Disruption of Healthy Tissue by the Immune Response – Ch 13

Autoimmune disease:

• Caused by an adaptive immune response that is misdirected and targets healthy cells and tissues of the body

• Represents a breach of tolerance

• Involves the activities of autoantibodies and autoimmune T cells that recognize self antigens
Autoantibodies and Graves’ disease

Endocrine glands are often targets of autoimmune disease:

- tissue-specific proteins
- highly vascularized

Role of autoantibodies in autoimmunity: can recognize cell surface receptors

1) receptor stimulation
2) block stimulation by the natural ligand

Graves’ disease: autoantibodies recognize thyroid stimulating hormone (TSH) receptor and induce increased levels of thyroid hormone production

- thyroid hormone normally acts on the pituitary to shut down TSH
- effect of autoantibodies: bypass negative feedback loop that would normally turn off production of thyroid hormone
Graves’ Disease - hyperthyroid condition caused by autoAbs

AutoAbs against TSH receptor results in over-production of thyroid hormones
How is disease classified as autoimmune?

Demonstration of autoAbs alone is not enough

Need to show that the Abs can cause disease

1) Adoptive transfer of Abs (passive transfer)
2) Experiments in nature: transfer from mother to fetus results in disease observed in newborn baby
IDDM: Insulin-dependent diabetes mellitus

Normal islet comprised of $\beta$ cells that produce insulin

(insulin stimulates body to take up glucose)

Inflamed islet consisting of lymphocytic infiltration - results in inefficient uptake of glucose via reduced insulin production
SLE: systemic lupus erythematosus

- autoimmune response to almost all tissues within the body
- primarily mediated by autoreactive antibodies
Rheumatoid arthritis

- disease is mediated by autoantibodies and autoreactive T cells
What causes autoimmune diseases to develop?

Multifactorial - both genetic predisposition as well as environmental influences can result in development of autoimmune diseases.

Cardinal feature of autoimmune diseases - breaking T cell tolerance i.e., T cells become capable of recognizing and responding to self.

True for T cell-mediated autoimmune diseases (e.g., MS, RA) as well as Ab-mediated autoimmune diseases.

Why?

B cells involved have switched isotype and undergone affinity maturation meaning help from Ag-specific T cells.
Role of T cells in generating autoreactive B cells

Mechanisms by which autoreactive B cells are eliminated rely primarily on T cell tolerance - this deprives them of T cell help.

Figure 11-16 The Immune System, 2/e (© Garland Science 2005)
Generation of autoreactive B cells in the GC

- Autoreactive B cells may be generated during somatic hypermutation in germinal center
- Ligation of autoantigen results in apoptosis in absence of T cell help
Role of anergy in peripheral T cell tolerance

Although negative selection may be working, autoreactive T cells can escape

How can activation be prevented?

Normally, cells within potential target tissue will not express co-stimulatory factors necessary for T cell activation - as a result, autoreactive T cells will become anergic

![Diagram showing T cell activation and anergy](image)

Figure 6-19 The Immune System, 2/e © Garland Science 2005)
Regulatory T cells protect from autoimmunity

- Regulatory T cell (Treg) exist and can also control autoreactive T cells

- Unique surface receptor phenotype (CD4+CD25+) distinguishes them from other T cells

- If Treg recognize auto-antigen (presented in context of MHC class II) and CTLA-4 signaling is induced via B7, the Treg will secrete anti-inflammatory cytokines (e.g., IL-4 and IL-10)

- Important - for optimal suppressive effect, the autoreactive T cell needs to be interacting with same APC

Figure 11-21 The Immune System, 2/e © Garland Science 2005
Genetic factors are important in the development of autoimmune diseases

HLA haplotype is important in the development of certain autoimmune diseases such as IDDM

![Figure 11-22 The Immune System, 2/e (© Garland Science 2005)](image)

Siblings that share haplotype have increased risk of both developing IDDM
<table>
<thead>
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<th>Disease</th>
<th>HLA allotype</th>
<th>Frequency (%)</th>
<th>Relative risk</th>
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Why are certain HLA’s associated with autoimmune disease?

An individual’s specific HLA repertoire determines their ability to present autoantigen to T cells - this stimulate autoreactive T cells in a certain way and can initiate autoimmunity

Therefore, certain disease-associated HLA allotypes are configured to present slightly different peptides, which can initiate disease.

![Table showing different DRB1*04 subtypes and their amino-acid positions in DRβ chain]

* Figure 11-26 The Immune System, 2/e © Garland Science 2005
Other autoimmune diseases in which genetic background is important: *Celiac disease*

- inflammatory autoimmune disease of the gut mucosa

- genetic predisposition is strong with 75% concordance between monozygotic twins

- disease is caused by immune response to gluten proteins of wheat flour

- persistent intake of gluten causes chronic inflammation in the gut and ultimately causes atrophy, malabsorption, diarrhea, and can lead to cancer

- patients need to stay on gluten-free diet
Mechanism of Celiac disease

- Gluten is degraded in the gut lumen to give a resistant fragment.
- Gluten fragment enters gut tissue and is deaminated by transglutaminase.
- Naive CD4 T cell responds to deaminated peptides presented by HLA-DQ.
- Inflammatory effector T cells cause villous atrophy.

Figure 11-28 The Immune System, 2/e (© Garland Science 2005)
Other contributing factors to the development of autoimmune diseases: physical trauma

- allows access of immune system to sites not routinely surveyed
- example: sympathetic ophthalmia