Disclosures: None

I will not be discussing non-FDA approved treatments/indications during my presentation today
Outline

• Basic principles of immunological tolerance and autoimmunity

• Differential roles of CTLA-4 and PD-1 in maintenance of tolerance

• Mechanisms of breakdown of tolerance by checkpoint blockade
Major Effector Cells of the Immune System

- B lymphocyte
- Helper T lymphocyte
- Cytotoxic T lymphocyte (CTL)

Neutralization of microbe, phagocytosis, complement activation
Activation of macrophages
Inflammation
Activation (proliferation and differentiation) of T and B lymphocytes
Killing of infected cell

- Pemphigus
- Myasthenia Gravis
- Graves’ Disease
- AIHA/ITP
- Type I Diabetes
- Polymyositis
- Rheumatoid arthritis
- Inflammatory bowel disease
- Multiple Sclerosis
- Celiac Disease
- Addison’s Disease
- Psoriasis
- Loss of function leads to autoimmunity

Abbas, Lichtman, Pillai; Basic Immunology 4th ed.
Most Autoimmune Diseases are due to Failure of T cell Tolerance

Immunologic Tolerance: unresponsiveness of T cells to self antigens
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>Birdshot chorioretinopathy</td>
<td>A29</td>
<td>&gt; 95</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>DQ6</td>
<td>&gt; 95</td>
<td>&gt; 40</td>
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<tr>
<td>Celiac disease</td>
<td>DQ2 and DQ8</td>
<td>95</td>
<td>30</td>
</tr>
<tr>
<td>Type 1 diabetes</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>
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<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>
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<tr>
<td>Myasthenia gravis</td>
<td>DR3</td>
<td>50</td>
<td>2</td>
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<tr>
<td>Type 1 diabetes</td>
<td>DQ6</td>
<td>&lt; 0.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Figure 13.24 The Immune System, 3rd ed. (© Garland Science 2009)
Central and Peripheral Tolerance

Central Tolerance
- For T cells it occurs in the thymus
- Fate of most self-reactive T cell is death (deletion) and removal from T cell pool
- Some survive as regulatory (suppressor) T cells while others escape to peripheral tissues

Peripheral Tolerance
- Self-reactive T cells are suppressed by regulatory T cells
- CTLA-4 and PD-1, among other molecules play a role in maintaining self-reactive T cells from becoming activated (anergic)

Abbas, Lichtman, Pillai; Basic Immunology 4th ed.
Peripheral tolerance occurs in the absence of CD28 dependent co-stimulation

**Both mechanisms are dependent on CTLA-4**

Abbas, Lichtman, Pillai; Basic Immunology 4th ed.
CTLA-4 inhibits co-stimulation by blocking interaction between CD28 and B7 molecules.
Anti-CTLA-4 can lead to breakdown of peripheral tolerance by restoring co-stimulation

Breakdown of peripheral tolerance leading to activation of self-reactive T cells

Dendritic Cell (Antigen Presenting Cell)

Anti-CTLA-4 (Ipilimumab)

MHC II

TCR

T cell activation

CTLA-4

MHC II

TCR

T cell activation blocked

Mary Nakamura
Regulatory T cells (Tregs) use CTLA-4 to remove B7 molecules from surface of antigen presenting cells to prevent activation of self reactive T cells.

Anti-CTLA-4 (Ipilimumab) may interfere with inhibitory function of Tregs.

Walker, L.; Immunology Letters; 2017; 184:43
Inhibitory receptors provide a second mechanism for maintenance of tolerance.

Abbas, Lichtman, Pillai; Basic Immunology 4th ed.
Interaction of PD-1 with its ligands, PD-L1/PD-L2 inhibits CD28 signaling in T cells

- PD-1 is upregulated on T cells after activation
- PD-L1 is found on both immune and non-immune cells in peripheral tissues
- PD-L2 is mostly found on immune cells in response to inflammatory stimuli
- In contrast, CTLA-4 and its ligands are only found on immune cells
- Mice deficient in PD-1 have delayed development of autoimmune disease compared to CTLA-4 deficient ones

Polymorphisms in CTLA-4 and PD-1 genes have been linked to human autoimmune diseases

<table>
<thead>
<tr>
<th>Autoimmune Disease</th>
<th>Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroiditis, Graves’ disease, Hashimoto’s disease</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Lupus</td>
<td>CTLA-4; PD-1</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>CTLA-4; PD-1</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>CTLA-4</td>
</tr>
</tbody>
</table>

Adapted from Michot JM, et al; European Journal of Cancer; 2016; 54:139
People with CTLA-4 haploinsufficiency develop a spectrum of autoimmune diseases similar to the irAEs observed with ipilimumab.

**CHAI/LATAIE Phenotype**

- Brain infiltrates
- Uveitis
- Autoimmune Thyroiditis
- Psoriasis, vitiligo, and other skin diseases
- Neutropenia
- Hepatitis
- Type I Diabetes
- Autoimmune Arthritis
- Gut infiltrates

**Ipilimumab irAEs**

- Hypophysitis
- Dry mouth
- Uveitis and orbital inflammation
- Hypothyroidism
- Pneumonitis
- Adrenal insufficiency
- Enterocolitis
- Arthralgia
- Rash and vitiligo
- Pancreatitis and auto-immune diabetes

Lo, B. *et al*; *Blood*; 2016; 128:1037

Michot JM, *et al*; *European Journal of Cancer*; 2016; 54:139
Early and late irAEs may occur by distinct mechanisms

**Early and common**
- Mucosal Colitis
- Rash
- Pneumonitis

- Global Regulatory T cell dysfunction
- Activation of Effector T cells (Th\(_{17}\))
- Recruitment of inflammatory cells (neutrophils)

**Late and rare**
- Specific organ Hypophysitis (other adrenal)
- Myocarditis; Neurologic Arthritis; Vitiligo

- Breakdown of organ specific tolerance
- Activation of tumor specific T cells that recognize antigen shared between tumor and healthy tissue: vitiligo, myocarditis
- Activation of tissue specific anergic T cells that recognize antigen distinct from the tumor
- T cell or antibody mediated tissue destruction
Summary: CTLA-4 and PD-1 are important in maintenance of peripheral immune tolerance

• CTLA-4 expression on effector and regulatory T cells prevents co-stimulation through CD28 and maintains T cell anergy and peripheral tolerance
• Activation of PD-1 on activated T cells by its ligands renders them non-functional
• PD-1 activates regulatory T cells to maintain peripheral tolerance
• Humans with CTLA-4 haploinsufficiency develop a spectrum of autoimmune manifestations similar to irAEs seen after treatment with Ipilimumab