</td>
<td>4–5</td>
</tr>
</tbody>
</table>
## Associations of infection with immune-mediated tissue damage

<table>
<thead>
<tr>
<th>Infection</th>
<th>HLA association</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A streptococcus</td>
<td>?</td>
<td>Rheumatic fever (carditis, polyarthritis)</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>HLA-B27</td>
<td>Reiter's syndrome (arthritis)</td>
</tr>
<tr>
<td>Shigella flexneri, Salmonella typhimurium, S. enteritidis, Yersinia enterocolitica, Campylobacter jejuni</td>
<td>HLA-B27</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>HLA-DR2, DR4</td>
<td>Chronic arthritis in Lyme disease</td>
</tr>
</tbody>
</table>
### TABLE 16-3

Molecular mimicry between proteins of infectious organisms and human host proteins

<table>
<thead>
<tr>
<th>Protein*</th>
<th>Sequence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human cytomegalovirus IE2</td>
<td>PDPLGRPDED</td>
</tr>
<tr>
<td>HLA-DR molecule</td>
<td>VTELGRPDAE</td>
</tr>
<tr>
<td>Poliovirus VP2</td>
<td>STTKESRGT</td>
</tr>
<tr>
<td>Acetylcholine receptor</td>
<td>TVIKESRGTK</td>
</tr>
<tr>
<td>Papilloma virus E2</td>
<td>SLHLESLKD</td>
</tr>
<tr>
<td>Insulin receptor</td>
<td>VYGLESLKD</td>
</tr>
<tr>
<td>Rabies virus glycoprotein</td>
<td>TKESLVIIS</td>
</tr>
<tr>
<td>Insulin receptor</td>
<td>NKESSLVISE</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> nitrogenase</td>
<td>SRQTDREDE</td>
</tr>
<tr>
<td>HLA-B27 molecule</td>
<td>KAQTDDREDL</td>
</tr>
<tr>
<td>Adenovirus 12 E1B</td>
<td>LRGRMFSPSQCN</td>
</tr>
<tr>
<td>α-Gliadin</td>
<td>LGQGSRPSPQN</td>
</tr>
<tr>
<td>Human immunodeficiency virus p24</td>
<td>GVETTTPS</td>
</tr>
<tr>
<td>Human IgG constant region</td>
<td>GVETTTPS</td>
</tr>
<tr>
<td>Measles virus P3</td>
<td>LECIRALK</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>LECIRACK</td>
</tr>
<tr>
<td>Measles virus P3</td>
<td>EISDNLQGE</td>
</tr>
<tr>
<td>Myelin basic protein</td>
<td>EISFKLQGE</td>
</tr>
</tbody>
</table>

*Cell 50:819 (1987)*
Insulin gene promoter (PI) → Insulin structural gene → IFN-γ gene

5' → 3'

Insulin gene terminator region

Poly A

IFN-γ gene

Insulin gene promoter

5' → 3'

Insulin gene terminator region

PI/IFN-γ transgene

IFN-γ

Pancreas

Cellular infiltration

Transgenic mouse developed IDDM

Figure 16-13a
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
Mechanism of Autoimmunity

Failure of Central Tolerance
  Thymic Selection is Flawed

Peripheral Tolerance Defective
  Failure of activation induced Cell death --AICD

Hyper Immune response
  Cytokine Imbalance
  Abnormal expression of co-stimulatory molecules

Cross-Reactivity
<table>
<thead>
<tr>
<th>Animal model</th>
<th>Possible human disease counterpart</th>
<th>Inducing antigen</th>
<th>Disease transferred by T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPONTANEOUS AUTOIMMUNE DISEASES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonobese diabetic (NOD) mouse</td>
<td>Insulin-dependent diabetes mellitus (IDDM)</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>(NZB × NZW) F₁ mouse</td>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>Obese-strain chicken</td>
<td>Hashimoto’s thyroiditis</td>
<td>Thyroglobulin</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>EXPERIMENTALLY INDUCED AUTOIMMUNE DISEASES</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental autoimmune myasthenia gravis (EAMG)</td>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Yes</td>
</tr>
<tr>
<td>Experimental autoimmune encephalomyelitis (EAE)</td>
<td>Multiple sclerosis (MS)</td>
<td>Myelin basic protein (MBP); proteolipid protein (PLP)</td>
<td>Yes</td>
</tr>
<tr>
<td>Autoimmune arthritis (AA)</td>
<td>Rheumatoid arthritis</td>
<td><em>M. tuberculosis</em> (proteoglycans)</td>
<td>Yes</td>
</tr>
<tr>
<td>Experimental autoimmune thyroiditis (EAT)</td>
<td>Hashimoto’s thyroiditis</td>
<td>Thyroglobulin</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*These diseases can be induced by injecting appropriate animals with the indicated antigen in complete Freund’s adjuvant. Except for autoimmune arthritis, the antigens used correspond to the self antigens associated with the human disease counterpart. Rheumatoid arthritis involves reaction to proteoglycans, which are self antigens associated with connective tissue.
Mice injected with myelin basic protein and complete Freund's adjuvant develop demyelinating disease (EAE)

The disease is mediated by myelin basic protein-specific inflammatory T cells ($T_{H1}$)

Disease can be transmitted by transfer of T cells from affected animal

(b) paralysis

© Current Biology Ltd/Garland Publishing
New Therapies

• Induce Tolerance--oral feeding of self-proteins

• Remove T cells--inject TCR peptides use anti-CD4

• Decoys (altered peptide) -make analogs of self peptide that bind to MHC Class II with high affinity but do not stimulate T cells

• Anti-inflammatory cytokines (anti-TNF)= Engineered EMBREL  TNFR/IgG FC - binds TNF and removes it
Figure 16-14
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
Figure 16-15
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
Activation of MBP-specific Th1 cells activates macrophages. Activated macrophages damage oligodendrocytes, causing demyelination of neurons.
Antibodies to MHC class II molecules block T-cell activation and inhibit demyelination.
(b) Immunosuppressive drugs kill dividing cells or inhibit inflammation

Cyclophosphamide

© Current Biology Ltd/Garland Publishing
(c) Immunosuppressive drugs kill dividing cells or inhibit inflammation

Prednisone