Endoglin has a crucial role in blood cell-mediated vascular repair

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NIH workshop – HHT  Bethesda, 8th June 2006
Background

- **Endoglin**: accessory receptor for TGF-β in vascular endothelial cells (EC)
  - Essential for angiogenesis (mouse development)
- **Hereditary hemorrhagic telangiectasia type 1 (HHT1)**: mutations endoglin gene
  - Vascular malformations increasing with age
  - Haploinsufficiency
  - Clinical manifestations variable
Background

- Mononuclear cells (MNCs) can express endoglin
  - Endothelial progenitor cells, circulating EC, bone marrow monocytic lineages
- MNCs contribute to vascular repair
  - Transdifferentiation to EC; vasculogenesis
  - Secretion growth factors and cytokines; angiogenesis
Hypothesis

• Vascular repair, mediated by MNCs, may be impaired in subjects with HHT1

• Model
  – HHT1 patients and mice for endoglin mutation
  – Myocardial infarction (MI) for angiogenesis and vasculogenesis
MI in mice

- Myocardial infarction or
- Sham thoracotony
- 4 week survival >60%
- Endoglin heterozygous mice ($Eng^{+/-}$)
- Wildtype littermates ($Eng^{+/+}$)
- Wildtype Balb/C
MNC injection

- Venous blood from HHT1 patients or healthy volunteers
MNC injection

• Venous blood from HHT1 patients or healthy volunteers
• Density gradient centrifugation → MNC population
• 1-3 hours after MI 5 million cells (or PBS) in tail vein
• Tacrolimus (Prograf®) for immunosuppression
Analysis

- Endoglin expression infarcted vs. healthy heart (human and mouse): ISH and IHC
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- Heart function: mouse MRI (1w, 4w)
Ejection Fraction (EF) = \frac{(EDD-ESD)}{EDD}

Cardiac index = EF \times EDD \times \text{heart rate} / \text{weight}
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- Heart function: mouse MRI (1w, 4w)
- Statistical analysis: Mann-Whitney U test
Endoglin expression

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<th>Azan</th>
<th>endoglin mRNA</th>
<th>PECAM</th>
<th>endoglin protein</th>
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<td>Infarct</td>
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- Endoglin upregulated in neoangiogenic vessels formed after MI (human and mouse)
Endoglin and neovascularization

Non-infarcted myocardium: no difference between \( \text{Eng}^{+/-} \) and \( \text{Eng}^{+/+} \)

- Reduced upregulation of endoglin and neoangiogenesis in \( \text{Eng}^{+/-} \) mice after MI
- CD45, CD68, Mac-3: no difference
• Neoangiogenesis defect in Eng+/− mice post-MI associated with impaired heart function
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• Partial rescue by injection of healthy MNCs
• HHT1-MNCs fail to stimulate neoangiogenesis and to accumulate in the infarct region of *Eng*+/+ mice
Conclusion

• Defective vascular repair –mediated by MNCs- is a significant component of the etiology of HHT1
• This may explain disease heterogeneity, since exposure to vascular damage or inflammation varies between patients
• In general, MNC characteristics in any patient may affect their efficiency of vascular repair
Acknowledgements

• Hubrecht Laboratory
  – Christine Mummery
  – Franck Lebrin
  – Sander van den Driesche
  – Alie Feijen
  – Mariette Driessens

• Heart Lung Center Utrecht
  – Pieter Doevendans
  – Marie-José Goumans
  – Simone Post
  – Maurits Jansen
  – Cees van Echteld

• St Antonius Hospital Nieuwegein
  – Cees Westerman
  – Repke Snijder
  – Johannes Mager

• Leiden University Medical Center
  – Peter ten Dijke

• University of Newcastle
  – Helen Arthur