Auto-Immune Diseases: Mechanisms of Immune Dysregulation

Intruder! DESTROY!

Wh-what?!

But I'm one of you!! Don't listen to her lies.

Autoimmune disorders in a nutshell. Beatrice the Biologist.
Objectives:

- Describe fundamental concepts in the development and maturation of immune cells.
- Explain basic mechanisms of central and peripheral immune tolerance at the molecular level.
- Understand the rationale for commonly used therapeutics in auto-immune diseases.
Statement of Disclosure:

I have no actual or potential conflict of interest in relation to this presentation.
Questions:

1. Does the generation of self-reacting lymphocytes always initiate auto-immune diseases?

2. How does the immune system recognize self from non-self?

3. What pathological mechanism(s) result in autoimmune diseases?

4. How are immune regulatory mechanisms exploited for therapeutic purposes?
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1. Does the generation of self-reacting lymphocytes always initiate auto-immune diseases?

NO
Auto-responsive clones (B cells/T cells) are generated in all people independently on whether they will eventually have an auto-immune disease.
T/B Cells are Generated in a Random Gene Recombination Scheme

The random assembly of 51 V, 27 D and 6 J gene segments gives a 8,262 different possible combinations for the heavy chain alone independently of mistakes, shifts and insertions.
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Immune Tolerance
(Central/Peripheral)
Week 0: Inject newborn mouse (strain A) with strain B mouse cells.

Week 6: Give mouse strain B and strain C skin grafts.

Week 7: Graft B survives and graft C is rejected.
Central Selection of T/B cells

Signal Strength

Survival

Death by Neglect

Positive selection

Negative selection

Death
Central and Peripheral Tolerance

B10 Cells: A Functionally Defined Regulatory B Cell Subset

*J Immunol* 2015; 194:1395-1401
Peripheral Tolerance: The “One Shot” Paradigm

Co-stimulatory signal and specific signal
- Activates T cell

Specific signal alone
- T cell becomes anergic

Co-stimulatory signal alone
- No effect on T cell

Figure B.18 The Immune System, 3rd ed. (© Garland Science 2009)
Lack Co-stimulatory signals (CD28)

Anergy and/or Apoptosis
<table>
<thead>
<tr>
<th>APC</th>
<th>T Cell</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD40</td>
<td>CD40-L</td>
<td>+</td>
</tr>
<tr>
<td>PD-1L</td>
<td>PD-1</td>
<td>-</td>
</tr>
<tr>
<td>ICOS-L</td>
<td>ICOS</td>
<td>+</td>
</tr>
<tr>
<td>CD80/86</td>
<td>CTLA4</td>
<td>-</td>
</tr>
<tr>
<td>MHC</td>
<td>TCR</td>
<td>+</td>
</tr>
<tr>
<td>CD80/86</td>
<td>CD28</td>
<td>+</td>
</tr>
<tr>
<td>PD-2L</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>B7-H3</td>
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Venn Diagram: Requirements for the Development of Autoimmune Disease

Focus on Autoimmunity
Nature Immunology, Sept 2001
APC process proteins they “swallowed” and present them on Major Histocompatibility Complex (MHC) II
### TABLE 20-3 MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

<table>
<thead>
<tr>
<th>Protein*</th>
<th>Residue†</th>
<th>Sequence‡</th>
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<tr>
<td>Human cytomegalovirus IE2</td>
<td>79</td>
<td>P D P L G R P D E D</td>
</tr>
<tr>
<td>HLA-DR molecule</td>
<td>60</td>
<td>V T E L G R P D A E</td>
</tr>
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<td>70</td>
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</tr>
<tr>
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<td>T V I K E S R G T K</td>
</tr>
<tr>
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<td>S L H L E S L K D S</td>
</tr>
<tr>
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<td>V Y G L E S L K D L</td>
</tr>
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<td>T K E S L V I S</td>
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<tr>
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<td>764</td>
<td>N K E S L V I S E</td>
</tr>
<tr>
<td>Klebsiella pneumoniae nitrogenase</td>
<td>186</td>
<td>S R Q T D R E D E</td>
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<td>HLA-B27 molecule</td>
<td>70</td>
<td>K A Q T D R E D L</td>
</tr>
<tr>
<td>Adenovirus 12 E1B</td>
<td>384</td>
<td>L R R G M F R P S Q C N</td>
</tr>
<tr>
<td>α-Gliadin</td>
<td>206</td>
<td>L G Q G S F R P S Q Q N</td>
</tr>
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<td>Human immunodeficiency virus p24</td>
<td>160</td>
<td>G V E T T T P S</td>
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<td>L E C I R A L K</td>
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*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.
†Each number indicates the position in the intact protein of the amino-terminal amino acid in the listed sequence.
‡Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

*Source: Adapted from MBA Oldstone, 1987, Cell 50:819.*
# Cross-Reactivity and Molecular Mimicry

## Table 20-3: Molecular Mimicry Between Proteins of Infectious Organisms and Human Host Proteins

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Additional Mechanisms of Autoimmunity

- Release of Sequestered Antigen

  Antibodies in blood can attack Myelin Basic Protein if Blood-Brain barrier is breached.

  Proteolytic cleavage of a matrix protein may unmask an antigen that appears new and foreign to the immune system
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TREATMENT OF AUTOIMMUNE DISEASES

A. Current Therapies
   1. Symptomatic relief
   2. Non-specific inhibition of the immune system
   3. Specific targeting of the immune system

B. Experimental Therapeutic Approaches
   – Desensitization therapy
Treatment Options

NSAIDs/Cox-2 Inhibitors
Methotrexate
Prednisone
Imuran/Azathioprine
Cellcept (Mycophenolate/Mofetil)
Dapsone
Cyclosporine/Tacrolimus
Quinine and related anti-malaria agents
Pentoxifylline/Trental
TNF INHIBITORS

- Enbrel (Etanercept)
- Humira (Adalimumab)
- Erelzi Biosimilar to enbrel (Biologics Price Competition and Innovation Act (BPCI Act).
- Amjevita Adalimumab-atto (psoriasis, Chron’s, UC)
- Cimzia (Certolizumab)
- Remicade (Infliximab)
- Inflectra infliximab-dyyb Chron’s, UC
- Simponi/Simponi Aria (Golimumab) Once every 2 months ankylosing spondylitis
**CYTOKINES**

Actemra (Tocilizumab) **IL6-R (RA)**
Kineret (Anakinra) **IL1-R Antagonist**
Ilaris (Canakinumab) **anti-IL1**
Stelara (Ustekinumab) P40 **IL17-23 (Also ABT-874 (Briakinumab))**
Tildrakizumab p19 Subunit of **IL-23 (Also BI-655066 (Boehringer Ingelheim), Guselkumab (CNTO 1959))**
Cosentyx (Secukinumab), anti **IL17 (Also, Ixekizumab (Eli Lily))**
Brodalumab(AstraZeneca) **IL17 RA**
Simulect (Basiliximab) **anti- IL2**
Zenapax (Daclizumab) (CD25-alpha subunit of **IL2**)

**AND OTHER THERAPEUTIC TARGETS**

Xolair (Omalizumab) inhibits the binding of **IgE** to the high-affinity IgE receptor (FcεRI)
Xeljanz (Tofacitinib) Janus Kinase (JAK) inhibitor
Arava (Leflunomide) dihydroorotate dehydrogenase (DHODH) - de novo synthesis of uridine monophosphate (rUMP)
BENLYSTA® (Belimumab) B-cell activating factor (BAFF)
Tysabri (Natalizumb) **alpha4 integrin**
Odulimimab (LFA-1)
Targeting Co-Stimulation

T Cells

B Cells

Rituxan (Rituximab) CD20
Arzerra (Ofatumumab)
Ocrelizumab (Ocerevus)
Gazyva (Obinutuzumab)

Orencia (Abatacept)
Nulojix (Belatacept)
(αCD28-CD80/86)

Blood 2010 116:3705-3714

Targeting Co-Stimulation

Memory T cell

CD28
CTLA-4
ICOS
TCRα
TCRβ
OX40
CD2
LFA-1

Abatacept/belatacept/CD28 dAbs
Anti-ICOS mAb
Oxelumab
Alefacpet
Efalizumab

CD80
CD86
ICOS-L
PMCH
OX40L
LFA-3
ICAM

APC
1. “A plasmid proinsulin gene for is injected intramuscularly into patients

2. Proinsulin is taken up by migrating APCs that do not present costimulatory factors on their surface.

3. The APCs travel to nearby lymph nodes, where they interact with T cells

4. Without the costimulatory factors, cytotoxic T cells become anergic or undergo apoptosis.”
We all produce self-reactive immunity. Due to various and complex mechanisms, in some of us, it may contribute to pathological processes.

We are at the early stages in a surge of therapeutic innovations to better control deleterious inflammation.
While we don’t fully understand its purpose, self-immunity has a role in maintaining homeostasis.
THANK YOU........

DO YOU HAVE ANY QUESTIONS?