Cancer Research in 2019: Dazzling Opportunities, Daunting Challenges

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Women in Oncology
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Limited $O_2$ Availability in Solid Tumors
Hypoxia Inducible Factor Pathways

A. Normoxia

1. PHD enzyme hydroxylates HIF-α
2. pVHL complex ubiquititates hydroxylated HIF-α
3. HIF-α destroyed by proteasome

B. Hypoxia

1. Oxygen is not available for hydroxylation
2. pVHL complex unable to ubiquitinate non-hydroxylated HIF-α
3. HIF-α remains intact and binds to HIF-1β
4. HIF-1α/1β complex translocates to nucleus
5. HIF-1α activates the transcription of genes that increase metabolism, angiogenesis, erythropoiesis, cell migration and invasion, cell proliferation, and inflammation

C. The von Hippel-Lindau Syndrome

1. pVHL function is abrogated or diminished
2. HIF-1α remains intact
3. HIF-1α activates the transcription of genes that increase metabolism, angiogenesis, erythropoiesis, cell migration and invasion, cell proliferation, and inflammation

Bill Kaelin, Peter Ratcliffe, Gregg Semenza win 2019 Nobel Prize!!!

Source: The Nobel Prize
“Perseverance when the going gets tough!!!”


3) Nothing worked for two years.

4) Almost quit…….
$O_2$ gradients in embryos and tumors
Abnormal angiogenesis in HIF-deficient embryos

Maltepe E et al. (1997) Nature 886:403
Oxygen diffusion limited in solid tissues…
Metabolic Pathways Active in Proliferating Cells

Question: Do disparate oncogenic changes converge on more common metabolic adaptations?
Clear Cell Renal Cell Carcinoma (ccRCC)

- 5 yr. survival
  - >85% if highly localized
  - <10% if metastatic
- Resistant to conventional chemo- and radiotherapy
- Hallmarks of disease:
  - Constitutive HIF activity
  - 100X cholesterol esters, 8X cholesterol, 20X triglycerides

*Qiu, B et al. (2015) Cancer Disc. 5:652*
Metabolic profiling of ccRCC tumor and normal kidney

- Urea cycle; arginine and proline metabolism
- Glycolysis, gluconeogenesis, and glucose-related sugars
- Nicotinamide (NAD) and Riboflavin (FAD) metabolism
- Carnitine metabolism
- Long chain fatty acid
- Lysolipids

Li, B et al. (2014) Nature 513:251
Hakimi, A et al. (2016) Cancer Cell 29:104
Metabolic Enzymes in Strange Places!!

Dazzling Opportunities:

1. Technology advancement.
2. Translational impact.
Daunting Challenges:

1. Longer “time to degree” time spans (especially MD/PhD and Vet/PhD students).
2. Longer postdoctoral fellowships.
3. Exceptionally long training periods for physician-scientists.
4. 2019 definition of a “publication unit”.
5. NCI FY2020 7% payline (Can this be possible??).
6. Pressure point: tenure track assistant professors.
7. Pressure point: first R01, K08 for clinical fellows.