Autoimmune diseases

- Well over one hundred distinct autoimmune diseases that vary according to the target tissue, cell or molecule and in the immunologic mechanisms that mediate target tissue injury
- Often serious and chronic, although they may fluctuate in intensity with spontaneous remissions and exacerbations
- Autoimmune diseases were thought to be due to collagen abnormalities and the term “collagen vascular” or “connective tissue” disease is still heard
- Many are characterized by hyper gammaglobulinemia and serum autoantibodies that led to the recognition of the autoimmune nature of these diseases, previously considered “collagen” diseases

Autoimmune diseases are relatively common- examples

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Prevalence in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis and psoriatic arthritis</td>
<td>2-3%</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>1-2%</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>1-2%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0.8%</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>0.1%</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>0.1%</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>0.1%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0.1%</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Autoimmune disease tissue injury results from a coordinated adaptive immune response involving most of the mechanisms used in responding to a pathogen

Dominant mechanisms of tissue injury may involve:

- T cell mediated injury by CD4 and/or CD8 T cells
- Antibodies directed to target cell or matrix antigens
- Antibodies directed to soluble circulating autoantigens that form immune complexes and elicit inflammation by engaging FcR, complement activation, etc.

No evidence of allergic / IgE-mediated injury

Injury Mechanism- CD4 and/or CD8 T cells

Examples:
- Type 1 diabetes mellitus *
- Anterior uveitis
- Multiple sclerosis
- Psoriasis / psoriatic arthritis
- Celiac disease *

*Antibodies are present and diagnostically/prognostically useful, but do not appear to be pathogenic

Injury Mechanism- Antibodies

Direct evidence for the pathogenic role of autoantibodies comes from transplacental transfer of maternal autoantibodies to the fetus that cause a transient, but sometimes devastating, autoimmune syndrome in the neonate

Autoimmune thrombocytopenia
- Coombs positive hemolytic anemia
- Systemic lupus erythematosus-complete congenital heartblock
- Myasthenia gravis
- Pemphigus vulgaris
- Grave’s disease
The detection of autoantibodies is still the major laboratory test used to confirm the diagnosis of many autoimmune disease

Example: Antinuclear antibodies, a hallmark of SLE

Autoimmune diseases: classification as organ-specific or systemic according to target antigen distribution

Organ-specific (antigen restricted in distribution)
- Autoimmune thrombocytopenia
- Coombs positive hemolytic anemia
- Myasthenia gravis
- Hashimoto’s thyroiditis
- Celiac disease
- Pemphigus vulgaris
- Type 1 diabetes mellitus
- Multiple sclerosis

Systemic (autoantigen widely distributed, or response involves immune complexes)
- Rheumatoid arthritis
- Psoriasis and psoriatic arthritis
- Systemic lupus erythematosus

Who develops an autoimmune disease?

Inherited susceptibility- a major clue

Identical twin concordance- 25-50%

Familial aggregation- (family history)

Recurrence rate $\lambda_s = \frac{\text{Frequency in sibs}}{\text{Frequency in population}}$

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency in sibs</th>
<th>Frequency in population</th>
<th>$\lambda_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>10-25%</td>
<td>0.1%</td>
<td>100-250</td>
</tr>
<tr>
<td>RA</td>
<td>5%</td>
<td>0.8%</td>
<td>6</td>
</tr>
</tbody>
</table>

What genes are responsible for the development of an autoimmune disease?

Inherited susceptibility associated with particular MHC alleles for virtually all autoimmune diseases

<table>
<thead>
<tr>
<th>Diseases</th>
<th>HLA specificities associated with susceptibility</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>HLA-DR2 (DR15, DR16)</td>
<td>4.8</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>HLA-B27</td>
<td>20.0</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>HLA-DR4</td>
<td>14.2</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>HLA-DR4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

This returns us to the processes involved in the determination of immunologic self

T cells
- Recognition of certain self-peptides presented by self-MHC
- Mechanisms of T cell repertoire selection and the development of immunologic self

MHC
- Binding and presentation of a particular self peptide is a “necessary” condition for development of autoimmunity
- The HLA alleles associated with autoimmune disease development are not mutant, “abnormal” genes
Autoimmune diseases: classification according to the class of the susceptibility MHC allotype and lineage of autoantigen specific T-cells mediating injury

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8</td>
<td>CD4</td>
</tr>
<tr>
<td>HLA-A, B, or C</td>
<td>HLA-DR, DQ, or DP</td>
</tr>
</tbody>
</table>

Psoriatic arthritis
Psoriasis
Reiter’s syndrome
Rheumatoid arthritis
Ankylosing spondylitis
Lupus erythematosus

Examples of MHC-T cell interactions in autoimmune disease

Identifying a probable inciting autoantigenic peptide recognized by CD4 T cells that provides help to autoantibody formation

Pemphigus vulgaris is a blistering disease of the skin and mucous membranes resulting from formation of high affinity IgG antibodies directed to a amino acids 200-229 of desmoglein 3 (DSG3) that forms the intercellular junctions of epidermal prickle cells

Susceptibility associated with DRB1*0402

The association of susceptibility to pemphigus with the DRB1*0402 allele suggests that CD4 T cells recognize a self peptide that provides help to B cells producing autoantibodies to desmoglein

- Knowing the autoantigen recognized by autoantibodies helped in the search for the peptide recognized by the T cell

The binding motif of the DRB1*0402 molecule was used to identify desmoglein peptides capable of binding to the MHC molecule

<table>
<thead>
<tr>
<th>Peptide binding motif</th>
<th>T cell proliferative response to desmoglein peptides by T cell lines made from</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI P4 P6</td>
<td>++++</td>
</tr>
<tr>
<td>L Y V</td>
<td>+++</td>
</tr>
<tr>
<td>N Y</td>
<td>+++</td>
</tr>
<tr>
<td>78-93 ATQKITYRSGVQID</td>
<td>+++</td>
</tr>
<tr>
<td>97-111 FGIPVDKNTGGEHE</td>
<td>+++</td>
</tr>
<tr>
<td>190-204 LNSKAPKVSSQEPAPA</td>
<td>++++++</td>
</tr>
<tr>
<td>206-220 TPHLLSSNTGEVRT</td>
<td>++</td>
</tr>
<tr>
<td>251-265 CECEKVVKVDNFGFP</td>
<td>++</td>
</tr>
<tr>
<td>512-526 SARTLNNRTYTGTF</td>
<td>++</td>
</tr>
<tr>
<td>762-786 QSTMTRYHTGYN</td>
<td>++</td>
</tr>
</tbody>
</table>

Wucherpfennig et al.

The T cell repertoire of pemphigus vulgaris patients contains CD4 clones that recognize desmoglein peptides presented by DRB1*0402 that likely provide help in the production of the pathogenic autoantibodies directed to desmoglein
Rheumatoid arthritis is another example of an autoimmune disease where there is an exquisitely precise instance of MHC susceptibility that can be mapped to a single peptide-binding pocket, but here the autoantigen is unknown.

<table>
<thead>
<tr>
<th>Serosal Specificity</th>
<th>DR1</th>
<th>DR2</th>
<th>DR3</th>
<th>DR4</th>
<th>DR4</th>
<th>DR4</th>
<th>DR5</th>
<th>DR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Association</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Motif of β-chain from 67-74 forming P4 pocket defines the molecular basis of susceptibility to RA:

Leu - Gln - Lys/Arg - Ala

Rheumatoid arthritis is associated with multiple HLA-DR alleles that in common implicate a motif of the P4 pocket that determines disease susceptibility.

Central lesson from rheumatoid arthritis - genetic susceptibility is not the property of a single allotype, but a common structural feature encoded by several otherwise different allotypes.

Importance of MHC haplotypes

Brief review

Each ethnically distinct population is dominated by a relatively few MHC haplotypes, the alleles of which exhibit strong linkage disequilibrium.

These reflect the selective effects of epidemics, local environment, founder effect, etc.

Through their strong effect on regulating adaptive immunity and the determination of self, certain combinations of alleles, in linkage disequilibrium, determine susceptibility to autoimmune diseases and other s.
Some clinically important instances of linkage disequilibrium relevant to disease reflect a variable duplication in class III genes. The HLA-A1-B8-DR3-DQA1*0501-DQB1*0201 haplotype has a deletion of 25kb of DNA including the C4B gene, which decreases the C4 level by ~half.

Because linkage disequilibrium includes non HLA genes, these are included in the susceptibility haplotype.

CYP21B(A2) encodes steroid 21 hydroxylase and its absence results in congenital adrenal hyperplasia, a recessive disease due to a failure to synthesize cortisol; this causes androgenic precursor over-production. Androgen excess leads to ambiguous genitalia in females, rapid somatic growth during childhood in both sexes, with premature closure of the epiphyses and short adult stature (Infant Hercules).

The haplotype HLA-A25-B18-DR2 contains a defective gene for C2 with a 28bp deletion that results in no product:
- No hemolytic activity in classic pathway
- Associated with autoimmune disease (SLE)
- Evidence mutation appeared ~1000 yrs ago

Lessons from animal models of autoimmune disease

Inherited susceptibility
Certain strains or crosses result in animals that spontaneously develop particular autoimmune diseases at high frequency.

Examples:
- New Zealand hybrid (NZB x NZW)F1 develops a lupus-like disease
- NOD model of type 1 diabetes mellitus

Lessons: Autoimmunity is genetically determined and regulated by interactions of a relatively small number of genes; studies of pathogenesis reveal importance of T cells.

Not all the genes in the MHC are obviously related to immune responsiveness.

Mispairing of class III regions that have one or two modules of C4 during cross over can result in an additional loss of CYP21B(A2).

CYP21B(A2) encodes steroid 21 hydroxylase and its absence results in congenital adrenal hyperplasia, a recessive disease due to a failure to synthesize cortisol; this causes androgenic precursor over-production.

Lessons: Autoimmunity is genetically determined and regulated by interactions of a relatively small number of genes; studies of pathogenesis reveal importance of T cells.

Animal models of autoimmune disease: lessons

- Induced certain strains immunized with adjuvant and a peptide develop disease at high frequency

Examples:
- Experimental autoimmune encephalomyelitis from MBP, a model of multiple sclerosis
- Lesion: Latently autoreactive T cells exist in the repertoire and can be activated by innate signals provided by the adjuvant

Reemphasize importance of MHC and other susceptibility genes.
Animal models of autoimmune disease

Single gene genetic manipulations: gene knockout or over expression of a transgene

Fact: lupus-"like" disease results from any of >> 50 gene manipulations

Lesson-provide evidence of multiplicity of pathways and genes potentially relevant to regulation of immunity and autoimmunity, some very intriguing

However, much caution needed in interpreting knockout and transgene experiments, since many things are altered by KO

Autoimmune diseases develop in previously healthy individuals many years after birth and the disease “appears” to be acquired

Pre-teen Adolescence Midlife ≥ 6th Decade
Young adulthood

Type I diabetes mellitus

Autoimmune thrombocytopenia
Coombs + hemolytic anemia
Myasthenia gravis
Grave’s disease
Celiac disease
Pemphigus vulgaris
Multiple sclerosis
Psoriasis and psoriatic arthritis
Systemic lupus erythematosus

Implies a stochastic or environmental factor

Return us to the concept of the genesis of immunologic self

Development of the self T cell repertoire and the events that sculpt the selected repertoire to give self “tolerance” are central to autoimmunity

Events in the development of an autoimmune disease

Stages to progression of autoimmune disease

<table>
<thead>
<tr>
<th>Genetic Predisposition</th>
<th>Initiation of Immune Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC allele (+ other genes?)</td>
<td>Event (+ other genes?)</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td>Bind self peptides</td>
</tr>
<tr>
<td>Coombs + hemolytic anemia</td>
<td>Select latently autoreactive TCR repertoire</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Giant cell arthritis</td>
</tr>
<tr>
<td>Grave’s disease</td>
<td></td>
</tr>
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Implies a stochastic or environmental factor

T cell repertoire: development of immune self

Central- thymic phase

- Positive selection of the self reactive repertoire
- Negative selection / deletion of overtly self reactive T cells central “self tolerance”
How can we explain the association of susceptibility to autoimmune diseases with MHC allotypes?

Positive selection of the self reactive T cell repertoire on self p-MHC

Properties of the MHC molecule itself influence repertoire selection in the central-thymic phase

Two hypotheses

One possibility:

- Disease-related MHC allotypes bind self-peptides with high affinity and select T cells that bind autoantigenic peptides with moderate to high affinity, then a defect in thymic selection allows moderate to high affinity clones to escape negative selection and populate the peripheral repertoire with pathologically self-reactive T cells

Second possibility:

- The weak binding of self peptides in the positive phase of repertoire selection in the thymus means that only T cells with very high affinity for self peptides are selected via normal positive selection mechanisms; these clones are not eliminated in normal negative selection because the overall avidity of the TCR for the pMHC complex is not high enough to trigger apoptosis

However, Ridgeway and Fathman noted facts inconsistent with this explanation for type 1 diabetes:

- Susceptibility in mouse and man is associated with HLA-DQ homozygosity for certain HLA-DQ haplotypes
- The susceptibility allotypes had poor binding affinity for self peptides and were structurally unstable

Stages to progression of autoimmune disease

Initiation of Immune Recognition Event (+ other genes?)

Effector mechanisms

T cell clonal Expansion, Spreading

B cell help

Autoimmune Disease