Mechanisms of Primary Graft Dysfunction following Lung Transplantation

Ankit Bharat MD FACS
Surgical Director, Lung Transplantation
PRIMARY GRAFT DYSFUNCTION

- Incidence >50-70%
- Occurs within first 24 hours following transplant
- Characterized by respiratory failure
- Leading cause of short-term mortality
- Predominant cause of chronic lung allograft rejection
“Garden-variety” ischemia-reperfusion injury

Complementary role in neutrophil trafficking

Bharat & Kreisel, Annals Thor Surg, 2018
Autoantibody-mediated rejection mimicking PGD

Pre-existing Autoimmunity & Autoantibodies

Teff

Col V KAT
(Sequestered lung-restricted antigens in native lungs)

CHRONIC INFLAMMATION

PGD

Bharat & Kreisel, Annals Thor Surg, 2018
NEUTROPHIL INFILTRATION MEDIATES PGD

PERFUSED HUMAN DONOR LUNGS CONTAIN MONOCYTES

Bharat et al, AJRCMB, Jan 2016

Zhikun et al, SCIENCE TM
Demonstration of non-classical nonocytes in the intravascular space of donor lungs.
Depletion of donor NCM abrogates neutrophil recruitment and ameliorates PGD
Monocyte subsets in mice and humans

Classical Monocyte (CM)

$\text{CCR2}^{+}\text{Ly6C}^{\text{high}}\text{CX}_{3}\text{CR1}^{\text{low}}$

Nonclassical Monocyte (NCM)

$\text{Ly6C}^{\text{low}}\text{CX}_{3}\text{CR1}^{\text{High}}\text{CCR2}^{-}$
Depletion of recipient’s classical monocytes impairs neutrophil extravasation
Spleen serves as a reservoir for inflammatory host-derived classical monocytes

Gas exchange

CM/mg lung

Extravasated neutrophils (%)

Pao2 (mmHg)
IL-1β production by host classical monocyte is necessary for neutrophil extravasation
Donor NCM initiate PGD

• Strategies to deplete NCM in donor lung
  ? Role of EVLP

• NCM damage-associated molecular patterns (DAMPs)
  - ? Reduce allograft tissue ischemia
EVLP for marginal donor lungs

<table>
<thead>
<tr>
<th>End Point</th>
<th>EVLP Lungs (N=20)</th>
<th>Control Lungs (N=116)</th>
<th>Absolute Difference†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donors without a Heartbeat (N=9)</td>
<td>Brain-Dead Donors (N=11)</td>
<td>Total (N=20)</td>
<td>percentage points (95% CI)</td>
</tr>
<tr>
<td>Primary end points§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 72 hr (%)</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at ICU arrival (%)</td>
<td>33</td>
<td>18</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 24 hr (%)</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 48 hr (%)</td>
<td>33</td>
<td>27</td>
<td>30</td>
<td>35</td>
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<tr>
<td>ECMO (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>PaO₂/FiO₂ on arrival in ICU (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>420</td>
<td>423</td>
<td>422</td>
<td>372</td>
</tr>
<tr>
<td>Range</td>
<td>85–518</td>
<td>86–538</td>
<td>85–538</td>
<td>49–591</td>
</tr>
<tr>
<td>Mechanical ventilation after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Range</td>
<td>1–27</td>
<td>1–101</td>
<td>1–101</td>
<td>1–43</td>
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<tr>
<td>ICU stay after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Range</td>
<td>1–34</td>
<td>1–101</td>
<td>1–101</td>
<td>1–103</td>
</tr>
<tr>
<td>Hospital stay after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>19</td>
<td>34</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Range</td>
<td>7–54</td>
<td>11–101</td>
<td>7–101</td>
<td>9–156</td>
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<tr>
<td>Airway complications (%)¶</td>
<td>11</td>
<td>0</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Mortality at 30 days (%)</td>
<td>22</td>
<td>0</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Cypel, NEJM, 2011
Increased levels of NCM in donor lungs from TBI or ECD donors

Fernandez et al, Under review
Donor NCM are mobilized during EVLP

Stone et al, JHLT, 2014
Increased allograft endothelial cell apoptosis with VA ECMO compared to VV ECMO

P<0.001
Nonclassical monocytes rapidly phagocytose apoptotic endothelial cells \textit{in vitro}

Murine NCM

Normal endothelial culture

CMP-induced apoptosis

Human NCM

Cell Tracker Green

Cell Tracker Red

91% 9%

81% 19%
Reducing lung allograft ischemia during PGD

Bharat et al, JAMA Cardiology, 2016
Acknowledgments

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