Exploring the Link Between Malignancy and Pulmonary Arterial Hypertension

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The "cancer paradigm" in pulmonary hypertension

Primary pulmonary hypertension between inflammation and cancer

PH between inflammation and cancer
Dysregulated Angiogenesis
Metabolic Shift
Genetic Selection
TGF-beta

Abnormal growth factor release

Cool, E., et al. AJR, 1999

Endothelial cell processes: proliferation

Early Lesions: Plexiform Lesions: Concentric Lesions:

MIB-1
Can EC pathology discriminate between mild vs severe pulmonary hypertension?

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Mild/Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plexiform Lesion</td>
<td>NO</td>
<td>YES All forms</td>
</tr>
<tr>
<td>Concentric lesion</td>
<td>NO</td>
<td>YES All forms</td>
</tr>
<tr>
<td>Angiomatoid Lesion</td>
<td>NO</td>
<td>YES All forms</td>
</tr>
</tbody>
</table>

Endothelial cell dysfunction in severe pulmonary hypertension

- **IPAH**
- Idiopathic
- Familial
- Liver cirrhosis
- HIV-related
- Drug induced: Phen-fen, Aminorex
- Collagen Vascular Diseases: CREST, Lupus Erythematosus
- Schistosomiasis
- High left-to-right heart malformations
- Secondary (2ry) PH

Where do pulmonary vascular lesions occur?

- Number of pulmonary Arteries (17 orders): 100 million
- Elastic (orders 17-10): 3,000
- Muscular (orders 9-5): 800,000
- Precapillary (orders 4-1; 25 um): 70 million

Three-dimensional organization of intima and plexiform lesions: 100-150 um

- 5-7 cm³/1000 sections/29 segments (700,000)

Clonal Growth of Endothelial cells in IPAH

Random X-chromosome inactivation

Monoclonal expansion in PPH

Paternal 

Maternal

Endothelial cells

Lee et al: JCI, 98  
Tuder et al, AJRCCM, 99

hMSH2 Intron 5 (A_{26})

TGF-β RII Exon 3 (A_{10})

BAX Exon 3 (G_{8})

DNA Pol δ → gaagg NNNNNNNNNNN gecctg

hMLH1

+2

+1

WT

-1

-2

Conceptual framework for severe PAH: selection of apoptosis resistance

EC Selection (action of growth factors/genes/virus) → Apoptosis resistance

Normal EC → Hypoxia/HIF

Dysfunctional EC → NO-PGL_{2}, serotonin

EC death (?)apoptosis

Clonal Growth

Neoplastic-like

Trigger agent → PAP, Shear Stress, Viral factors, Drugs


Approach to Inhibit KDR: SU 5416 (Sugen)

SU 5416:
- Highly lipophilic kinase inhibitor
- Group of 3-substituted indolin-2-ones
- Localizes to the ATP binding site of RTK
- IC50=1.04 uM (20uM for PDGFr and 100 uM for EGFr)
- Used for anti-angiogenic therapies for Kaposi’s Sarcoma and Renal cell Carcinoma

KDR

SU 5416

Shear Stress Viral factors Drugs

How to best model RV failure: SU5416+CH rat model

IPAH
Time: Unknown
mPAP 50-75 mmHg

SPH
Time: 3 weeks
mPAP 45-65 mmHg

Taraseviciene-Stewart et al, Faseb J 2001

Role of EC APOPTOSIS in the genesis of severe PH
SU5416+CH and MCT Models

SU5416+CH
Chronic hypoxia
Chronic hypoxia + SU5416
Activated caspase 3

Monocrotaline

Caspase inhibition prevents severe pulmonary hypertension and endothelial cell proliferation induced by chronic hypoxia+SU5416

Factor VIII

SMA

Activated caspase 3
BMPs Inhibits Apoptosis in human PAEC post serum withdrawal

Duncan Stewart, Circ Res

Conceptual framework for severe PAH: selection of apoptosis resistance

Angiogenic switch: the HIF/VEGF paradigm

Hypoxia facilitates genetic instability (if apoptosis resistant)


Semenza G. Nature Cancer Rev, 03
Hyperproliferative apoptosis-resistant endothelial cells in idiopathic pulmonary arterial hypertension


- Increased proliferation
- Decreased apoptosis
- Increased angiogenic tube formation

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IPAH Endothelial cell energetic switch: the HIF/VEGF paradigm in cultured human IPAH cells

Fijalkowska et al. Submitted. 2009

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IPAH-ECs energetic switch: Decreased mitochondria

Fijalkowska, Xu et al, Submitted. 2009

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PH Endothelial Cells: Shift to a Glycolytic Pathway


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Standardized uptake values (SUV) of FDG-PET

Xu et al. *PNAS*, 2007
PH Endothelial Cells: Shift to a Glycolytic Pathway

HIF-1α target: Carbonic anhydrase IX

IPAH-ECs energetic switch: decreased mitochondria

Resistance to apoptosis
Somatic Mutations: clonal expansion
Growth factors
Excessive cell growth

Oxidative stress, Gene microarray, Models
Expression studies
In vivo imagining

Fijalkowska, Xu et al, Submitted. 2009

How to best model RV failure: SU5416+CH rat model

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EVIDENCE OF HYPOXIA IN SU5416+CH (3 weeks)

SU+CH
Hydroxyprobe

CH+Vehicle

Taraseviciene-Stewart et al, Faseb J 2001
2-metoxy-estrodial (2ME) in PH

2ME2 Mechanisms of Action in Oncology

Teresa LaVallee EntreMed

PANZEM: Treatment

SU5416+CH: Panzem SU5416+CH: Vehicle

Treatment: days 21-42

Conceptual framework for severe PAH: selection of apoptosis resistance

EC Selection (action of growth factors/genes/virus)
Apoptosis resistance

Clonal Growth

Normal EC Dysfunctional EC
NO-PGL2, serotonin

EC death (apoptosis)

Neoplastic-like

Trigger agent

PAP Shear Stress Viral factors Drugs

PH Endothelial Cells: Shift to a Glycolytic Pathway

HIF-1α targets

- Parvalbumin
- pyruvate kinase
- MDR
- survivin
- EGFR-3

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- EntreMed: Teresa LaValle

The Cancer Paradigm of Severe Pulmonary Arterial Hypertension

Pradeep R. Rabi, Carlyle D. Cool, Judy A. King, Troy Stevens, Nana Burns, Robert A. Winer, Michael Kaiser, and Norbert F. Voelkel