Emphysema Induces Lung-Specific Autoantibodies that Exacerbate Ischemia Reperfusion Injury Post-Lung Transplantation


Medical University of South Carolina
Charleston, SC
## Adult Lung Transplants
### Indications (Transplants: January 1995 – June 2015)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Detailed diagnosis</th>
<th>N (%) (N=36,237)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COPD</strong></td>
<td>COPD/EMPHYSEMA</td>
<td>10,462 (28.9%)</td>
</tr>
<tr>
<td></td>
<td>OTHER SPECIFY</td>
<td>1 (&lt;0.05%)</td>
</tr>
<tr>
<td><strong>AIATD</strong></td>
<td>ALPHA - 1 - ANTITRYPSIN DEFICIENCY</td>
<td>1,350 (3.7%)</td>
</tr>
<tr>
<td><strong>IIP</strong></td>
<td>DESQUAMATIVE INTERSTITIAL PNEUMONITIS (DIP)</td>
<td>11 (&lt;0.05%)</td>
</tr>
<tr>
<td></td>
<td>IIP: ACUTE INTERSTITIAL PNEUMONIA</td>
<td>2 (&lt;0.05%)</td>
</tr>
<tr>
<td></td>
<td>IIP: BOOP/COP</td>
<td>50 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>IIP: DESQUAMATIVE INTERSTITIAL PNEUMONIA</td>
<td>10 (&lt;0.05%)</td>
</tr>
<tr>
<td></td>
<td>IIP: IDIOPATHIC PULMONARY FIBROSIS (IPF)</td>
<td>9,655 (26.6%)</td>
</tr>
<tr>
<td></td>
<td>IIP: LYMPHOCYTIC INTERSTITIAL PNEUMONIA (LIP)</td>
<td>11 (&lt;0.05%)</td>
</tr>
<tr>
<td></td>
<td>IIP: NONSPECIFIC INTERSTITIAL PNEUMONIA</td>
<td>189 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>IIP: RESPIRATORY BRONCHIOLITIS</td>
<td>2 (&lt;0.05%)</td>
</tr>
<tr>
<td></td>
<td>USUAL INTERSTITIAL PNEUMONITIS</td>
<td>106 (0.3%)</td>
</tr>
<tr>
<td><strong>ILD-not IIP</strong></td>
<td>ALVEOLAR PROTEINOSIS</td>
<td>18 (&lt;0.05%)</td>
</tr>
<tr>
<td></td>
<td>AMYLOIDOSIS</td>
<td>3 (&lt;0.05%)</td>
</tr>
</tbody>
</table>
Adult Lung Transplants
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 – June 2014)

Kaplan-Meier Survival by Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1ATD (N=3,004)</td>
<td>6.7</td>
</tr>
<tr>
<td>CF (N=7,815)</td>
<td>8.9</td>
</tr>
<tr>
<td>COPD (N=16,045)</td>
<td>5.6</td>
</tr>
<tr>
<td>IIP (N=11,609)</td>
<td>4.8</td>
</tr>
<tr>
<td>ILD-not IIP (N=2,356)</td>
<td>6.1</td>
</tr>
</tbody>
</table>

All pair-wise comparisons were significant at p < 0.05 except A1ATD vs. ILD-non IIP and COPD vs. ILD-non IIP.
Adult Lung Transplants
Kaplan-Meier Survival by Diagnosis Conditional on Survival to 3 Months  (Transplants: January 1990 – June 2014)

Median survival (years):
A1ATD: 7.9
CF: 10.3
COPD: 6.3
IIP: 5.9
ILD-not IIP: 7.1

All pair-wise comparisons were significant at p < 0.05 except A1ATD vs. ILD-non IIP; COPD vs. IIP and COPD vs. ILD-non IIP
Medan survival (years):
- A1ATD: 8.9
- CF: 11.7
- COPD: 7.1
- IIP: 7.0
- IIP-not IIP: 8.0

All pair-wise comparisons were significant at p < 0.05 except:
- A1ATD vs. IIP-not IIP
- COPD vs. IIP
• Recognition of antibody mediated injury in LTx is on the rise

• Pre-transplant autoantibodies are associated with worse PGD.\(^1\)
  • 88% vs 54%

• Ab depletion in patients with DSA post-LTx lowers the risk for chronic rejection\(^3\)
  • But not effective for all patients

• Where do COPD fit in?

Tiriveedhi et al. JHLT 2013
Witt et al. JHLT 2013
Hachem et al. JHLT 2010
AUTOANTIBODIES IN COPD

• Increase in B cell follicular formations as disease progresses
  Brussells et al. Lancet. 2011 Sep 10;378(9795):1015-26

• Increase autoantibodies following chronic smoke exposure
  • Epithelial cells, endothelial cells, extracellular matrix proteins, modified proteins
    Brandsma et al. BMC Pulmonary Medicine 2010, 10:64
    Lee et. al. Nat Med. 2007 May;13(5):567-9
    Greene e.t.al Am J Respir Crit Care Med. 2010 Jan 1;181(1):31-5
ANTIBODIES IN EMPHYSEMA

- Collagen I
- Elastin
- Decorin
- Rheumatoid factor (RF)
- Cyclic citrullinated peptides (CCPs)
- HSP70

Brandsma et al. BMC Pulmonary Medicine 2010
NON-HLA AUTOANTIBODIES IN LTx

• Abs against Non-HLA self Antigens implicated in worse short- and long-term outcomes
  • Development has largely been noted to occur post-transplantation

• K-alpha Tubulin
• Collagen V
• Collagen I

Tiriveedhi et al. JHLT 2013
DO COPD-RELATED AUTOANTIBODIES HAVE SIGNIFICANCE FOR LTx?
EMPHYSEMA MOUSE MODEL

- Cigarette smoke exposure
  - 5 hours a day
  - 5 days a week
  - 6 months
ELASTIN AND COLLAGEN AUTOREACTIVE ABS EXIST IN MOUSE MODEL AND CORRELATE WITH SMOKE EXPOSURE

Serum Ab Elisa to self extracellular matrix proteins

ELASTIN AND COLLAGEN AUTOREACTIVE ABS EXIST IN MOUSE MODEL AND CORRELATE WITH SMOKE EXPOSURE
CS-MODIFIED ELASTIN INDUCES IgG RESPONSE OF COMPLEMENT FIXING SUBTYPES
DOES PRE-EXISTING AUTO-REACTIVITY IMPACT POST TRANSPLANT OUTCOMES?
TRANSPLANT MODEL

- Allogeneic Balb/c \( \rightarrow \) C57Bl/6
- C57Bl/6 recipients
- CS exposed 6 months
- NO CS exposure post-LTx
- All age matched
- Ischemia reperfusion – 48 hrs

Smoking schematic for the dumb people to easily understand.
RECIPIENT CS EXPOSURE EXACERBATES IRI

NS CONTROL

CS RECIPIENT
RECIPIENT CS EXPOSURE EXACERBATES IRI

Cumulative Score (0-12)

##p<0.001. n=5

NS

CS
COMPLEMENT DEPOSITION AND IgM/IgG SIGNIFICANTLY INCREASED IN CS VS NS

**IgM**
- NS: [Bar graph]
- CS: [Bar graph]

**IgG**
- NS: [Bar graph]
- CS: [Bar graph]

**C3d**
- NS: [Bar graph]
- CS: [Bar graph]

**Co-Localization**
- [Image with markers]

**Legend**
- DAPI
- C3d-488
- IgM-555
- Co-Localization

**n=5**
SYNGENEIC RAG-/- TRANSPLANTS

Recipients reconstituted with serum from NS or CS mice immediately prior to transplant.

Analyzed 6hrs post-transplant.

- B6.Rag1-B6
- B6.Rag1-B6.Rag1
- +NS serum
- +CS serum

Cumulative Histology Score 0-12

- B6
- B6.Rag1
- B6.Rag1+NS
- B6.Rag1+CS
- B6.Rag1
- CS-Ig Depleted

Images show histological analysis:

- Rag1+ CS
- Rag1+ CS-Ig Depleted
ANTIBODY DEPOSITION IN CS-RECONSTITUTED RAG LTx IS SIGNIFICANTLY INCREASED
CONCLUSIONS

• Recipient autoreactivity primes for IRI

• CS exposure induces the development of lung specific autoantibodies that can exacerbate IRI and even drive IRI in the absence of alloimmunity

• Complement-fixing subtypes of antibodies are upregulated and may represent an appropriate therapeutic target

• Recipient CS exposure associated with worsened acute rejection
  • Implications for current LTx research and the animals models of LTx presently employed