Allograft Tolerance

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The Dilemma of Transplantation

‘Disease 1’
End-Stage Organ / Tissue Failure

Tx with Transplantation

‘Disease 2’
• Drug-Related Toxicity
• Chronic Graft Injury

Tx with management

Tx with **immune tolerance**
Ongoing Goal: Tolerance Induction

• How does allograft tolerance occur?

• What prevents this from happening?
A Definition of Allograft Tolerance

A *donor-specific* response to the transplant that results in indefinite allograft survival
T cell activation is *more* than just ‘on’ versus ‘off’
‘Plasticity’:
A hallmark feature of the immune system
Allograft

- No Response (‘ignorance’)
- Destructive Immunity (Rejection)
- Non-destructive Reactivity (Tolerance)
  - Deletion/Inactivation
  - Active Regulation
Tolerance might be can be a ‘default’ consequence of antigen recognition:

Accidental lesson from studying allograft immunogenicity

- Lafferty et al. Science 188:4185, 1975

Kevin J. Lafferty, PhD
APC-Depleted Transplant
95% O₂ + 5% CO₂
In Vitro Depletion of Donor-Type APCs Prevents Islet Allograft Rejection

Adoptive Transfer of Tolerance from Recipients of APC-depleted Islet Allografts

Donor-Type or 3rd Party Islets

Immune-Deficient (SCID) Host

CD4+ or CD8+ spleen cells from ‘tolerant’ mice

CD4+ or CD8+ spleen cells from naïve mice
CD4-Dependent Tolerance to APC-Depleted Islet Allografts


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**Work in Progress: Varied Phenotypes of 'Regulatory' T cells**

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Application or system tested</th>
<th>Mechanism <em>in vitro</em></th>
<th>Mechanism <em>in vivo</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;Reg&lt;/sub&gt; cells</td>
<td>Mouse autoimmunity, GVHD and transplantation Human <em>in vitro</em></td>
<td>Cell–cell contact, CTLA4&lt;sup&gt;<em>&lt;/sup&gt;, IL-10&lt;sup&gt;</em>&lt;/sup&gt;, TGF-β&lt;sup&gt;*&lt;/sup&gt;</td>
<td>CTLA4, IL-10, TGF-β</td>
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<tr>
<td>Expanded T&lt;sub&gt;Reg&lt;/sub&gt; cells</td>
<td>Mouse and human diabetes and GVHD</td>
<td>Cell–cell contact, TGF-β</td>
<td>TGF-β</td>
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<tr>
<td>T&lt;sub&gt;n1&lt;/sub&gt; cells</td>
<td>Mouse colitis Human <em>in vitro</em></td>
<td>Cell–cell contact&lt;sup&gt;?&lt;/sup&gt;, IL-10 Cell–cell contact&lt;sup&gt;*&lt;/sup&gt;, IL-10</td>
<td>IL-10 ND</td>
</tr>
<tr>
<td>T&lt;sub&gt;H3&lt;/sub&gt; cells</td>
<td>Mouse oral tolerance Mouse transplantation</td>
<td>Cell–cell contact, TGF-β or IL-10 Cell–cell contact</td>
<td>TGF-β or IL-10 IL-4, IL-10</td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt; T cells</td>
<td>Human transplantation</td>
<td>Cell–cell contact, ILT3, ILT4</td>
<td>ILT3, ILT4</td>
</tr>
</tbody>
</table>

*Evidence in some, but not all, settings. <sup>*</sup>Not tested. CTLA4, cytotoxic T-lymphocyte antigen 4; GVHD, graft-versus-host disease; IL, interleukin; ILT, immu
like transcript; ND, not determined; TGF-β, transforming growth factor-β; T<sub>H3</sub>, T helper 3; T<sub>n1</sub>, T regulatory 1; T<sub>Reg</sub>, CD4<sup>+</sup>CD25<sup>+</sup> regulatory T.
Key Points

- The Allograft *is* the ‘tolerogen’ (*no* additional treatment)

- *Active* tolerance can be a natural consequence of alloantigen exposure
**Proposition:** Context of APC : T cell interaction dictates T cell fate towards immunity versus tolerance

- **Limited APC Stimulation / Regulatory T cells**
  - **Regulatory Phenotype**

- **APC Stimulated by Memory T cells and/or inflammation**
  - **Effector Phenotype**
We can get spectacular results in Animal models:
Efficacy of Anti-CD154 + Anti-LFA-1 Combination Therapy
(BALB/c → C57Bl/6)
Problems with small animal models

• We tend to transplant recipients without pre-existing diseases

• We tend to use ‘favorable’ donor-recipient strain combinations

• We normally use non-brain-dead donors with little ischemia time

• We tend to transplant genetically simple recipients without an immunological ‘history’
Focus on Two Issues

- The role 'memory' T cells in tolerance inhibition
- The role of pathogens and innate immune signals in tolerance inhibition
Pre-Existing Memory Cells
Peripheral Tolerance Achieved by Targeting Key Immuno-Receptors
Long-Term Islet Allograft Survival in Naïve, Young Recipients with anti-CD154 Treatment

Anti-CD154 mcAb
d -2,2,7,9

Michelle Nelsen (unpublished)
Prior Stimulation with Donor Cells Prior to Transplantation (d-60) Completely Abrogates Allograft Survival with anti-CD154 Treatment (MR-1 Ab)

Michelle Nelsen (unpublished)
Heterologous immunity provides a potent barrier to transplantation tolerance


Repeated Infections Decrease the Efficacy of Tolerance-Promoting Therapy

Prediction: By chance, pathogen-specific T cell repertoire contains a subset of alloreactive T cells.

‘Heterologous’ alloreactive T cell
Infection / Innate Stimulation
Toll Like Receptors (TLRs): ‘Sensors’ of Pathogen Associated Molecular Patterns (PAMPs)
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- Activate APC
- Induce Inflammation
- Cytokines/Chemokines
‘Danger’ Associated Molecular Patterns (DAMPs):
*Endogenous* signals of tissue injury / distress
Infection that breaks *existing* tolerance: Antigen specific or non-specific?

Infection with the Intracellular Bacterium, *Listeria monocytogenes*, Overrides Established Tolerance in a Mouse Cardiac Allograft Model

T. Wang^a^, E. B. Ahmed^a^, L. Chen^b^, J. Xu^a^, J. Tao^a^,
C.-R. Wang^c^, M.-L. Alegre^b^ and A. S. Chong^a^,*

*Am. J. Transplant 10:1524, 2010*
Listeria infection breaks tolerance and this requires MyD88-dependent TLR signaling

Combined IL-6 + IFN-β treatment can substitute for actual pathogen infection to break tolerance

Do memory cells or innate stimulation have a greater impact on disrupting tolerance?
Ross Kedl immunization model:
[50 ug αCD40 + 50 ug Poly I:C] plus antigen (Ovalbumin)
Mice with extensive immunization (memory cell generation) can *still* be tolerized!

*Michelle Nelsen (unpublished)*

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**Figure: Graft survival**

- Memory + anti-CD154
- Naive' + anti-CD154 (n=11)
- Adjuvant' + anti-CD154 (n=9)
- Ovalbumin'/Adjuvant' + anti-CD154 (n=16)
- Untreated young and naive (n=9)

*days post-transplantation*
However, innate stimulation with the adjuvant alone completely disrupts tolerance

Michelle Nelsen (unpublished)
**Conclusion:** Both antigen-specific T cells and innate signals can drive the response towards immunity rather than tolerance.
Implications for Transplant Tolerance

- It may be difficult (or even undesirable) to globally block/deplete memory T cells

- However, targeting rate-limiting pathways of APC activation (e.g. TLRs, IL-6, IFNα/β, IL-1) may have therapeutic potential
Strategies for Clinical Transplant Tolerance

- Progress towards increasingly ‘tolerance friendly’ agents

- Target features of immune memory and/or inflammation that inhibit tolerance
Conundrum

Because tolerance is the *specific* outcome of an *active* response to antigens, it can be *blocked*!
Cytokines with ‘Split Personalities’

IL-2

T Cell Proliferation

Increased AICD (Activation Induced Cell Death)

Enhance Tregs
Anti-CD25 (IL-2Ra) prevents prolonged skin allograft survival following donor-specific transfusion (DST) + anti-CD154

From: S Banuelos et al. Transplantation 78:660, 2004
Conventional immunesuppressive agents that can inhibit anti-CD154 induced kidney allograft survival in primates

Many Candidate Therapeutics Under-utilized in Transplant

Nat Rev Nephrol doi:10.1038/nrneph.2009.70
B lymphocyte Targeting: A Major Opportunity?

(1) = Rituximab (anti-CD20)
(2) = Epratuzumab (anti-CD22)
(3) = Abetimus (anti-BCR)
(4) = CTLA4-Ig / Belatacept (B7 blockade)
(5) = IDEC 131 (anti-CD154)
(6) Belimumab (anti-Blyss)

Are we approaching a ‘tipping’ point towards tolerance in clinical transplantation?
Collaborators

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