Exploring Lung Cancer Metabolome: In vivo and Ex vivo for Individualized Medicine

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Abstract # 2502: Liquid diet introduction of tracers into mice for stable isotope-resolved metabolomics (SIRM) investigations

Adapted from Fan et al., Pharmacology & Therapeutics 133, 366-391, 2012
SIRM Study of Human NSCLC patients \textit{in vivo}

\textbf{Tumor from Patient \#6}

\textbf{Patient \#6 large tumor 5/1/06}

\textbf{Patient \#6 cut tumor 5/1/06}

\textbf{13C6-glucose infusion}

\textbf{benign ——— tumor}

Fan et al. (2009) Altered Regulation of Metabolic Pathways in Human Lung Cancer Discerned by \textit{13}C Stable Isotope-Resolved Metabolomics (SIRM). Molecular Cancer. 8:41
Pyruvate carboxylase is activated in NSCLC


PC KO inhibits A549 cell xenograft growth

size=14+0.076t²
SIRM Study of Human NSCLC patients *ex vivo*

**Advantages of *ex vivo* human tissue slice studies**

- Maintain 3D human tumor architecture and microenvironment.
- Acquire target tissue metabolism w/o systemic influence.
- Paired cancerous and non-cancerous tissue design for the same patient eliminates genetic, physiological, and nutritional variables.
- Flexibility in treatments and ability to observe individualized response.
NSCLC tissue slices maintain distinct metabolism


Selenite effect ex vivo
SeO$_3$ effects on lung cancer cells are recapitulated in ex vivo cancer tissues

Ex vivo CA slices

A549 cells

M1 macrophage modulator β-glucan (WGP) effect ex vivo
βGlucan (WGP) induces M1 macrophage metabolic reprogramming in NSCLC tissues

Fan et al., Cold Spring Harb Mol Case Stud, 2(4):a000893

UK021

UK049

PCNA
RIP-1
PCNA
RIP-1
CA-Ct1
CA-WGP

Mitotic Index
Necrosis
Mitotic Index
Necrosis
NSCLC patients have opposite Gln oxidation in response to WGP

UL049 pt non-responder

UL058 pt responder

CA-Control
CA-β-Glucan

UL049 pt non-responder

CA-Control
CA-β-Glucan

Cytokine release

IL-10
IL-12p40
IL-1B
TNFα

NSCLC patients have opposite Gln oxidation in response to WGP.

Fan et al., Cold Spring Harb Mol Case Stud, 2(4):a000893
WGP-sensitive NSCLC pt tissues exhibit enhanced Gln oxidation via the Krebs cycle

Conclusion

• SIRM application to lung cancer patient in situ uncovers activation of pyruvate carboxylase, but not glutaminase.

• SIRM application to shPC-KD lung cancer cells and xenograft shows that PC enhances anabolic pathways to promote cell and tumor growth.

• Metabolic network mapping by SIRM in human lung cancer tissues ex vivo uncovers distinct individualized patient response to immune modulator β-glucan and anti-cancer agents

• Understanding therapeutics-induced metabolic reprogramming in ex vivo tissue studies may help predict the efficacy of given therapeutics in individual patients
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