Autoimmunity

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Autoimmunity

• Definition: immune response against self (auto-) antigen

• General principles:
  - Significant health burden, 5% of population
  - Multiple factors contribute to autoimmunity, including genetic predisposition, infections
  - Fundamental problem is the failure of self-tolerance

• Problems:
  - Failure to identify target antigens, heterogeneous disease manifestations, disease usually presents long after initiation
Examples of autoimmune disease

Graves' Disease (thyrotoxicosis)
Hashimoto's thyroiditis
pernicious anaemia
Addison's disease
insulin dependent diabetes mellitus
Goodpasture's syndrome
myasthenia gravis
multiple sclerosis(?)
autoimmune haemolytic anaemia
idiopathic thrombocytopenic purpura
rheumatoid arthritis
scleroderma
systemic lupus erythematosus (SLE)
Classification of Autoimmune Diseases

- Broadly separated by the type of effector mechanism (similar to hypersensitivity classification scheme)
- Three classes:
  - Type II: Antibody against cell-surface antigen or matrix antigens
  - Type III: Immune-complex disease
  - Type IV: T cell-mediated disease
## Type II: Antibody-mediated diseases

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rh blood group antigens, I antigen</td>
<td>Destruction of red blood cells by complement and phagocytes anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia purpura</td>
<td>Platelet integrin gpllb:IIIa</td>
<td>Abnormal bleeding</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Non-collagenous domain of basement membrane collagen type IV</td>
<td>Glomerulonephritis, pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Epidermal cadherin</td>
<td>Blistering of skin</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle</td>
<td>Arthritis, myocarditis, late scarring of heart valves</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Thyroid-stimulating hormone receptor</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Progressive weakness</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor (antagonist)</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Insulin receptor (agonist)</td>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>

Figure 11-1 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)
Graves' disease
Graves' disease: Proof that it's antibody mediated

- Patient with Graves' disease makes anti-TSHR antibodies
- Transfer of antibodies across placenta into the fetus
- Newborn infant also suffers from Graves' disease
- Plasmapheresis removes maternal anti-TSHR antibodies and cures the disease

Figure 11-7 The Immune System, 2/e (© Garland Science 2005)
Myasthenia Gravis

In this disease, autoantibodies to the Acetylcholine receptor block neuromuscular transmission from cholinergic neurons by blocking the binding of acetylcholine and by causing downregulation (degradation) of its' receptor.
Type III: Immune-complex mediated diseases

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-complex disease (type III)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute bacterial endocarditis</td>
<td>Bacterial antigen</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Mixed essential cryoglobulinemia</td>
<td>Rheumatoid factor IgG complexes (with or without hepatitis C antigens)</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, histones, ribosomes, snRNP, scRNP</td>
<td>Glomerulonephritis, vasculitis, arthritis</td>
</tr>
</tbody>
</table>

Figure 11-1 part 2 of 3  The Immune System, 2/e (© Garland Science 2005)
Review: Immune complex formation

- Blood-borne antigen
- Antigen:antibody complexes
- Antibody against blood-borne antigen
- Intravenous injection
- Fever, vasculitis, arthritis, nephritis

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Figure 11-10 The Immune System, 2/e (© Garland Science 2005)
A model for the pathogenesis of SLE
SLE: Immune complexes in the kidney

Figure 13-33 Immunobiology, 6/e. (© Garland Science 2005)
Type IV: T cell-mediated diseases

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>Pancreatic β-cell antigen</td>
<td>β-cell destruction</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Unknown synovial joint antigen</td>
<td>Joint inflammation and destruction</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Myelin basic protein, proteolipid protein</td>
<td>Brain degeneration. Paralysis</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Gluten modified by tissue transglutaminase</td>
<td>Malabsorption of nutrients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrophy of intestinal villi</td>
</tr>
</tbody>
</table>
T cell mediated effects (cellular immune)

- Direct T cell cytotoxicity via CD8+ CTL
- Self-destruction of tissue cells induced by cytokines, eg, TNFα
- Recruitment and activation of macrophages leading to bystander tissue destruction
- Induction of target tissue apoptosis by the T cell membrane protein FasL
Type I Diabetes: a T cell-directed attack against the β-cells of the pancreatic islet
Type I Diabetes

- T cell response to antigens expressed in the b-cells of the islets
  - Proinsulin/Insulin, GAD, I-A2
  - T cell response is Th1 “like”, makes γ-IFN and helps recruit a tissue/cell destruction response
- >90% islet destruction needed for the disease to be expressed
- Patients also have autoantibodies to islet antigens
Tetramers: flow studies on PBMC

**DR0401-MOG**

**DR0401-Control**

**DR041-IGRP**

**DR401-control**

**DR042-desmoglienn**

**DR042-control**

**DR3-proIns**

**DR3-Control**

**DR404-GAD-555**

**DR404-control**

**DRB4-GAD557I**

**DRB4-control**
Why do autoimmune diseases occur?

Answer: Failure in T cell tolerance
## Mechanisms of immune tolerance

<table>
<thead>
<tr>
<th>Type of tolerance</th>
<th>Mechanism</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central tolerance</td>
<td>Deletion Editing</td>
<td>Thymus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Antigen segregation</td>
<td>Physical barrier to self-antigen access to lymphoid system</td>
<td>Peripheral organs (eg, thyroid, pancreas)</td>
</tr>
<tr>
<td>Peripheral anergy</td>
<td>Cellular inactivation by weak signaling without co-stimulus</td>
<td>Secondary lymphoid tissue</td>
</tr>
<tr>
<td>Regulatory cells</td>
<td>Suppression by cytokines, intercellular signals</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
<tr>
<td>Cytokine deviation</td>
<td>Differentiation to $T_\text{H}2$ cells, limiting inflammatory cytokine secretion</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
<tr>
<td>Clonal exhaustion</td>
<td>Apoptosis post-activation</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
</tbody>
</table>
Overview of Autoimmunity

- Genetic Predisposition
- Environmental Factors
- Failure of central or peripheral tolerance
- Specialized cells present self-tissue proteins
- Autoreactive B Cells
- Autoantibodies
- CD4+ T Cell Driving Force
  - IFN-gamma
  - IL-2, etc.
- CD8+ T Cell Driving Force
  - Tissue injury; release of self antigens; activation of self-reactive lymphocytes
Because Autommunity is so complex, how can we figure out how it happens?

Answer:
1) Use genetics
2) Animal models
Genetic basis of autoimmunity

- **Genetic predisposition of autoimmune diseases**
  - Increased incidence in twins
  - Identification of disease-associated genes by breeding and genomic approaches

- **Multiple genes are associated with autoimmunity**
  - No single mutation causes autoimmunity

- **MHC genes**
  - Major genetic association with autoimmune diseases (relative risk)
  - Disease-associated alleles may be found in normal individuals

- **Non-MHC genes**
  - Many loci identified by genomic methods, animal studies
  - Mutations in complement genes predispose to lupus
HLA (or MHC) is the strongest genetic factor for susceptibility to autoimmune disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA allotype</th>
<th>Frequency (%)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>&gt; 95</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>DQ6</td>
<td>&gt; 95</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>DQ2 and DQ8</td>
<td>95</td>
<td>30</td>
</tr>
<tr>
<td>IDDM</td>
<td>DQ8 and DQ2</td>
<td>81</td>
<td>14</td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td>B35</td>
<td>70</td>
<td>14</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>DQ6</td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>DR4</td>
<td>81</td>
<td>9</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>DR8</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>Psoriasis vulgaris</td>
<td>Cw6</td>
<td>87</td>
<td>7</td>
</tr>
<tr>
<td>Addison's disease</td>
<td>DR3</td>
<td>69</td>
<td>5</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>DR3</td>
<td>65</td>
<td>4</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>DR3</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>IDDM</td>
<td>DQ6</td>
<td>&lt; 0.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Figure 11-23 The Immune System, 2/e (© Garland Science 2005)
Figure 13-21 Immunobiology, 6/e. (© Garland Science 2005)
How does MHC predispose?
How do you find non-MHC genes with weak effects?

GWAS (Genome Wide Association Study)
SNP-Chip (an array of over 500,000 SNP’s!)
<table>
<thead>
<tr>
<th>Chromosomal Region</th>
<th>Gene of Interest</th>
<th>Function</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p13</td>
<td><strong>PTPN22</strong></td>
<td>Protein tyrosine phosphatase; role in T and B cell receptors signaling</td>
<td>RA, T1D, IBD</td>
</tr>
<tr>
<td>1p12</td>
<td><strong>CD2/CD58</strong></td>
<td>Costimulation of T cells</td>
<td>RA, MS</td>
</tr>
<tr>
<td>1p31</td>
<td><strong>IL23R</strong></td>
<td>Component of IL-23 receptor; role in generation and maintenance of T&lt;sub&gt;H&lt;/sub&gt;17 cells</td>
<td>IBD, PS, AS</td>
</tr>
<tr>
<td>1q32</td>
<td><strong>IL10</strong></td>
<td>Downregulates expression of costimulators, MHC molecules, IL-12 in dendritic cells; inhibits T&lt;sub&gt;H&lt;/sub&gt;1 responses</td>
<td>IBD, SLE, T1D</td>
</tr>
<tr>
<td>2q33</td>
<td><strong>CTLA4</strong></td>
<td>Inhibitory receptor of T cells, effector molecule of regulatory T cells</td>
<td>T1D, RA</td>
</tr>
<tr>
<td>4q26</td>
<td><strong>IL2/L21</strong></td>
<td>Growth and differentiation factors for T cells; IL-2 is involved in maintenance of functional Tregs</td>
<td>IBD, CeD, RA, T1D, MS</td>
</tr>
<tr>
<td>5q33</td>
<td><strong>IL12B</strong></td>
<td>p40 subunit of IL-12 (T&lt;sub&gt;H&lt;/sub&gt;1-inducing cytokine) and IL-23 (T&lt;sub&gt;H&lt;/sub&gt;17-inducing cytokine)</td>
<td>IBD, PS</td>
</tr>
<tr>
<td>8p23</td>
<td><strong>BLK</strong></td>
<td>B lymphocyte tyrosine kinase, involved in B cell activation</td>
<td>SLE, RA</td>
</tr>
<tr>
<td>10p15</td>
<td><strong>IL2RA</strong></td>
<td>IL-2 receptor α chain (CD25); role in T cell activation and maintenance of regulatory T cells</td>
<td>MS, T1D</td>
</tr>
</tbody>
</table>

**Genes Involved in Responses to Microbes**

<table>
<thead>
<tr>
<th>Chromosomal Region</th>
<th>Gene of Interest</th>
<th>Function</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>16q12</td>
<td><strong>NOD2</strong></td>
<td>Cytoplasmic sensor of bacteria</td>
<td>IBD</td>
</tr>
<tr>
<td>2q37</td>
<td><strong>ATG16</strong></td>
<td>Autophagy (destruction of microbes, maintenance of epithelial cell integrity)</td>
<td>IBD</td>
</tr>
<tr>
<td>7q32, 2q24</td>
<td><strong>IRF5, IFIH1</strong></td>
<td>Type I interferon responses to viruses</td>
<td>SLE</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; CeD, celiac diseases; IBD, inflammatory bowel disease; MS, multiple sclerosis; PS, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes.

Data from Zenewicz L, C Abraham, RA Flavell, and J Cho. Unraveling the genetics of autoimmunity. Cell 140:791-797, 2010, with permission of the publisher.
Genetics of autoimmunity: recent successes of genomics

- **NOD2**: polymorphism associated with ~25% of Crohn’s disease
  - Microbial sensor in intestinal epithelial cells
- **PTPN22**: commonest autoimmunity-associated gene; polymorphism in RA, SLE, others
  - Phosphatase; mechanism of action?
- **CD25 (IL-2Rα)**: associated with MS, others; genome-wide association mapping
  - Role in Tregs or effector cells?
- **ATG16**: autophagy gene
  - Role of autophagy in IBD (resistance to microbes?)
- **IL-23R**: receptor for Th17-inducing cytokine
  - Effect on Th17 responses
Informative single-gene models of autoimmunity

- Fas/FasL (ALPS): peripheral deletion of T and B cells
- FoxP3 (IPEX): Treg
- CTLA-4 (mouse KO): anergy; Treg
- IL-2, IL-2Rα/β (mouse KO): Treg
- Many others reported

BUT: not the basis of most autoimmune diseases
<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Hereditary C1q deficiency</th>
<th>SPENCDI</th>
<th>AGS</th>
<th>ALPS</th>
<th>IPEX</th>
<th>APS1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene(s)</td>
<td>C1qA, C1qB, C1qC</td>
<td>TRAP (ACP5)</td>
<td>TREP1, RNaseH2 and/or H2 (A, B, C), SAMHD1</td>
<td>FAS, FASLG, CASP10</td>
<td>FOXP3</td>
<td>AIRE</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal dominant, autosomal recessive, variable penetrance</td>
<td>X-linked</td>
<td>Autosomal recessive*</td>
</tr>
<tr>
<td>Main features</td>
<td>SLE and SLE-like disease, Recurrent bacterial infections</td>
<td>Skeletal dysplasia, Cerebral calcifications and CNS symptoms, SLE</td>
<td>Basal ganglia calcifications, neurologic dysfunction, SLE</td>
<td>Lymphoproliferation (lymphadenopathy and/or splenomegaly), Autoimmune cytopenias, Malignancy</td>
<td>Autoimmune enteropathy, Neonatal diabetes, Thyroiditis, Eczema</td>
<td>Hypoparathyroidism, Adrenal insufficiency (Addison's disease), Mucocutaneous candidiasis</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Systemic</td>
<td>Systemic</td>
<td>Systemic</td>
<td>Systemic, organ-specific</td>
<td>Systemic, organ-specific</td>
<td>Organ-specific</td>
</tr>
<tr>
<td>Autoimmune features</td>
<td>SLE, glomerulonephritis, angioedema, +ANAs, +RNP Abs</td>
<td>SLE, thrombocytopenia, hemolytic anemia, +ANAs</td>
<td>SLE, chilblains, hemolytic anemia, +ANAs</td>
<td>Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, neutropenia)</td>
<td>Enteropathy Type 1 diabetes</td>
<td>Multi-organ disease, +Organ-specific autoAbs, anti-IFN Abs, NALP5 Abs</td>
</tr>
<tr>
<td>Tolerance defect</td>
<td>Impaired clearance of apoptotic material</td>
<td>Activation of Type 1 interferon signaling</td>
<td>Activation of type 1 interferon signaling</td>
<td>Defective lymphocyte apoptosis</td>
<td>Loss of Tregs</td>
<td>Defective deletional tolerance</td>
</tr>
<tr>
<td>Central versus peripheral tolerance mechanism</td>
<td>Peripheral</td>
<td>Peripheral</td>
<td>Peripheral</td>
<td>Peripheral</td>
<td>Peripheral</td>
<td>Central, ?peripheral?</td>
</tr>
<tr>
<td>Innate versus adaptive immune defect</td>
<td>Innate</td>
<td>Innate</td>
<td>Innate</td>
<td>Adaptive</td>
<td>Adaptive</td>
<td>Adaptive</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Susceptibility to encapsulated bacteria</td>
<td>None described</td>
<td>None described</td>
<td>Not generally described</td>
<td>Recurrent infections</td>
<td>Candidiasis</td>
</tr>
</tbody>
</table>
Animal models of autoimmunity

• NOD mouse- model of type 1 diabetes
• NZBxNZW mouse-model of Lupus
• KBxN mouse-model of rheumatoid arthritis
• EAE- induced model of multiple sclerosis whereby disease is induced by injecting proteins of the myelin sheath with adjuvant
• Knockouts that get autoimmunity
Recent work in this model suggests Th17 cells are important!

Figure 13-3 Immunobiology, 6/e. (© Garland Science 2005)
Additional CD4 subsets

IL-12Rβ1 ko
IL-12/23 p40 ko

IL-12: p35/p40 :: IL-12Rβ1/IL-12Rβ2
IL-23: p19/p40 :: IL-12Rβ1/IL-23R
Th17 cells mediate neutrophil inflammation

**Type 1**

Systemic Immunity
- Phagocyte activation
- Opsonizing Ab
- CTL, NK cells

*Antigen Elimination*

**Type 17**

Inflammatory Immunity
- Neutrophils
- Monocytes

*Acute Inflammation*
Figure 13-17  Immunobiology, 6/e. (© Garland Science 2005)

NOD mouse spontaneously gets diabetes
The islets of Langerhans contain several cell types secreting distinct hormones. Each cell expresses different tissue-specific proteins. In insulin-dependent diabetes, an effector T cell recognizes peptides from a β cell-specific protein and kills the β cell. Glucagon and somatostatin are still produced by the β and δ cells, but not insulin can be made.
B7.1/B7.2 KO's get worse diabetes in the NOD background?

Benoit Salomon, Deborah J. Lenschow, Lesley Rhee, Neda Ashourian, Bhagawith Singh, Arlene Sharpe, and Jeffrey A. Bluestone


Figure 1. Increased Incidence and Early Onset of Diabetes in B7-Deficient NOD Mice
Blood glucose levels were checked weekly in B7-deficient (B7−/−, closed circles), B7 heterozygous (B7+/−, dashed line) and B7 wild-type (B7+/+, open circles) females (left) and males (right). Ten to twenty-seven mice were analyzed per group.
Answer is Treg's, need B7's to generate Treg's effectively
Forward genetics to find autoimmune disease genes

Figure 2. Breeding of ENU-Treated Mice to Reveal Recessive Mutations on Wild-Type Genetic Background
G1 mice carrying approximately 100 independent loss-of-function mutations become the founders of independent pedigrees by outcrossing G1 males to wild-type females (1) or intercrossing unrelated mutagenized G1 mice (2). Recessive mutations become homozygous in G3 mice, and these mice are screened for specific immunological phenotypes.

Christopher C. Goodnow, Australia
ARTICLES

A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity

Carola G. Vinuesa¹, Matthew C. Cook², Constanza Angelucci¹, Vicki Athanasopoulos¹, Lixin Rui¹, Kim M. Hill¹, Di Yu¹, Heather Domaschenz¹, Belinda Whittle¹,³, Teresa Lambe⁴, Ian S. Roberts⁵, Richard R. Copley⁶, John I. Bell⁴, Richard J. Cornell⁴ & Christopher C. Goodnow¹,³
ENU screen finds a line with autoantibodies, glomerulonephritis, and splenomegaly.
Mice have increased germinal centers and a defect in a gene (Sanroque) that represses follicular T cells
What triggers autoimmune disease?
Infections and autoimmunity

• Infections trigger autoimmune reactions
  - Clinical prodromes, animal models
  - Autoimmunity develops after infection is eradicated (i.e. the autoimmune disease is precipitated by infection but is not directly caused by the infection)

• Some autoimmune diseases are reduced or prevented by infections
  - Increasing incidence of type 1 diabetes, multiple sclerosis in developed countries; experimental - NOD mice: mechanism unknown
  - The “hygiene hypothesis” (originally proposed to describe effects of infections on asthma)
Mechanisms by which microbes may promote autoimmunity.

A. Self-tolerance (anergy)
   "Resting" tissue APC, T cell, Self-antigen
   Self-tolerance: anergy

B. Induction of costimulators on APCs
   Microbe, Activation of APC, B7, CD28, Self-reactive T cell, Self-antigen, Self-reactive T cell that recognizes microbial peptide, Self-tissue
   Autoimmunity

C. Molecular mimicry
   Microbe, Microbial antigen, Self-reactive T cell that recognizes microbial peptide, Self-tissue
   Autoimmunity
Endocrine factors

• Most autoimmune disease do not occur with equal frequency in males and females. For example Graves' and Hashimoto's are 4-5 times, and SLE 10 times, more common in females while Ankylosing Spondylitis is 3-4 × more frequent in males. These differences are believed to be the result of hormonal influences.

• A second well documented hormonal effect is the marked reduction in disease severity seen in many autoimmune conditions during pregnancy. Rheumatoid arthritis is perhaps the classic example of this effect. In some cases there is also a rapid exacerbation (rebound) after giving birth.
Microbes and autoimmunity?
Treatment

What would be the ideal way to treat autoimmune disease?

Answer: remove only the antigen-specific response
Reality: Unable to remove the antigen-specific response in general

Mainstay of treatment: anti-inflammatories and global immunosuppression if symptoms are severe enough to warrant it
Therapeutic approaches for immune disorders

- CTLA-4.Ig (block costimulation)
- Calcineurin, mTOR inhibitors (inhibit signaling)
- Anti-IL-2R (block cytokine receptor)
- Anti-IL-17A

- TNF, IL-1 antagonists (block cytokines)
- Anti-p40
- Anti-integrin antibodies (block adhesion)

- APC
- TCR
- IL-2
- IL-12, IL-23 (p40)
- IL-17A

- Inflammation
Therapeutics based on the B7:CD28/CTLA-4 family
1. Costimulatory blockade

CTLA-4.Ig (extracellular portion of CTLA-4 fused to Fc portion of IgG) binds to B7, blocks CD28 recognition and T cell activation

CTLA-4.Ig is used for diseases caused by ....?
Therapeutics based on the B7:CD28/CTLA-4 family
1. Costimulatory blockade

CTLA-4.Ig is used for diseases caused by excessive T cell activation -- rheumatoid arthritis, graft rejection; not yet approved for IBD, psoriasis.
Therapeutics based on the B7:CD28/CTLA-4 family
2. Inhibiting the inhibitor

Anti-CTLA-4 antibody blocks CTLA-4 and prevents inhibitory signals

Anti-CTLA-4 antibody is used for ....?
Anti-CTLA-4 antibody is approved for tumor immunotherapy (enhancing immune responses against tumors).
Even more impressive early clinical trial results with anti-PD-1 in cancer patients.
Type 1 Diabetes - A Disease of the Immune System

Type 1 Diabetes is caused by the autoimmune destruction of insulin producing β-cells

T-cell mediated killing of β-cells
Progression in Type 1 Diabetes

- Genetic Predisposition
- Environmental Insult
- %Beta Cell Mass
- AutoAbs
- Abnormal IVGTT
- Clinical Diagnosis
- Honeymoon

Years

- 100
- 75
- 50
- 25
- 10
Checkpoints in the development of autoimmune diabetes

Checkpoint 1  Insulitis

- Starts at weaning: immunological changes related to food uptake and changes in the intestinal flora
- Increased homing of T cells: expression of addressins MadCam and PNAd on pancreatic blood vessel epithelium

Checkpoint 2  Beta cell loss and diabetes

- T cells gain more aggressive effector mechanisms: Th1/Th2 balance, cytokines,
  Expression of Fas Ligand on CTLs
- Loss of protective mechanisms: Protective cytokines, Regulatory cells
- Amplification: Epitope spreading
Anti-CD3 mAb Treatment for Autoimmunity

Monoclonal Antibodies Bind to TCR and the CD3 Complex

ISLETS

Orthoclone OKT® 3 Cytokine Study
Typical First-Dose Reactions

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<thead>
<tr>
<th></th>
<th>IL-2</th>
<th>TNFα</th>
<th>IFNγ</th>
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</thead>
<tbody>
<tr>
<td>Chills</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Headache</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Pyrexia</td>
<td>+</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Diarrhea</td>
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<td>Tachycardia</td>
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<tr>
<td>Hypotension</td>
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<tr>
<td>Bronchospasm</td>
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<tr>
<td>Arthralgia</td>
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Cellular Activation Induced by OKT3 mAb

FcR Non-Binding Anti-CD3 mAb: Multiple Approaches

F(ab)², mutated Fc binding region, chimera with low FcR affinity isotype
Suppression of autoimmunity with anti-CD3

Need to give at disease onset!
Results of Herold anti-CD3 Phase I/II trial in Type 1 Diabetes

Study Protocol
• New onset Type 1 diabetes mellitus in stable metabolic condition
• Within the first 6 weeks since diagnosis
• Age 8 – 35
• Two week single treatment with increasing doses of anti-CD3 mAbs
  $5 \mu g \rightarrow 4 \text{ mg/dose.}$
• 23 treated patients and 23 control subjects undergoing metabolic studies over 2 years

*p=0.003 vs control

**p<0.02 vs control
Autoimmune diseases

• Animal models are revealing pathways of immune regulation and why it fails
• Genetic studies are identifying underlying defects in human diseases
• Analytical methods for human diseases are improving

• Challenges:
  - From genes to pathways (molecular and functional)
  - Using the knowledge to develop therapies