Detection of Transplantation Rejection:
A. Old/Present – Biopsy
B. Future – Cell tracking and functional Imaging by MRI (Magnetic Resonance Imaging)

Lecture 22: Tolerance & Autoimmunity

Tolerance: Fundamental characteristic of a healthy immune system - system is usually unresponsive to antigen, unless there is a threat ("Danger hypothesis")

Central Tolerance:
Usual self-tolerance checkpoints in B and T-cell development (expression of all antigens in thymus by mTEC – AIRE factor).

Peripheral Tolerance:
Anergy: B-cells
- Recognition of self-antigen will result in the presentation of self-peptides on MHC II, poor stimulation of T<sub>H</sub> cells.
- Without strong 2<sup>nd</sup> signal from CD40-CD40L, B-cell becomes anergic.

Anergy: T – cells
- B7-CD28 required for complete T-cell activation – only provided by activated DCs, macrophages, B-cells. APCs only express high levels of B7 during activation, typically associated with the presence of a pathogen:
  - complement receptor on B-cell).
  - LPS + TLR 4 on macrophages,
- Without 2<sup>nd</sup> signal, T-cell becomes anergic

T<sub>REG</sub> cells
- Produced in T-cell development, recognize self-peptides.
- Express CD25 as a cells surface marker and Foxp3 transcription factor.

Immunosuppressive functions:
- Possess the α chain of IL2R, enhanced binding of IL-2 and preventing it from activating other T-cells.
- Secrete TGFβ (transforming growth factor) which inhibits T-cell activation.
- T<sub>REG</sub> cells bind to self-antigen/MHC II complex, interaction of B7-CTLA-4 causes production of cytokines that suppress antigen presentation by APCs.
Immunology

Lecture 22  
November 28, 2016

Immuno-privileged sites: Eye/brain, reproductive organs.

Oral tolerance – Unique environment of gastrointestinal mucosa tissue.
- Low levels of antigen induce the production of $T_{H3}$ cells in the intestinal mucosal (known as adaptor T-regulatory cells or induced T-regs).
- High levels of antigen may become systemic, however presentation by unactivated macrophages leads to anergy of B/T cells, not an acquired immune response.

Autoimmunity:
Activating mechanism:
- Molecular mimicry (MM)
- Release of normally sequestered antigens
- Coincident activation of autoimmune cells by activation.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantigen</th>
<th>Consequence</th>
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<tbody>
<tr>
<td><strong>Cellular Antigens (Type II HS)</strong></td>
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<tr>
<td>Rheumatic fever</td>
<td>Streptococcal cell wall</td>
<td>Scarring of heart valves</td>
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<td>Graves’ disease</td>
<td>TSH receptor</td>
<td>hyperthyroidism</td>
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<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Muscle weakness</td>
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<tr>
<td><strong>Soluble Antigens (Type III HS)</strong></td>
<td>DNA, histones</td>
<td>Glomerulonepritis, vasculitis, arthritis.</td>
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<td><strong>$T_{H3}$ + Macrophages (Type IV HS)</strong></td>
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<tr>
<td>Diabetes – type I</td>
<td>$\beta$-cell antigen</td>
<td>$\beta$-cell destruction</td>
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<tr>
<td>Rheumatoid Arthritis</td>
<td>unknown</td>
<td>Joint inflammation and destruction.</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Myelin basic protein</td>
<td>Degeneration of nervous system</td>
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</tbody>
</table>

Rheumatic Fever:
Antibodies against cell-wall of *Streptococcus pyogenes* cross react with epitopes on heart, joints, kidney.
- Activation of complement and ADCC by NK cells leads to tissue damage and inflammation.
- Response limited because auto antigens don’t activate $T_{H1}$ cells, once the pathogen is gone antibody production drops.

Type I diabetes:
- Insulin produced by $\beta$-cells in the pancreas in response to high blood glucose levels.
- Genetic predisposition for certain alleles of HLA-DQ, one of the many class II human MHC.
- Residue $57\beta$ = Asp, protective, others increase risk.
- Although insulin is expressed by mTEC cells (thymocytes) its binding to non-Asp$57$ HLA-DQ is weak, therefore T-cells that recognize insulin are not killed by self-tolerance selection.
  - $T_{H3}$ cells can become activated by presentation of insulin on proAPC. Secrete IFN\(_\gamma\) which activates macrophages, leading to destruction of insulin producing $\beta$-cell.
  - Antigens released by $\beta$-cells can lead to additional autoimmune (antigen spreading), leading to rapid death of $\beta$-cell due to recognition of other $\beta$-cell antigens.

Why is $57\beta$ = Asp protective? What are the properties of that MHC?