Can we separate the GVL effect from GVHD?

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Our knowledge and the future

“Prediction is very difficult, especially if it's about the future.”

Niels Bohr
Some Terms

• **GVH reaction**: presumably present in every allogeneic HCT

• **GVHD**: clinical manifestations of the GVH reaction

• **GVL effect**: anti-leukemic effect associated with the GVH reaction (*with or without clinical manifestations of GVHD*)

• Anything else is **graft engineering**: modifications that are *not part of the “intrinsic” GVH reaction*
Antileukemic Effect of GVHD

AML + ALL

Weiden et al., NEJM 300: 1068, 1979
Antileukemic Effect of GVHD

AML + ALL

Weiden et al., NEJM 304: 1529, 1981
Antileukemic Effect of GVHD

Horowitz et al., Blood 1990, 75: 555
Tissue-specific Expression of Minor H Antigens May Permit Selective GVL Activity

Epithelium

GVHD and GVL?

Donor T Cell Specific For Minor H Antigen

Hematopoietic cells including APC

Donor T Cell Specific For Minor H Antigen

Leukemia

GVL?
What do we actually know about genetic diversity?
HA-1

• HA-1, probably the best studied “minor antigen” (presented by HLA-A2)
• Expression is restricted to hematopoietic cells

**BUT**

• Even after >15 years of research, there is no compelling, undisputed evidence for correlation with acute GVHD
Red = major clusters; black = CD8/class I; green = CD4/class II; blue = CD8 and CD4;
1,000 Genome project
(www.1000genomes.org)

• Individuals differ from the reference genome sequence at 10,000 – 11,000 non-synonymous sites (different protein sequences)

• Similar differences are likely between any two individuals

• If only 1% of those polymorphisms lead to MHC presentable peptides, mutual alloreactivity between two individuals is highly likely

Nature, 2010
Target antigens

• Most known alloantigens (~80%) are not restricted to hematopoietic cells
• If target antigen range is narrow, antigen loss and tumor escape are likely
• If target antigen range is broad, reactivity likely includes non-intended targets
And soluble mediators?
Three Phase GVHD Model

1. Recipient conditioning
   - Tissue Damage
   - Host tissues
   - Small intestine
   - LPS
   - TNF-α

2. Donor T cell activation
   - Host APC
   - IL-12
   - IL-1
   - IFN-γ
   - IL-2
   - CTL
   - Perforin FasL TNF-α
   - Target cell apoptosis

3. Cellular and inflammatory effectors
   - NK
Other Cytokines and Chemokines

• IL-23 blockade (R. Das)
  – Selective protection of the colon
    • Reduced GVHD, maintained GVL effect
• CCR-7 (J. M. Coghill)
• Th1 and Th17 (Y. Yu)
  – Blockade may reduce acute GVHD without altering the GVL effect

• Others……..
Will studies of the intestinal microbiom provide new insights and, as a result, new modalities of intervention?

A very intriguing speculation, but we are not there yet – certainly not in humans.
...and then the endothelium

O. Penack et al, Blood 2011
Endothelium and GVHD

- **Fas/Fas-ligand interactions** (A. Janin; S. Bair)
- $\uparrow$ **Angiopoietin 2** (Th. Luft)
  - $\downarrow$ thrombomodulin
- $\downarrow$ **VEGF**
- **Pulmonary cytolytic thrombi** (A.R. Smith)
  - $\uparrow$ GVHD, $\downarrow$ relapse
Complex effects of therapeutic immunosuppression (GVHD Prophylaxis and therapy)
Immunosuppressive therapy (IST) and relapse

- In patients **with GVHD**, withdrawal of IST upon resolution of GVHD
  - did not change the risk of relapse
- In patients **without GVHD**, withdrawal of IST
  - resulted in reduced risk of relapse during first 18 months, but
  - risk of relapse after 18 months remained considerably higher than in patients with GVHD

IST and relapse


Number at risk

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GVH Reaction

GVHD + GVL

HJ Deeg
So, what do I think?

• I see no current technique that separates GVL from GVHD in the clinic.
• An approach that completely prevents GVHD will likely also prevent a potent GVL effect
• However, we may then be able to design anti-tumor strategies – graft engineering - that are added to the GVHD prevention approaches
A citation from the literature:

• “… a verbatim quote: ‘Ultimately, advances in separation of GVT from GVHD will further enhance the potential of allogeneic HCT as a curative treatment for hematological malignancies’ (Rezvani, A.R. and Storb, R.F., Journal of Autoimmunity 30:172-179, 2008 ). It may be added: for cure, a combination of the GVT effects with new targeted therapeutic modalities, ……. will be necessary”.

JG Sinkovics, AMIH, 2010
….and what will be those modalities?

“It’s tough to make predictions, especially about the future.”

Yogi Berra
Finally a philosophical perspective

• Nature has invested a hundred million years into mechanisms that protect our individuality – why should a few short-lived primates be able to break down that marvel, having invested just a few decades?
Thank you

- H.E. Warren
- R. Storb
- J. Radich