Autoimmune Diseases


Outline

• Normal maintenance of tolerance
• Breakdown of tolerance
  - autoimmune disease
• Genetic factors
• Environmental factors
• Summary
Tolerance

- Immune system protects the body from foreign antigens
  - has to tolerate self
- Tolerance = Non-responsiveness to a self antigen
- Encounter of an antigen can result in:
  - Lymphocyte activation → immune response
  - Lymphocyte inactivation/deletion → tolerance
  - No reaction → ignorance

Central T Lymphocyte Tolerance

- In the thymus- during development
- **Negative selection/Clonal Deletion**
  - self antigens present in thymus
  - If T lymphocyte recognises self antigens, they will be deleted by apoptosis
Peripheral T Lymphocyte Tolerance

- Mature T lymphocytes exit the thymus and enter the periphery
- If recognises self in peripheral tissue, this leads to
  - Ignorance
  - Anergy
  - Deletion/Apoptosis
  - Phenotypic skewing

Peripheral T Lymphocyte Tolerance

- **Anergy** = Functional unresponsiveness
  2 signals are needed for full T Cell activation
  - Signal 1 - from antigen
  - Signal 2 - costimulators expressed on APC
    - When costimulators are not present, it results in T cell inactivation
- **Ignorance**
  - Due to inaccessible or low concentration of self-antigen
Peripheral T Lymphocyte Tolerance (contd.)

- **Deletion** = Activated-induced cell death
  - Mechanisms:
    1) Stimulation of Fas/CD95/Apo-1 (transmembrane glycoprotein receptor) by FasL (Fas Ligand) – which induces apoptosis by activation of cytosolic enzymes
    2) Production of pro-apoptotic proteins in T cell, induced by antigens

- **Phenotypic Skewing**
  - Full activation of T cells, however do not express pathogenic cytokine and chemokine receptors

Central B Lymphocyte Tolerance

- **Bone Marrow**

- **Negative Selection/Clonal Deletion**
  - similar to T cell negative selection

- **Receptor editing**
  - Express new Ig light chains that associate with previous Ig heavy chains = new antigen receptor
Peripheral B Lymphocyte Tolerance

- **Anergy**
  - T-dependent:
    Tolerance is induced when there is a lack of T helper cells, causing B cells to become anergic
  - T-independent:
    Tolerance when intracellular signals fail to trigger B cell activation

Autoimmune Diseases (AD)

- AD are the result of specific immune responses directed against structures of self.
- Defined as the **breakdown of tolerance**
  - Autoreactive cells may be activated in the **absence** of self-recognition.
- AD are primarily T- or B-cell mediated.

Note: controlled autoreactive immune responses do occur naturally during an inflammatory response. These differ from AD, as the latter are sustained and persistent immune responses.
Breakdown of Tolerance

- Tolerance may be broken down at the T- and/or B-cell level.
- Autoantigens may exist within the body, either because they are not deleted during ontogenesis or are generated *ex novo*.
  - In the case of autoantigen-driven B cell clonal selection, CD4+ T cells need to be present.

<table>
<thead>
<tr>
<th>Table 2: Mechanisms hypothesized to be involved in the breakdown of tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to delete autoreactive lymphocytes</td>
</tr>
<tr>
<td>Central tolerance failure</td>
</tr>
<tr>
<td>Peripheral tolerance failure</td>
</tr>
<tr>
<td>Molecular mimicry</td>
</tr>
<tr>
<td>Abnormal presentation of self antigens</td>
</tr>
<tr>
<td>Aberrant expression of major histocompatibility</td>
</tr>
<tr>
<td>class II molecules</td>
</tr>
<tr>
<td>Coupling of self and nonself antigens</td>
</tr>
<tr>
<td>Overproduction of self antigens</td>
</tr>
<tr>
<td>Disclosure of cryptic T-cell epitopes</td>
</tr>
<tr>
<td>Release of sequestered self antigens</td>
</tr>
<tr>
<td>Epitope spreading</td>
</tr>
<tr>
<td>Polyclonal lymphocyte activation</td>
</tr>
</tbody>
</table>


Mechanisms of Breakdown of Tolerance

- **Failure to delete autoreactive lymphocytes**
  - Genetic inability to delete all autoreactive T- and B-cell clones during ontogenesis.
  - No direct evidence that AD may have originated from these autoreactive clones.
  - Healthy individuals still retain some autoreactive lymphocytes (low affinity to self), to ensure a wide repertoire of T- and B-lymphocytes
    - Account for similarities that may exist between self and non-self proteins.

- **Molecular mimicry (e.g. acute rheumatic fever)**
  - An immune response may be mounted against a foreign antigen that will also attack a self antigen due to sequence similarities between them.
  - These similarities may either occur randomly or due to phylogenetic conservations during evolution.
Mechanisms of Breakdown of Tolerance

Abnormal presentation of self antigens:

1. **Aberrant expression of MHC class-II molecules**
   - During inflammation, *in situ* release of cytokines (IFN-γ) may induce the expression of MHC class-II molecules on cells that under normal conditions would not express them.
   - This may allow the presentation of yet unknown self antigens to autoreactive CD4+ T cells, leading to an autoimmune reaction.

2. **Binding of exogenous antigens to self antigens**
   - Exogenous antigen (eAg) binding to a self antigen (sAg), and simultaneous activation of CD4+ T cells specific to eAg.
   - CD4+ T cells will then help activate B cells that will act as specific APCs against the sAg.
   - The B cells will present the sAg-eAg complex to Th cells, which will then be activated and perpetuate the immunological response.

3. **Overproduction of autoantigens**
   - Immunological Ignorance
     - When low affinity autoreactive clones are not deleted during ontogenesis, they reach the periphery but remain inactive as the concentration threshold for their activation is not reached.
   - During inflammation an excessive release of autoantigens may cause the breakdown of immunological ignorance
     - In this case the threshold concentration is reached, the autoreactive clones are activated and an autoimmune response is triggered.

4. **Disclosure of cryptic T-cell epitopes**
   - Protein sequences which represent T-cell epitopes can either be immunodominant or cryptic.
     - The former are readily recognised by T cells, whereas the latter are not, as they cannot reach the threshold for T-cell activation.
   - Autoreactive T cells deleted during ontogenesis will be specific to immunodominant epitopes.
   - Cryptic epitopes are able to circulate freely and harmlessly, unless a triggering event subverts the hierarchy of epitopes, allowing the presentation of the cryptic ones.

5. **Release of sequestered self antigens** (e.g. sympathetic ophthalmia)
   - Immunologically privileged sites (i.e. brain, eye, testis, and uterus) are not patrolled by immune sentinels.
   - Once the barriers of these tissues are broken down, these sites immediately become targets for autoimmune reactions.
Mechanisms of Breakdown of Tolerance

• **Epitope spreading (e.g. allergic encephalomyelitis)**
  - After the presentation of a self epitope and the initiation of a specific immune response against it, this may spread to other self epitopes, previously ignored.

• **Polyclonal lymphocyte activation (e.g. SLE-Systemic lupus erythematosus)**
  - T- and B- cells can become activated in the absence of antigen.
    - Polyclonal T-cell activation may also occur due to the presence of several stimuli (e.g. superantigens, adjuvants).
    - Antigen-independent B-cell activation may be due to an inherited abnormality of B cells.

Antibody-mediated Mechanisms

• **Type I – Immunoglobin E-mediated diseases**
  - Is characterized by the interaction of an antigen with the IgE antibodies bound to basophils and mast cells.
  - There is a subsequent release of soluble proinflammatory factors.

• **Type II – IgG or M-mediated diseases**
  - IgG & IgM may cause a disease by several different mechanisms
    - IgG specific for antigens expressed on RBCs may bind to the cell surface & cause cell destruction by:
      - Activating the complement cascade;
      - Clearing opsonised RBCs (through interactions of the Ab Fc receptors on macrophages);
      - Or by both processes (i.e. complement opsonising the RBCs and the macrophages engulfing them).
    - Autoantibodies can also interact with cell surface receptors and cause aberrant function on the target tissue, through different mechanisms.
Antibody-mediated Mechanisms

- **Type III - Diseases mediated by immunocomplexes** (e.g., SLE – Systemic Lupus Erythematosus)
  - Immunocomplexes are formed during an immune response when soluble antigens are available.
  - Normally they are cleared by cells bearing Fc and complement receptors, and cause no damage.
  - However if the immunocomplexes are present in excess, the scavenger system will not be able to clear them up, and these will precipitate on tissues causing their damage.
  - This is usually a transient disease, that will disappear as the complexes are cleared.

Bellone M. (2005), 'Autoimmune Disease: Pathogenesis', ELS.

Cellular-mediated Mechanisms

- **Type IV – CD4+ T-cell-mediated diseases**
  - CD4+ T cells upon activation cause the release of cytokines (e.g., IFNγ), which can:
    - Act against a target tissue;
    - Deliver help to autoreactive B cells;
    - Activate delayed-type hypersensitivity reaction;
    - Cause alterations in the surrounding tissues, involving unusual molecules in the immune response.

- **Type IV – CD8+ T-cell-mediated diseases**
  - Infiltrate the tissue targets of autoimmune reactions, and kill the target cells.

Bellone M. (2005), 'Autoimmune Disease: Pathogenesis', ELS.
Initiation and progression of the pathogenic process

- Autoimmune reactions are common during the development of an immune response, but they stop immediately once the exogenous antigen has been eliminated.

- Autoimmune Disease – is a sustained, persistent autoimmune response in the absence of the exogenous antigen.

- “Danger theory” – hypothesises that the immune system discriminates between safe and dangerous rather than self and non-self
  - Meaning that autoimmunity is not a defect in the immune system.
  - It occurs naturally within the body, where the determination of safe and dangerous depends on the way the antigen is presented, rather than its presence.

Risk Factors

- Both genetic and environmental factors contribute to development of autoimmune disease

- Genetic factors – 30% of risk
  - Environmental factors – 70% of risk

- Involvement of genetic factors is reinforced by the assertion that, unlike genetically related siblings, nonbiological siblings e.g. adopted, do not have a greater risk of developing an autoimmune disease
Polygenic Basis

- Most autoimmune diseases are polygenic
  - could require several genes with additive affect
  - fewer genes susceptible to environmental factors
- Since the immune response involves multiple different immune cells it is not surprising that autoimmune disease is polygenic

MHC-linked genes

- Genetic susceptibility is mainly due to these genes
- In humans the genes that encode the MHC molecules are HLA genes
  - these genes are polymorphic
- Particular MHC haplotypes/alleles are linked to susceptibility to specific autoimmune diseases
  e.g. HLA-DR4 is associated with Rheumatoid arthritis
  HLA-B27 is associated with ankylosing spondylitis
- Mechanisms by which MHC molecules evoke autoimmune disease susceptibility is not known
  - not necessarily the same for all autoimmune diseases
  however each disease does not have its own distinct mechanism
Non MHC-linked genes

- Have been many non-MHC genes linked to autoimmunity
  - however, few of these linkages have been replicated independently
- Unique to each disease
- Thought to be normal allelic variants which alone do not heighten risk of disease but in combination with particular variants of other genes increase susceptibility to autoimmune disease
- Mechanisms are not known

Sex-linked Factors

- Generally women are more susceptible than men
- Affected by both sex hormones and genes linked to the X and Y chromosomes
- Oestrogen makes autoimmune diseases worse
- Androgen protects against autoimmune disease
Environmental Factors

- Monozygotic twins = 10-50% concordance
- Factors:
  - Hormones
  - Diet
  - Drugs
  - Toxins
  - Infections
  - Other (Age)

Environmental Factors
Hormones

- Hormones acquired from diet (soy), drugs (contraceptives) and produced naturally (steroids)
- Effect Ab and immune cell proliferation
- Influence type/prevalence of autoimmune diseases e.g.
  - Women = Elevated Ab response
  - Men = Severe inflammation
Environmental Factors
Hormones (cntd)

80% autoimmune diseases in women
(exceptions = diabetes mellitus,
ankylosing spondylitis + inflammatory
heart disease)

- Sex hormones interact with
  surface/internal receptors on immune cells
- Sex hormones effect AD:
  - Female oestrogen exacerbates AD
  - Male testosterone protects from AD

Environmental Factors
Infection

- Infection (viral and bacterial) linked to AD
- Link = circumstantial only infections hard to pinpoint
- Epstein-Barr virus effects:
  - Systemic Lupus erythematosus
  - Rheumatoid Arthritis
  - Multiple Sclerosis
- Cytomegalovirus effects:
  - Diabetes Mellitus
- Mycobacterial infections:
  - Rheumatoid Arthritis
- Many different infections cause one AD
- Many AD caused by one infectious agent
Environmental Factors
Infection (cntd)

• How do infections effect AD?
  – Direct viral damage
  – Autoreactive cells exposed to inflammatory cytokines
  – Antigenic cross-reactivity
  – Molecular mimicry
  – Bystander activation + Adjuvant effect
• All infectious agents cause AD by common mechanism?
• Inflammatory response to infection = more important than the infectious agent trigger

Environmental Factors
Diet

• Chemical food additives + Pesticides
  – Genetically engineered food
  – Fluoride + chloride
  – Antibiotics given to farm animals
• Thyroid disease:
  – Iodine from iodized salt
  – Iodine binds thyroglobulin (thyroid hormone precursor)
  – Autoantibodies against thyroglobulin and inflammation in gland
• Coeliacs disease:
  – Gluten sensitivity
  – Inflamed intestines
  – Autoantibodies against Transglutamimase
• Low vitamin D levels occurs in:
  – Multiple sclerosis
  – Diabetes mellitus
  – Rheumatoid Arthritis
Environmental Factors

Drugs

• Therapeutic drugs: produce AD symptoms e.g.
  – Lupus symptoms induced by procainaminde + hydralazine
  – Myasthenia Gravis symptoms induced by penecillamine
  – Hemolytic anaemia symptoms induced by α-methylldopa

Drug induced AD disappears once drug is removed

Environmental Factors

Toxins

• Toxins: heavy metals in diet (e.g. mercury)

• Animal models: AD in mice caused by mercury, silver + gold

Other:
• Ageing = more common to acquire AD
Summary

• The pathogenesis of autoimmune diseases occurs through the breakdown of tolerance, and other mechanisms that may be mediated either cellurally or by antibodies.
• Both environmental and genetic factors play a role in autoimmune disease.
• Genetic factors include both MHC-linked and non MHC-linked genes.
• Environmental factors can trigger AD in those people who already have a genetic predisposition.