The metabolic basis of PAH and cancer

Evangelos D. Michelakis, MD, FACC, FAHA

Pulmonary Hypertension Program
University of Alberta
Take a walk in Academia...

Aristotle, a faculty member in Plato’s Academy, used to lecture while walking, and founded the Peripatetic School of Philosophy

*Peripatos* = stroll, walk
Proliferative-antiapoptotic diseases

Degenerative diseases

Inflammatory diseases

Targets unique to the pulmonary circulation

PAH
Right Ventricle

- Normal RV
- Healthy PA endothelium
- Thin walled-relaxed PAs
- Large capillary network

- Normal CO
- Normal PVR
- Normal perfusion

Pulmonary Arteries

- Normal CO
- Normal PVR
- Normal perfusion

Compensation

- Hypertrophied RV
- Abnormal PA endothelium
- Constricted-stiff PAs
- Loss of microvessels

- Normal CO
- Mild increase in PVR
- Moderate decrease in perfusion

Failure

- Dilated RV
- Cell proliferation in the PA wall
- Obliterative PA remodeling

- Severe decrease in CO
- Severe increase in PVR
- Severe decrease in perfusion
Apoptosis (measured by TUNEL)

Proliferation (measured by PCNA)

Untreated PAH

Treated PAH

PASMC pro-apoptotic therapies
- Elastase inhibitors
- EGF receptor inhibitors
- Dichloroacetate
- Simvastatin
- Anti-survivin
- Imatinib
- Sildenafil
- Cyclosporine
The opposing effects of hypoxia in the PA vs RA are in part due to differences in the $O_2$ sensor, i.e. the SMC mitochondria

E. Michelakis et al, CircRes, 2002
PAH: a state of insulin resistance?

1. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. Hansmann et al, Circulation, 2007


• Mice with SMC targeted deletion of PPAR$_\gamma$ develop PAH

• PPAR$_\gamma$ agonists (rosiglitazone, pioglitazone) can reverse PAH by activating pro-apoptotic and suppressing pro-proliferative genes
Sense
(supply of O\textsubscript{2} and demand for fuel)

execute

Can match fuel generation (ATP) with demand
LIVE

Cannot match fuel generation (ATP) with demand
DIE
- Is not he who can best strike a blow in a boxing match or any kind of fighting, best able to ward off a blow?
- Certainly
- And he who is most skilled in preventing or escaping from a disease is best able to create one?
- True
- And is he the best guard of a camp who is best able to steal a march upon the enemy?
- Certainly
- Then he who is a good keeper of everything is also a good thief?
- That I suppose is to be inferred
- Then if the just man is good at keeping money he is good at stealing it
- That is implied in the argument
Socrates and Polemarchus:

- Is not he who can best strike a blow in a boxing match or any kind of fighting, best able to ward off a blow?
  - Certainly
- And he who is most skilled in preventing or escaping from a disease is best able to create one?
  - True
- And is he the best guard of a camp who is best able to steal a march upon the enemy?
  - Certainly
- Then he who is a good keeper of everything is also a good thief?
  - That I suppose is to be inferred
- Then if the just man is good at keeping money he is good at stealing it
  - That is implied in the argument

The Republic, Plato
Otto Warburg

Born October 8, 1883, Freiburg
MD in 1911, Heidelberg

Nobel Prize 1931
“For his discovery of the nature and mode of action of the respiratory enzyme”

Stoffwechsel der Tumoren, 1926

The Warburg effect:
“Cancer is caused by abnormal metabolism of the cells: due to abnormal mitochondria the cancer cells use glycolysis, and not oxidative phosphorylation for energy production, even in the absence of hypoxia.”
DCA therapy induces apoptosis in the PA wall and reverses vascular remodeling.
Normal PASMC ΔΨm

Vehicle  DCA

Red Fluorescence (FU)

Vehicle  DCA

NS

Normal PASMC TUNEL

Vehicle  DCA

TUNEL  Propidium iodide  TUNEL  Propidium iodide

10x

Normal Rat PVRi (mmHg*min*g/ml)

Vehicle  DCA

NS

…without affecting normal cells and rats
DCA reverses established vascular remodeling in rodent PAH
The MCD-KO mice have a normal phenotype at normoxia and are resistant to CH-PHT.

Mean PAP (mmHg)

Distance (m)

RV / LVS
Glucose oxidation

Glucose oxidation involves the conversion of glucose to pyruvate, which is then further oxidized in the mitochondria. This process is regulated by several factors, including HIF activation, Akt/PTEN, and p53 loss. The pathway is characterized by the production of lactate and the consumption of ATP. The depolarization of mitochondria is a key event in this process, leading to the release of calcium ions and activation of apoptosis. The glucose uptake is mediated by PDGF and survivin, while proliferation is regulated by Akt/PTEN and PDK.

Apoptosis and proliferation are two critical processes in cancer biology. Apoptosis is a programmed cell death, while proliferation is the process of cell division. The balance between these two processes is crucial for the development and progression of cancer.

Michelakis, Br J Cancer, 2008
Mitochondrial membrane potential

Control (non small cell lung cancer)

DCA-treated (non small cell lung cancer)

TMRM: red
DAPI: blue

Cancer Cell, 2007
Cancer biology

Cramping tumours
Jan 18th 2007
From The Economist print edition

An old observation about cancer cells may lead to a new treatment

Buzz for a Potential New Cancer Drug
Scientists and patients are buzzing about DCA, an existing drug newly recognized as a potentially powerful cancer treatment. But, of course, more research is needed.
WEB EXCLUSIVE
By Jerry Adler
Newsweek
Updated: 4:46 p.m. MT Jan 23, 2007

Metabolic Targeting as an Anticancer Strategy: Dawn of a New Era?
James G. Pan and Tak W. Mak (10 April 2007)
Sci. STKE 2007 (381), pe14. [DOI: 10.1126/stke.3812007pe14]

“DCA treatment may be an important example of anticancer intervention through metabolic targeting.”
Hello I am Brenna. I made coasters for cancer research, I sold them at school. I raised $75.00. I wanted to change the world. I spool knitted them.

Brenna.
Golden Years Truly Are Golden
Massive phone survey reveals that people are happier after age 50

Fruit Bat Sex Chat Prompts Sexual Harassment Spat
Fellatio, fruit bats, and allegations of sexual harassment. These are the ingredients of a scandal boiling over in Ireland at the University College Cork (UCC). Last year, a formal...

Obama Adviser John Holdren on Why We Don’t Know the Size of the Oil Gusher
Academic scientists quoted in stories late last week by NPR and The New York Times suggested that the amount of oil spewing out from the broken pipe on the...

Herschel’s First Images Spark Star-Formation Debate
When the Herschel telescope was launched into space last May, it promised new insights into our universe, detecting far-infrared and submillimeter wavelengths of radiation that have eluded previous missions
A) PET-MRI merged images showing changes over time with DCA treatment and surgery (x2). Inset diagrams illustrate the timeline from baseline, pre-DCA, post-DCA, +9 months, and +15 months.

B) Immunohistochemistry images of PDKII, PCNA, MERGE+DAPI, and TUNEL +DAPI staining, with comparisons of Pre-DCA and Post-DCA conditions.

C) Graphs illustrating PDH activity (AFU) and %PCNA (+) with error bars, showing significant differences between groups (GBM +DCA, P2, P3, P4).
**In Vitro**

**CONTROL - CSC**

- CD133
- NESTIN
- TUNEL
- MERGE
- DIC

**DCA**

**DCA+TMZ**

**In Vivo**

- Pre DCA
  - TUNEL
  - CD133
  - wWF
  - MERGE
  
  x25

- Post DCA
  - TUNEL
  - CD133
  - wWF
  - MERGE
  
  x100

- Post DCA
  - TUNEL
  - CD133
  - NESTIN
  - MERGE

- In Vitro

- CONTROL - CSC

- Pre DCA
  - TUNEL
  - CD133
  - PDKII
  - MERGE
  
  x25

- Post DCA
  - TUNEL
  - CD133
  - wWF
  - MERGE
  
  x100

- Post DCA
  - TUNEL
  - CD133
  - NESTIN
  - MERGE
Nogo-/- PASMCs Are Resistant To Hypoxia-Induced ER-Mito Separation

Structural Disruption

Nogo +/-
- Normoxia
- Hypoxia
- Mito-ER Distance (nm)

Nogo -/-
- Normoxia
- Hypoxia

Functional Disruption

Endoplasmic Reticulum

Ptd.SER Synthase

Ptd.Etn

Ptd.SER Decarboxylase

Ptd.Ethanolamine (10^3 DPM/µg protein)
Nogo K.O. PASMCs maintain mitochondrial Ca$^{++}$ and Ca$^{++}$-sensitive enzymes in hypoxia

![Diagram showing changes in mitochondrial Ca$^{++}$ levels and PDH activity under normoxic and hypoxic conditions for Nogo$^{+/+}$ and Nogo$^{-/-}$ cells.](image-url)
**Nogo**/– PASMC are resistant to hypoxia induced mitochondrial hyperpolarization and decreased mitochondrial ROS.
*Nogo* 

**Nogo**/- mice are resistant to chronic-hypoxia PHT

**Mean PAP (mmHg)**

- **Normoxia**: 20
- **Hypoxia**: 40

**RV/(LV+Septum)**

- **Normoxia**: 0.2
- **Hypoxia**: 0.4

**% Medial Wall Thickness**

- **Normoxia**: 20
- **Hypoxia**: 40

**Systemic B.P. (mmHg)**

- **Normoxia**: 120
- **Hypoxia**: 160

*P* values indicated for significant differences between conditions.
Nogo Expression Increases in Human PAH

Serum Nogo Levels

Nogo (nM)

1000
800
600
400
200
0

PAH (41)
Normal (18)
Sec (6)

Patient 1 (33y M)
Patient 1 (36y F)

Healthy
PAH

SMA
MERGE
NOGO
DIC

Patient 1 (33y M)

Nogo (nM)

PAH (41)
Normal (18)
Sec (6)

Patient 1 (33y M)

Nogo (nM)

PAH (41)
Normal (18)
Sec (6)

Patient 1 (33y M)
Thank you

Sebastien Bonnet
Sean McMurtry
Ken Petruk
Gopi Sutendra
Peter Dromparis
Jayan Nagendran
Linda Webster

Ballarina II, Joan Miro, 1925
The RV and the LV are embryologically different


The molecular and metabolic profile of the normal RV is different compared to RVH
FDG-18/PET IMAGING
DCA: a positive RVH inotrope

Nagendran et al, JTCS, 2008
Increased RV Glu uptake in iPAH

Flolan decreases RV Glu uptake

Oikawa et al, JACC 2005

Before

After

Increased lung glucose uptake in iPAH patients

Xu et al, PNAS, 2007