Autoimmunity and immune-mediated inflammatory diseases

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Lecture outline

- Pathogenesis of autoimmunity: why self-tolerance fails
- Genetics of autoimmune diseases
- Therapeutic approaches, animal models and biomarkers
Autoimmunity

- Definition: immune response against self (auto-) antigen, by implication pathologic (harmful)
  - Target antigens often unknown (self or microbe?)
  - Basis for designation of “autoimmune” often imprecise

- Much of our knowledge of immunological disorders is based on mouse models of diseases

Types of hypersensitivity disease

<table>
<thead>
<tr>
<th>Type of hypersensitivity</th>
<th>Pathogenic immune response</th>
<th>Mechanism of tissue injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate hypersensitivity (Type I)</td>
<td>IgE antibody, mast cells</td>
<td>Mast cell mediators</td>
</tr>
<tr>
<td>Antibody mediated (Type II)</td>
<td>IgM and IgG antibodies against cell and matrix antigens</td>
<td>Phagocytosis, Complement, Interference with cell functions</td>
</tr>
<tr>
<td>Immune complex mediated (Type III)</td>
<td>Complexes of circulating antigens and IgM or IgG antibodies</td>
<td>Complement and Fc receptor mediated inflammation</td>
</tr>
<tr>
<td>T cell mediated (Type IV)</td>
<td>CD4 and CD8 T cells</td>
<td>Inflammation; Delayed type hypersensitivity, Killing by CTLs</td>
</tr>
</tbody>
</table>
Immune-mediated inflammatory diseases

- Chronic diseases with prominent inflammation, often caused by failure of tolerance or regulation
  - RA, IBD, MS, psoriasis, many others
  - Affect 2-5% of people, incidence increasing

- May result from immune responses against self antigens (autoimmunity) or microbial antigens (Crohn’s disease?)

- May be caused by T cells and antibodies

Features of autoimmune diseases

- Fundamental problem: imbalance between immune activation and control
  - Underlying causative factors: susceptibility genes + environmental influences
  - Immune response is inappropriately directed or controlled; effector mechanisms of injury are the same as in normal responses to microbes

- Nature of disease is determined by the type of dominant immune response

- Many immunological diseases are chronic and self-perpetuating
Balancing lymphocyte activation and control

Tolerance
Regulatory T cells

Failure of tolerance
Lymphocyte activation
Effector T cells

Normal

Inflammatory disease, e.g.
reactions against self tissues

Pathogenesis of organ-specific autoimmunity

Genetic susceptibility
Infection, inflammation

Infection, tissue inflammation

Failure of self-tolerance

Failure of self-reactive lymphocytes

Targets of most current therapies: end stages of the reaction
Genetic basis of autoimmunity

• Genetic predisposition of autoimmune diseases
  - Increased incidence in twins (more in monozygotic)
  - Identification of disease-associated genes by breeding and genomic approaches

• Multiple genes are associated with autoimmunity
  - Most human autoimmune diseases are multigenic
  - Single gene defects reveal pathways of self-tolerance and why it fails (e.g. AIRE, Fas, Foxp3, many others)

Genetic basis of autoimmunity -- 2

• MHC (HLA) genes
  - Major genetic association with autoimmune diseases (relative risk of disease in individuals with particular HLA haplotypes)
  - Disease-associated alleles are present in normal individuals

• Non-MHC genes:
  - Many loci identified by genomic methods
  - Most are chromosomal locations; actual genes and functions are often unknown; many SNPs are in non-coding regions
  - Recent genome-wide association studies
Genetics of autoimmunity: some recent successes of genomics

- **PTPN22**: commonest autoimmunity-associated gene; polymorphism in RA, SLE, others
  - Phosphatase
- **NOD2**: polymorphism associated with ~25% of Crohn’s disease
  - Microbial sensor
- **CD25 (IL-2Rα)**: associated with MS, others; genome-wide association studies
  - Role in generation and maintenance of Tregs or effector/memory cells?

Genetics of autoimmunity: challenges

- Relating complex genotypes to phenotypic and functional abnormalities, to better understand pathogenesis
  - Strongest association is with HLA, defined decades ago, but role of HLA polymorphisms in autoimmune diseases still not understood
- Limitations of GWAS
  - Detect only common variants
- Predictive value of genetic polymorphisms
  - Unlikely because of low odds ratios
- Using polymorphisms to identify therapeutic targets
  - Difficult because any one gene makes a small contribution
## Some mutations that cause autoimmune disease

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype of mutant or knockout mouse</th>
<th>Mechanism of failure of tolerance</th>
<th>Human disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIRE</td>
<td>Destruction of endocrine organs by antibodies, lymphocytes</td>
<td>Failure of central tolerance</td>
<td>Autoimmune polyendocrine syndrome (APS)</td>
</tr>
<tr>
<td>C4</td>
<td>SLE</td>
<td>Defective clearance of immune complexes; Failure of B cell tolerance?</td>
<td>SLE</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Lymphoproliferation; T cell infiltrates in multiple organs, especially heart, lethal by 3-4 weeks</td>
<td>Failure of energy in CD4+ T cells</td>
<td>CTLA-4 polymorphisms associated with several autoimmune diseases</td>
</tr>
<tr>
<td>Fas/FasL</td>
<td>Anti-DNA and other autoantibodies; immune complex nephritis; arthritis, lymphoproliferation</td>
<td>Defective deletion of anergic self-reactive B cells; reduced oxidation of mature CD4+ T cells</td>
<td>Autoimmune lymphoproliferative syndrome (ALPS)</td>
</tr>
<tr>
<td>FoxP3</td>
<td>Multi-organ lymphocytic infiltrates, wasting</td>
<td>Deficiency of regulatory T cells</td>
<td>IPEX</td>
</tr>
<tr>
<td>IL-2/IL-2Ra/β</td>
<td>Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies</td>
<td>Defective development, survival or function of regulatory T cells</td>
<td>None known</td>
</tr>
<tr>
<td>SHP-1</td>
<td>Multiple autoantibodies</td>
<td>Failure of negative regulation of B cells</td>
<td>None known</td>
</tr>
</tbody>
</table>

**Abbreviations:** AIRE, autoimmune regulator gene; IL-2, interleukin-2; IPEX, immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome; SHP-1, SH2-containing phosphatase-1.

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## Infections and autoimmunity

- **Infections trigger autoimmune reactions**
  - Clinical prodromes, animal models
  - IBD is dependent on gut commensals

- **Some autoimmune diseases are prevented by infections** (type 1 diabetes, multiple sclerosis, others? -- increasing incidence in developed countries): mechanism unknown
  - The “hygiene hypothesis”
Immune-mediated diseases

- The nature of the disease is determined by the type of dominant immune response
  - Th1 response: inflammation, injurious antibodies; many autoimmune diseases
  - Th2 response: IgE + eosinophil-mediated inflammation; allergic reactions
  - Th17 response: acute (and chronic?) inflammation; increasingly recognized in immune-mediated diseases
Immune-mediated diseases

- Immunological diseases tend to be chronic and self-perpetuating, because --
  - The initiating trigger can often not be eliminated (self antigen, commensal microbes)
  - The immune system contains many built-in amplification mechanisms whose normal function is to optimize our ability to combat infections
  - “Epitope spreading”: reaction against one antigen releases other antigens and new lymphocytes begin to react against these

Amplification loop in cell-mediated immunity

Cytokines are powerful amplifiers of immune reactions

Cytokines: IFN-γ

Macrophage

Cytokines: TNF, IL-12

T lymphocyte
What initiates inflammatory diseases?

- Role of infections, tissue necrosis, TLR signals?

- Loss of immune regulation (intrinsic lymphocyte abnormality) leads to chronic responses without strong extrinsic stimuli?

Immune-mediated inflammatory diseases

- Immune-mediated inflammatory diseases develop because the normal controls on immune responses fail

- The phenotype of the disease is determined by the nature of the immune response

- These diseases often become self-perpetuating

Take home messages
Risks of immune therapies

- Predictable: blocking disease mechanisms lowers resistance to infections
  - Because mechanisms of tissue damage in immune diseases are the same as the effector mechanisms that eliminate microbes

- Unexpected: unrecognized expression of molecules thought to be restricted to the immune system
  - For example, CD40-ligand on platelets
Biomarkers of human immune diseases

- Major goal of current research is to identify biomarkers for efficacy, toxicity, and disease progression
- High-throughput screens for transcripts and proteins associated with disease
- **Practical limitations:**
  - Rely mainly on assays of serum and whole blood cells, but key abnormalities may be in selected lymphocyte populations in tissues
- **Nevertheless, some emerging successes:**
  - Type I interferon “signature” in lupus

Immune-mediated inflammatory diseases

- Experimental models are revealing pathways of immune regulation and why it fails
- Genetic studies are identifying underlying defects in human diseases
- Improving technologies are enabling analyses of patients
- **Challenges:**
  - From genes to pathways (molecular and functional)
  - Using the knowledge to develop therapies

*Take home messages*