Summary of Basic Sciences

HHT International Conference 2007

Capri

Douglas Marchuk, Ph.D.

Endoglin/ALK1 in Circulating Cells

Christine Mummery (no. 1)

- Mononuclear cells from HHT1 patients are impaired in ability to repair site of myocardial infarction

Simone Post (no. 22)

- Endoglin-deficient mononuclear cells show impairing homing to sites of injury. Cells show imbalance of the CXCR4/CD26 proteins

L. Zucco (no. 46)

- EPCs (endothelial progenitor cells (from HHT patients)
- eNOS expression much lower than controls, impaired response to VEGF in migration assay

Remaining Question:

Do any of these circulating cell types play a role in HHT pathogenesis?

A New Ligand for ALK1

Laurent David (no. 2)

- BMP9 is a specific ligand for ALK1
- BMP9 stimulation inhibits EC migration
- Endoglin enhances BMP9 stimulation of ALK1
- BMP9 is highly expressed in the liver and present in serum

This discovery has now been confirmed by two other groups

Question: Is BMP9, rather than TGF-beta, the relevant ligand for HHT pathogenesis?

First “View” of Endoglin

Francesco Blanco (no. 35)

- Structural model of endoglin (extracellular domain) using single particle electron microscopy plus computational prediction
- Map missense mutations on the structure
- Attempt to identify other important features; cleavage site for sEng, etc. Not yet able to predict binding site for ligands

Tissue Distribution of Endoglin and ALK1 in Murine Lung

Marwa Mahmoud (abstract 21)

- Both proteins co-localized only in distal arterial branches
- Evidence of functional significance - phosphorylated Smad1/5/8 also in same location

Remaining Question

Possible explanation for location of PAVMs?

Pulmonary Arterial Hypertension in Murine Model of HHT1

Mourad Toporsian (no. 44)

- Pulmonary arterial hypertension in HHT1 mouse model
- Pruning of lung vasculature
- Proposed model where PAVMs may be formed in HHT1 to counteract the increased arterial pressure
- Spirited debate of this model during discussion as not all were in agreement

New Animal Models for HHT

Helen Arthur (no 21)

- Conditional knockout allele for murine endoglin - early days, but promise for a better model of HHT1

Paul Oh (no 36)

- Conditional (only in endothelial cells – control of time of deletion) knockout allele for murine ALK1
- **Creation of first viable model of HHT with widespread AVM formation, especially lung**
- Using same strategy, deletion of other TGF-beta receptors in ECs only did NOT result in HHT phenotype
- **Significance, further evidence that TGF beta may not be the (most) relevant ligand for HHT pathogenesis.**