**Pathogenesis of GvHD**

**Paris Nov 16th**

**E Holler**

Abteilung Hämatologie/Onkologie, Universität Regensburg

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**Acute GvHD**

**Phase I:**

*Conditioning associated inflammation and activation of APCs*

- Clinical evidence:
  - Release of TNFa during conditioning predicts TRM and severe GvHD
  - Higher doses of TBI result in more severe GvHD
  - Less and delayed GvHD in non-myeloablative SCT
  - Depletion of Langerhans cells by prophylactic UVB delays GvHD

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**Antigen Presenting Cells and GvHD**

![Diagram showing the interaction between host APCs and donor T cells](image_url)

Chronic GvHD = Donor APC present host mHag to donor T cells
Prophylactic UVB irradiation reduces LCs and delays GvHD in patients

Kreutz et al, J Inv.Derm. 2012

Systemic immunomodulatory effects of prophylactic UVB

Kreutz et al, J Inv.Derm. 2012

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Phase II: Donor T cell activation

- cellular composition of the graft: number and quality of T lymphocytes:
  - T cell depletion and use of ATG (J Finke et al, Lancet Oncol 2009)
    - stem cell source: bone marrow vs. peripheral blood
  - role of regulatory T cells (M Edinger, P Hoffmann, 2002, 2003…)

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Serial analysis of GI biopsies: Loss of FoxP3 cells after SCT

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<td>1.7 (1)</td>
<td>1.3 (1)</td>
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<td>CD8 LP</td>
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<td>1.4 (1)</td>
<td>0.9 (1)</td>
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K Rieger, 2006, K Landfried, F Bataille 2009, E Huber (ongoing study)

Skin biopsies in 72 patients: Low FoxP3 count but not Lerner grading predicts outcome following allogeneic SCT
Acute GvHD

Phase III: Apoptotic damage

- T (+NK) cell mediated killing:
  - CD4-cells:
    - Fas-L, TNFα, LT, TRAIL.....
  - CD8-cells:
    - perforin, granzyme, Fas-L (?)
Intestinal biopsies: High correlation apoptosis-CD8 (r= 0.52, p 0.001)
- damage by macrophage mediators:
  - TNFα, IL 1, NO
Cytokines as effectors of GvHD: The TNF-IL10 axis - Reactive release of IL10 associates with severe GvHD

Pathophysiology of acute GvHD - challenges

How do we explain late acute GI GvHD - after cessation of immunosuppression -after DLI?

Additional mechanisms of epithelial damage?
Loss of immunoregulation?

**GvHD damages epithelial stem cells – Protection by R-Spondin1**

![Graph showing protection by R-Spondin1](image)

Teshima et al, J Exp Med 2011

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**NOD2/CARD15 SNPs and GvHD: A role of disturbed intestinal inflammation?**

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<td><strong>GvHD III/IV:</strong></td>
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<td>Cohort 1</td>
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<td>48%</td>
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<td>Cohort 2</td>
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<td>Cohort 2</td>
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<td><strong>TRM overall</strong>:</td>
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<tr>
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<td>59%</td>
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<td>Cohort 2</td>
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<td>45%</td>
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</table>

*NOD2/CARD15 variant in R or R & D independent risk factors in multivariate analysis!

Holler et al, Blood 2004, 2006

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Antimicrobial defense in vivo: Failure to mount Defß2 and cathelicidin LL-37 responses in pts with NOD2/CARD15 SNPs and bacterial translocation (IBD study)

![Graph showing Defß2 and LL-37 responses in different conditions.]

Reg3a is binding to enterococci and selectively increased in intestinal GvHD (Ferrara et al, Blood 2011)

![Graph showing Reg3a expression in different conditions.]

Elafin as a biomarker of skin GvHD (Paczesny S et al, Sci Transl Med 2010)

Elafin = antimicrobial activity
Paneth cells produce defensins and Reg3a and protect epithelial stem cells from invasion by microbiota

A role of IDO in GvHD and intestinal immunoregulation?

Tryptophan metabolites associate with severity of GvHD and poor outcome after allogeneic SCT

Landfried K, Zhu W et al, Blood 2011
Regulatory loops linking innate and adaptive immunity in (intestinal) GvHD

The microbiome: Multiple inflammatory Checkpoints for GvHD?

TLR-activated Langerhans cells license T cell recruitment and killing
(R Chakraverty et al, Blood 117, 2011)
**Chronic GvHD – continuous development from acute GvHD?**

Gillam and Murphy, GVHD 2nd ed., 1997, p. 299

**Chronic GvHD – or different entities**

- Progressive chronic GvHD:
  - Continuing from acute GvHD – continuous role of alloreactive T cells (ATG prophylaxis effective)

- De novo chronic GvHD:
  - True auto-reactivity?
  - Role of thymic damage?
  - Shift from Th1 to Th2 and fibrosis inducing cytokines?
  - B cell activation and dysfunction: BAFF, B cell precursors and immature B cells

Defective wound healing – A Janin, Paris
Autoantibodies and chronic GvHD

F Patriarca et al, Exp Haematology 2006

Antibody response to DBY minor histocompatibility antigen is induced after allogeneic stem cell transplantation and in healthy female donors

David B. Miklos, Haeseok T. Kim, Emmanuel Zom, Ephraim P. Hoebenberg, Luxuan Guo, Alex Martinez-Ritz, Sebastien Vatte, Robert J. Soffter, Joseph H. Axels, and Jerome Ritz

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Acute -> chronic GvHD

- Donor T lymphocytes + memory stem cells?
- Host reactive Th1
- Rapid AICD
- Donor T reg's
- Host allo-reactive Th2, B cell help
- B/T cell auto- and allo-reactivity
- "Auto-reactive" donor T cells
- Dysfunctional B cell control
- Disturbed B cell development
- Dysfunctional T cell
- Selection of newly formed T cells
- Thymic and B cell niche damage

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