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

• Genetic predisposition is clear; identical twin concordance and familial aggregation is substantial

• The mode of inheritance of most common autoimmune diseases is not clearly dominant or recessive (non-Mendelian)

• Disease phenotype behaves like a complex trait: several genes determine susceptibility

• Penetrance moderate (from identical twin concordance rate (25-50%): implies a non-germline event triggers disease

Autoimmune diseases are relatively common- examples

Diseases	Prevalence in USA
Psoriasis and psoriatic arthritis	2-3%
Hashimoto's thyroiditis	1-2%
Celiac disease	1-2%
Rheumatoid arthritis	0.8%
Myasthenia gravis	0.1%
Pemphigus vulgaris	0.1%
Type 1 diabetes mellitus	0.1%
Multiple sclerosis	0.1%
Systemic lupus erythematosus	0.1%

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 I 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

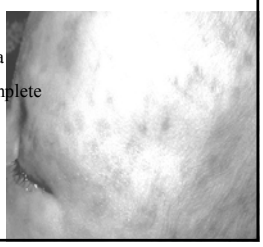
Coombs positive hemolytic anemia

Systemic lupus erythematosus-complete congenital heartblock

Myasthenia gravis

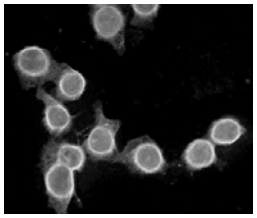
Pemphigus vulgaris

Grave's disease

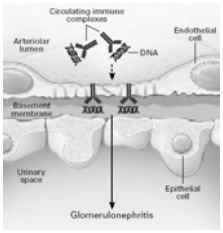


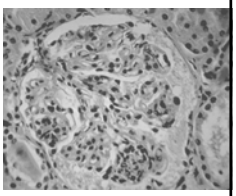
The detection of autoantibodies is still the major laboratory test used to confirm the diagnosis of many autoimmune disease

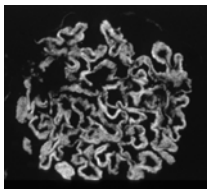
Example: Antinuclear antibodies, a hallmark of SLE



Injury Mechanism-Immune Complex formation and deposition







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

Organ-specific (antigen restricted in distribution)

Autoimmune thrombocytopenia	Platelet
Coombs positive hemolytic anemia	RBC
Myasthenia gravis	ACH R of muscle
Hashimoto's thyroiditis	Thyroid
Celiac disease	Intestine
Pemphigus vulgaris	Skin
Type 1 diabetes mellitus	Pancreatic islets
Multiple sclerosis	CNS

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)

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

Disease	Frequency in sibs	Frequency in population	λ_S
SLE	10-25%	0.1%	100-250
RA	5%	0.8%	6

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

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

$$\text{Relative Risk (Odds ratio)} = \frac{\text{Probability of finding allele in disease group}}{\text{Probability of finding allele in control group}}$$

Diseases	HLA specificities associated with susceptibility	Relative Risk
Multiple sclerosis	HLA-DR2 (DR15, DR16)	4.8
Ankylosing spondylitis	HLA-B27	20.0
Pemphigus vulgaris	HLA-DR4	14.2
Rheumatoid arthritis	HLA-DR4	4.2

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

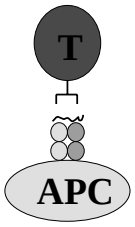
T cells

- 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

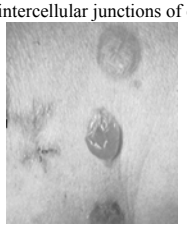


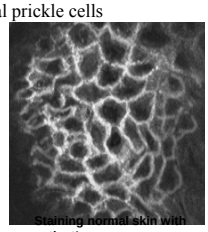
Class I	Class II
CD8	CD4
HLA-A,B, or C	HLA-DR, DQ, or DP
Psoriasis	Multiple sclerosis
Psoriatic arthritis	Pemphigus vulgaris
Reiter's syndrome	Rheumatoid arthritis
Ankylosing spondylitis	Lupus erythematosus

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





Staining normal skin with patient's serum

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

Peptide binding motif

P1	P4	P6
I	R	S
V	K	T
L		V
M		Y

Seven desmoglein peptides exhibit the DRB1*0402 binding motif

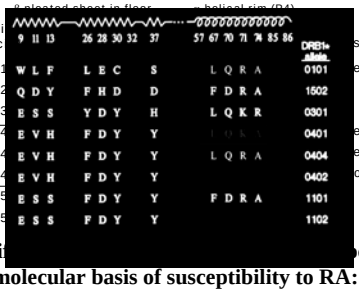
		T cell proliferative response to desmoglein peptides by T cell lines made from	
		Patient G	Patient R
78–93	ATQKITYRISGVGID		
97–111	FGIFVVDKNTGDINI		
190–204	LNSKIAFKIVSQEPA	++++	++++
206–220	TPMFLLSRNTGEVRT	++	
251–265	CECNIKVKDVNDNFP	++	
512–526	SARTLNNRYTGPYTF		
762–786	QSGTMRTRHYTGGTN		++

Wucherpfennig et al. (DRB1*0402 APC)

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

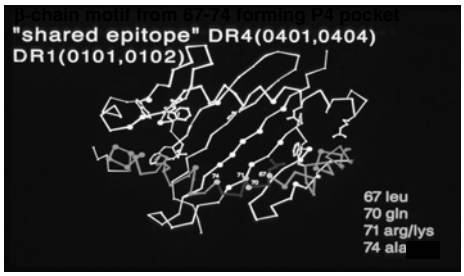
Rheumatoid arthritis is another example of an autoimmune disease where there is an exquisitely precise instance of MHC susceptibility that can be mapped to a single peptide-binding pocket, but here the autoantigen is unknown

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



Moti… …cket defines the molecular basis of susceptibility to RA:

Leu - Gln -Lys/Arg - Ala



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

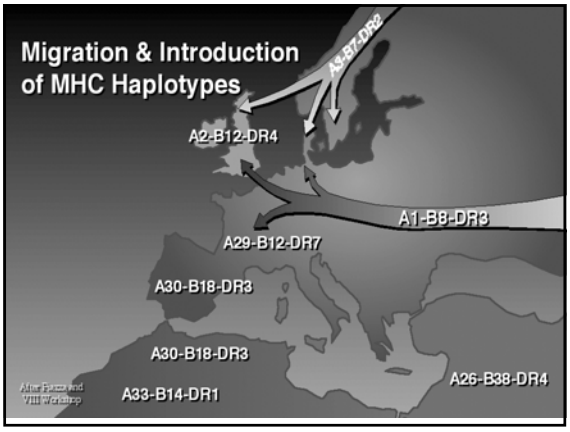
Importance of MHC haplotypes

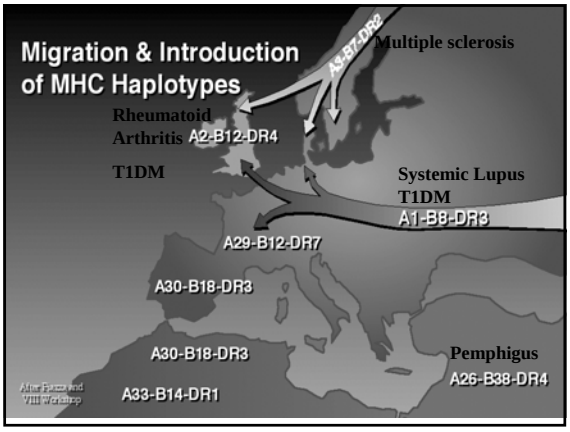
Brief review

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

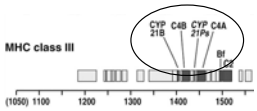
These reflect the selective effects of epidemics, local environment, founder effect, etc.

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

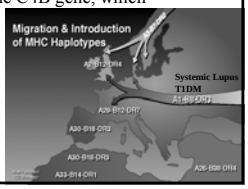




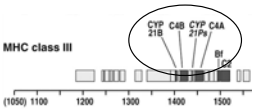
Some clinically important instances of linkage disequilibrium relevant to disease reflect a variable duplication in class III genes



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

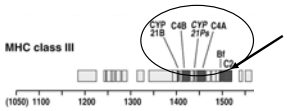


Not all the genes in the MHC are obviously related to immune responsiveness

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

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)



C3 convertase genes are MHC encoded

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

Alleles of major DQ-DR haplotypes that exhibit linkage disequilibrium influence susceptibility to type I diabetes mellitus

DQB1	DQA1	DRB1	HLA-DR	T1DM
***0602**	***0102**	***1501**	**DR2**	Dom. Protective
***0601**	***0103**	***1502**	**DR2**	Neutral
***0201**	***0501**	***0301**	**DR3**	**Strong Suscept.**
***0302**	***0301**	***0401**	**DR4**	**Strong Suscept.**
***0302**	***0301**	***0402**	**DR4**	**Weak Suscept.**
***0301**	***0301**	***0401**	**DR4**	Neutral
***0303**	***0301**	***0401**	**DR4**	Neutral
***0303**	***0201**	***0701**	**DR7**	Dom. Protective

T1DM susceptibility also influenced by DQA1 and DRB1 alleles

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

Lesson-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

Lesson-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

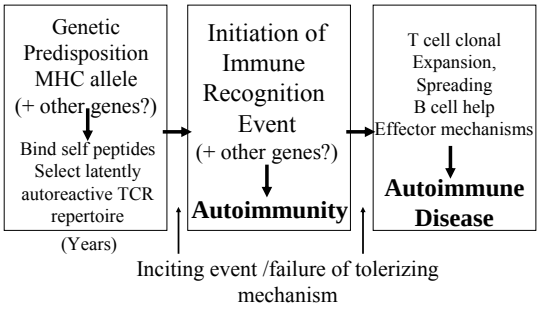
Events in the development of an autoimmune disease

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

Pre-teen	Adolescence Young adulthood	Midlife	≥6th Decade
Type 1 diabetes mellitus	Rheumatoid arthritis Hashimoto's throiditis		
	Autoimmune thrombocytopenia Coombs + hemolytic anemia Myasthenia gravis Grave's disease Celiac disease Pemphigus vulgaris Multiple sclerosis Psoriasis and psoriatic arthritis Systemic lupus erythematosus		Polymyalgia rheumatica Giant cell arteritis

Implies a stochastic or environmental factor

Stages to progression of autoimmune disease



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

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

= High avidity MHC peptide binding + defect in thymic selection

However, Ridgeway and Fathman noted facts inconsistent with this explanation for type 1 diabetes: Science 284, 749,1999

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

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

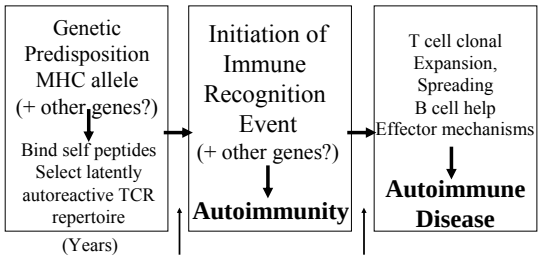
Properties of the MHC molecule itself influence repertoire selection in the central- thymic phase

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

= primary defect in MHC ability to bind a self peptide

Stages to progression of autoimmune disease



Inciting event /failure of peripheral self-tolerizing mechanisms

This phase will be covered in the lecture on immune regulation