II. Pathobiology of pulmonary arterial hypertension

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European Cardiology Society, Nice, 2012
Pulmonary Hypertension: Future expectations
(Revisited) Key features of cancer

Emerging Hallmarks
- Deregulating cellular energetics
- Avoiding immune destruction
- Tumor-promoting inflammation

Enabling Characteristics
- Genome instability and mutation

Hanaham and Weinberg, Cell 2010
Variability of pulmonary vascular lesions

A

Coefficient of Variation (SD / Mean)

Wall Thick., Intima Thick., Media Thick.

B

Coefficient of Variation (SD / Mean)

Plex. Les.

Stacher et al., AJRCCM, 2012
Where do pulmonary vascular lesions occur?

- Number of pulmonary Arteries (17 orders)
  \[10^8\]

- Elastic (orders 17-10): 3,000
- Muscular (orders 9-5): 800,000
- Precapillary (orders 4-1; 25 um): 70 million
Predominance of PAH in women

Stacher et al., AJRCCM, 2012
17β estradiol

BMPRII

HPAH

SMC IPAH

CYP1B1

Sert Overexpressor

Overexpression in cancers

4 and 16-hydroxylation of estrogen

Dehydro epiandrosterone

White, MacLean. Circulation, 2012
CYP1B1 causes pulmonary hypertension

2,3,4,5-tetramethoxystilbene (TMS)

16-OH estrogen

CYP1B1

White, MacLean. Circulation, 2012
Morphometric parameters: control vs. PAH

Stacher et al., AJRCCM, 2012
Conceptual framework for severe PAH: selection of apoptosis resistance

Normal EC -> Trigger agent -> EC death

Clonal Growth

Shear Stress Viral factors Drugs

Key features of cancer

Hanaham and Weinberg, Cell 2010
(Revisited) Key features of cancer

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Hanahan and Weinberg, Cell 2010
HIFs and Pulmonary Hypertension

Hypoxic

GLUT 1 & 3

HKII

HIF-1α

HIF-1β

CA IX

HCO₃⁻

CO₂

G-6-P

G
**PH Endothelial Cells: Shift to a Glycolytic Pathway**

**PH ECs have less mitochondria**

![Graph showing glucose consumption]

- **Normal**
- **PAH**
- **PAH + NO**

Cleveland Clinic: Serpil Erzurum, Weiling Xu, Suzy Comhair, Raed Dweik, Kewal Asosingh

Xu W et al. PNAS 2006
IPAH-ECs energetic switch:

- Decreased mitochondria

BMPRII: worse pulmonary vascular remodeling

Stacher et al., AJRCCM, 2012
Plexiform lesions

Stacher et al., AJRCCM, 2012
Morphometric parameters and pathological PAH subphenotypes: plx lesions

A

B

Stacher et al., AJRCCM, 2012
Role of EC APOPTOSIS in the genesis of severe PH SU5416+CH and MCT Models

**Chronic hypoxia CH+ SU5416**

Active Caspase 3/Vessel

- **Monocrotaline**

- **CH**
- **CH+SU5416**

Graphs showing changes in active caspase 3/vessel over time:
- D7, D14, D21, D42

Statistical significance:
- p<0.001

Graphs showing caspase positive/perimeter:
- Con, D14, D21, D30

Stewart et al. Faseb Journal, 2001

Zaiman A et al. AJRCCM, 2008
Role of EC APOPTOSIS in the genesis of severe PH SU5416+CH and MCT Models

SU5416+CH

N=12

N=14

N=5

Chronic Hypoxia

PAP (mmHg)

Control

Z-Asp

-CH 2

SU5416

Monocrotaline

P < 0.0003

P < 0.0005

Control

MCT

MCT

+Z-Asp

Stewart L. Faseb Journal 2001

Duncan Stewart
VEGF receptor blockade: SU5416+CH rat model of human PAH with endothelial cell proliferation

Human IPAH

Rat IPAH-like

Abe et al Circulation, 2010; courtesy: Ivan McMurtry
Schistosomiasis

Cercariae

Egg

*S mansoni* and *S japonicum*
200 million people affected by Schistosomiasis
Schistosomiasis-PAH: Pathology

Courtesy Prof. Zilton Andrade
Mouse model of Schisto-PH

- Purified ova
- Cercariae
- Infected mouse
- Worms

3 weeks

Graph showing RVSP (mmHg) with two groups: Unexposed and IPTV Eggs.
Th2 Peri-Egg Granulomas

- Myocyte/Myofibrocyte
- Macrophage
- Eosinophil

- IL-4Rα
- IL-13Rα1
- IL-13Rα2

- STAT-6
- Adenosine
- VEGF
- TGF-β1
- MMPs
- UPA
- Chemokines
- CCR2

- Mucus
- Blood vessel alterations
- Fibrosis
- Inflammation

- αSM-actin
- MAC-3
- MBP

Wild-Type
Schisto-PH: combined remodeling and vasoconstriction (Rho kinase)
Lack of role for selective loss of either Smad2 or Smad 3 in hypoxic PH

Hypoxia: 50% 3 weeks

TGF-β → RII → Smad3

Smad2

+/−

Graphs showing RVSP (mmHg)

S3+/+ Nx, S3+/− Nx, S3+/+ Hx, S3+/− Hx

S2+/+ Nx, S2+/− Nx, S2+/+ Hx, S2+/− Hx
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- Genome instability and mutation
- Emerging hallmarks

Hanaham and Weinberg, Cell 2010

17β estradiol → CYP1B1
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