Induction of persistent tolerance to lung transplants by IL-2 complex-stimulated regulatory T cells in vivo

Walter Brendel Award Session

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Acute cellular rejection (ACR) after lung transplantation (Tx)

Incidence of ACR

Pathology of ACR

Scientific Registry of Transplant Recipients, USA, 2014
Course of rejection after mouse lung Tx

days after transplantation

BALB/c^{H-2d} → C57BL/6^{H-2b}
Activation of immune cells after lung Tx
Stimulation of T cells by IL-2 complexes (cx) for Treg proliferation

High affinity IL-2Rα + AB bind selectively on CD25+ T cells

High-affinity IL-2R

Intermediate-affinity IL-2R

IL-2

IL-2

CD25

β

CD122

CD132

Strong signal for Tregs

Weak signal for CD8+ T cells
NK cells
Experimental set up – 3 times of IL-2cx treatment before Tx

C57BL/6

BALB/c

IL-2cx

Allo Tx

Harvest

Day -4 -3 -2 -1 0

at day 5, 15, 28 and 56
IL-2cx treated recipients showed macroscopic normal appearance.
Histologically (H&E) preserved grafts in IL-2cx-treated recipients
Lymphocytes infiltrated less in IL-2cx treated recipients

AR score

* * * * * p<0.05

* p<0.05
IL-2cx – treated recipients showed better compliance and improved PaO₂

**day 5**

**Lung compliance of allograft**

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<tr>
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<th>Control</th>
<th>IL-2cx</th>
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<td>(µl/cmH₂O)</td>
<td>2</td>
<td>6</td>
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**PaO₂ from allograft**

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<td>(mmHg)</td>
<td>100</td>
<td>400</td>
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* p<0.05
**FoXP3+CD4+CD25+ cells in IL-2 cx treated allografts**

**Day 5**

Allograft

**Control**

**IL-2cx**

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<thead>
<tr>
<th>Day</th>
<th>Control</th>
<th>IL-2cx</th>
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<td>5</td>
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<td><img src="image2.png" alt="Image" /></td>
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* p<0.05
Naïve right lungs had increased numbers of Foxp3+ cells early after Tx

Day 5

Naïve right lung

Control

IL-2cx

* p<0.05
Spleens had increased numbers of Foxp3⁺ cells early after Tx

Day 5

Spleen

Control

IL-2cx

* p<0.05
Loss of function experiments

B6-Foxp3^{DTR}

B6-Foxp3^{DTR} BALB/c

IL-2cx Allo Tx

Day -4 -3 -2 -1 0 1 2 3 14 15

Diphtheria toxin (DT)

Harvest
IL-2cx-treated B6-Foxp3\textsuperscript{DTR} receiving diphterie toxin develop severe ACR

B6-Foxp3\textsuperscript{DTR} allograft on day 15
Summary & Conclusion

• IL-2 cx treatment before lung transplantation induces long term acceptance, histologically and functionally

• The presence of Tregs within allografts suggests that this cell population is responsible for allograft acceptance

• Preliminary data from loss of function experiments confirms the tolerogenic role of Tregs

• These data may have implications for immune protocols for Treg modulation in human lung transplantation
Thanks to

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CD4+ Foxp3+ cells were increased in IL-2cx allografts