TODAY

Immunological Tolerance, Chapter 18
Autoimmunity, Chapter 19
Note: “Peripheral” vs. “Central” Tolerance, anatomical distinction...
Central Problem of Tolerance:

Random generation of diversity is **dangerous**.

How to deal with self-reactive receptors??
Tolerance in dizygotic cattle twins
Owen, 1942

Shared placenta, exchange of hemopoietic stem cells
Stable chimeras
No formation of isoantibodies
No rejection of tissue grafts

Human dizygotic twins, unlike cattle, do not normally share a common placenta. However...

- **Sex-discordant twins**
- **Monochorionic, shared fetal circulation**
- **Blood chimerism (many allelic DNA markers)**
- **Product of in vitro fertilization (relevant?)**

*These siblings should display the same mutual tolerance shown by Owen’s cattle twin chimeras – but not reported.*
Hypothesis: Tolerance develops to antigens present during development of immune system

Medawar experiments - Induction of tolerance to skin grafts can be induced by inoculation of F1 spleen cells into parental inbred newborn mice.

Burnet, “Clonal Selection” hypothesis – Clonal deletion of self-reactive cells occurs during the development of immunocompetent cells.
Three mechanisms for maintenance of tolerance

* Clonal deletion
  Suppression
  Receptor blockade
Clonal Deletion of Self-Reactive AFCPs

Pre-B-cell

Immature B-cell

Mature B-cell

No membrane Ig

Membrane Ig

Random receptor

Survives

Dies

Self-reactive

Not self-reactive
T-Cell diversity poses a special problem

T-Cells *require* the ability to recognize self-MHC — how to prevent this from becoming autoreactive??

*Positive & Negative Selection during intrathymic development*
Intrathymic T-cell maturation: Two ways to die

Thymic T-Cell Education: Positive & Negative Selection

TcRs are almost autoreactive; they must not undergo somatic mutation…
Experimental Model of Clonal Deletion: Cytoxan-Induced Tolerance in Mice

• Antigen, followed 1-2 days later by cytoxan
• Proliferating cells are selectively killed
• Short-term tolerance

(remember Mishell/Dutton $^3$HTdR experiments)

...in Humans? Not yet.
Three mechanisms for maintenance of tolerance

Clonal deletion
* Suppression
Receptor blockade
Prediction: If tolerance is maintained by clonal deletion, then the tolerant state should not be transferable.
Clonal deletion cannot account for all models of tolerance

Transfer of tolerance to H-Y antigen

Must hypothesize active “suppression”, T_{reg} cells

Weissman, Transpl.15:265, 1973

- Mouse skin graft model
- Induce tolerance to allogeneic grafts
- Transfer tolerance with tolerated skin grafts
- *Grafts are colonized by CD4+ regulatory T-cells which can emigrate in a new recipient and establish a permanent state of tolerance*

“It has long been observed that multiple blood transfusions prior to grafting increase the survival of human kidney transplants. Recent findings reviewed in this publication suggest that this effect may be due to the presence of CD4+ suppressor cells in the transfusions.”

[& Waanders 2005, helps to have at least one HLA allele in common (for presentation?)]
Three mechanisms for maintenance of tolerance

Clonal deletion
Suppression
* Receptor blockade
Ag-presentation: (Ag/ClassII + costimulation)

T/B Cooperation in Primary Response

Antigen phagocytosed by macrophage

Antigen "processing"

T-cell help: IL-4

Differentiation to AFC

B_{(V)}-CELL

T_{H(V)}-CELL

1

2

("C"=carrier determinant, "H"=hapten determinant)

Antigen bound by Ig receptors ...cross-linking

"Antigen PRESENTATION BY MACROPHAGE TO T_{H(V)}-CELL"
B-CELL TOLERANCE BY RECEPTOR BLOCKADE

Excess of soluble antigen, receptor occupancy without cross-linking.

No Signal 1

Little Class II Ag-presentation

Tolerance

B-CELL TOLERANCE BY RECEPTOR BLOCKADE
Ag excess – no cross-linking
**B-CELL TOLERANCE BY RECEPTOR BLOCKADE**

- Excess of soluble antigen, receptor occupancy without cross-linking.
  - No Signal 1
- Little Class II Ag-presentation
  - No Signal 2 (…for $B_M$)

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**B-CELL TOLERANCE**

- **Tolerance**

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**Significant mechanism for maintaining tolerance to serum proteins (soluble and abundant)**
Three mechanisms for maintenance of tolerance

Clonal deletion

Suppression

Receptor blockade

“CENTRAL” TOLERANCE

“PERIPHERAL” TOLERANCE
Immune Reactions: 
Balance between Immunity and Tolerance

Tolerance $\xrightarrow{T_{\text{reg}}}$ Antigenic Challenge $\xrightarrow{T_{\text{H}}}$ Immunity
## Immunity vs. Tolerance

<table>
<thead>
<tr>
<th>Influencing Factor</th>
<th>To Induce Immunity:</th>
<th>To Induce Tolerance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of antigen</td>
<td>Aggregated, insoluble</td>
<td>Monomeric, soluble</td>
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<tr>
<td>Dose of antigen</td>
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<td>Very high or low doses</td>
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<td>Route of immunization</td>
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<tr>
<td>Adjuvant</td>
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