Antoine Toubert | Thymic function in the transplant setting

Thymic function in human allogeneic HSCT

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Squaring the circle...towards GvL, tolerance and immune recovery

Conditioning

Donor
Stem cell source
Dose, administration
Manipulation (TCD)...

Recipient
Disease,
HLA and genetics,
Age,
Immune status...

Differentiation
and maturation
of HSC and progenitors in an allogeneic environment

GvHD and IS treatments
**T-cell reconstitution in HSCT: it's not just about numbers**

- **Donor cells**
  - HSCs
  - Precursor T cells
  - Memory T cells

- **Post-graft T-cell Reconstitution**
  - Naive T-cells
    - Full Repertoire
    - Response to infection
  - Memory T cells
    - Skewed repertoire
    - Limited response to infections

**Thymus and T-cell differentiation**
Thymic function assessment: the “TREC” assay


T-cell receptor excision circles (TREC) Assay

Quantification of sjTREC Using real-time PCR
Thymic function in human allogeneic HSCT

- Impact of recipient pretransplant thymic function on HSCT outcome
  - How acute GVHD impacts thymic function?
  - Thymic function and leukemic relapse in haploidentical HSCT

Pretransplant recipient thymic function and HSCT outcome in adults

- Thymic function decreases with age (25 years \textsuperscript{+/-} 5 years) but is highly variable among healthy individuals

- Could an impaired thymic function in recipients pretransplant be a risk factor for developing GVHD independently of age?

\textit{Clave et al., Blood 2005}
Pretransplant recipient thymic function matters...

102 HLA-genoidentical HSCT patients (no TCD, no RIC)

Multivariate analysis
(age, D/R CMV serology, ABO, sex mm, disease status)
- survival $p = 0.002$ HR = 6.6
- cGvH $p = 0.011$ HR = 2.2
- CMV $p = 0.06$ HR = 2

* Prognostic value of thymic function in addition to age
  ➢ Identification of patients at risk
  ➢ Close monitoring of GVHD and infections
* Rate of thymic-dependent T cell reconstitution is function of thymic function before allo-HSCT in pediatric patients
  (Chen et al Blood 2005; Olkinuora et al., BMT 2007)

Clave et al., Blood 2005

Thymic attack by alloreactive T cells

Weinberg, Blood 2007
Hauri-Hohl et al., Blood 2007
Thymus is a GVHD target

- How is thymic function affected by acute GVHD?

- Could we precise mechanisms of thymic dysfunction during acute GVHD?

Clave et al., Blood 2009

Acute GvHD delays the naïve CD4 T-cell reconstitution

Naïve CD4 but not CD8 are decreased in case of aGVHD

\* P < 0.05
Acute GvHD delays the recovery of thymic output

- The decrease of sjTREC is not due to the proliferation of memory T cells

Acute GvHD impacts thymic function is reversible in young adult patients

- Thymus is affected by acute GVHD in young patients (<25 yrs.) but this is reversible at 1 yr. post-transplant
Age and acute GvHD have an independent impact on thymic function

Univariate and multivariate analysis of factors influencing sjTREC reconstitution after HSCT

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>N</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before 3 6 12</td>
<td>Before 3 6 12</td>
</tr>
<tr>
<td>aGVHD: 0 vs 1234</td>
<td>25/68</td>
<td>- - .019 .009</td>
<td>.049 .288</td>
</tr>
<tr>
<td>cGVHD: no vs yes</td>
<td>40/40</td>
<td>- .006 - .001</td>
<td>.064</td>
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<tr>
<td>Age: &lt; 25yrs vs ≥25yrs</td>
<td>31/62</td>
<td>.015 .048 .016 &lt;.001</td>
<td>.300 .278 .006 .022</td>
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<tr>
<td>Stem Cell Source BM vs PB</td>
<td>56/37</td>
<td>.004 - .044</td>
<td>.174 .487</td>
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<td>TBI: yes vs no</td>
<td>46/40</td>
<td>- - -</td>
<td>-</td>
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<tr>
<td>Myeloablative conditioning (yes vs no)</td>
<td>79/14</td>
<td>- - -</td>
<td>-</td>
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<tr>
<td>Underlying disease (malignant vs not)</td>
<td>81/12</td>
<td>&lt;.001 - -</td>
<td>.040</td>
</tr>
</tbody>
</table>

*= p < .05

Thymus is a sensitive target of acute GvHD

Subclinical grade 1 acute GvHD impacts thymic function

* p < .05
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**T-cell receptor excision circles (TREC) Assay**

- **TCRB locus**
- **TCRA/D locus**

**THYMUS**
- ETP recombination
- \( \gamma \delta \) lineage
- \( \alpha \beta \) lineage

**PERIPHERAL BLOOD**
- \( \gamma \delta \) and \( \alpha \beta \) TREC don't replicate during T cell proliferation

**Aging and thymic function**

- **\( s_j \)TREC**
  - Graph showing \( s_j \)TREC vs. age
  - Graph showing \( s_j/\beta \)TREC ratio vs. age

- **\( \beta \)TREC**
  - Graph showing \( \beta \)TREC vs. age
  - Graph showing \( s_j/\alpha \beta \)TREC ratio vs. age

➢ The age-related decrease of thymic output is mainly due to a decrease in the intrathymic proliferative capacity of the thymocytes
Acute GvHD is associated with a decrease in \( \beta \)TREC counts at month 6 post-transplant

* \( P < 0.05 \)

\( \rightarrow \) Acute GvHD impacts thymic function before TCR \( \beta \)-chain recombination

**Thymus and GVHD**

- The thymus is a sensitive target of aGVHD
- Thymic function may be restored in young adult patients (< 25 yr.) after aGVHD
- \( \beta \)TREC analysis suggest defects in early thymic progenitors and/or in early thymic differentiation

Clave et al., Blood 2009
Leukemia relapse and thymic function

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Haploidentical Stem Cell Transplantation

- TCD to prevent GVHD
  - High-risk of delayed immune recovery
  - Thymopoiesis as the only mechanism for T-cell reconstitution

- Comparison with a group of unrelated cord blood transplanted paediatric patients (U-CBT)

- Thymic function in Haplo SCT?
Thymic reconstitution and type of transplant (Haplo-SCT vs. MU-CB)

Thymic reconstitution in Haplo-SCT (n=33) is comparable to MU-CB (n=24) transplants.

Thymic function and relapse

- Patients who relapse have persistently low sj and βTREC counts

- Patients with undetectable βTREC relapse more frequently

Clave et al., Leukemia 2012
Thymus is a key target to improve HSCT outcome

- Recipient pretransplant thymic function impacts clinical outcome
- Acute GVHD sensitively impacts thymic function
- A favorable thymic function may be associated with a lower relapse rate in acute leukemia patients
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