The Intersection of Genetics with Tumor Metabolism: Opportunities for Drug Repurposing and Nutraceuticals

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Innovating with Existing Drugs and Nutraceuticals conference

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Mechanism-driven understanding of pathogenic link between diet and cancer

Mechanism and/or genetic background-based rationales for clinical and epidemiological studies
Metabolic reprogramming is common in cancer cells, which is mediated at least in part through post-translational modifications of metabolic enzymes.
Metabolic intermediates function as signaling molecules and contribute to metabolic reprogramming in cancer.

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**A**

Glycolysis

- G-6-P → 6-PG
- 6-PGD
- 3-PG
- PGAM1
- 2-PG

**B**

Oxidative PPP

- 6PGD
- 6-PG
- Ru-5-P → nucleotides
- p-PYR → serine

**C**

Serine biosynthesis

- PHGDH

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Hitosugi (2012) *Cancer Cell*
Lin (2015) *Nature Cell Biology*
OxiPPP regulates AMPK homeostasis by balancing the opposing LKB1 and PP2A.

"Dead-end" metabolites function as signaling molecules.

Do specific oncogenic mutations require distinct metabolic alterations?
Do extracellular “blood chemicals” have metabolic and/or signaling functions?

Gao et al. Mol Cell (online Oct 3, 2019)
Identification of oncogene (BRAF-V600E)-specific metabolic “synthetic lethal” partners

Xia (2017) *Cell Metabolism*
Oncogenic mutation specific neo-function

BRAF V600E-specific metabolic “rewiring and reprogramming”

MAPK pathway

Ketogenesis

HMGCS1

HMGCL

Acetoacetate (AA)

Acetone
β-hydroxybutyrate
Ketone bodies

Melanoma cell proliferation and tumor growth
BRAF V600E positive melanoma patients should watch out for ketogenic and low carbohydrate diet.
Lipid lowering agents (e.g. fenofibrate, niacin, statin) selectively attenuate BRAF V600E-positive melanoma growth.
DHAA selectively inhibits melanoma cells expressing BRAF V600E

Dehydroacetic acid (DHAA)
Dietary fat-fueled BRAF V600E tumor growth
Associations of Statins and Diabetes with Diagnosis of Ulcerated Cutaneous Melanoma

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“The histopathologic features of tumor thickness, ulceration, and mitotic activity are considered the hallmarks of rapidly growing melanomas (Balch et al., 2009; Thompson et al., 2011); hence, the presence of ulceration likely reflects a highly proliferative phenotype…

… These findings support our hypotheses that statin use is inversely associated, and diabetes is positively associated, with ulcerated melanoma.”
Is the CSGlcA-T-CHSA axis selectively important for BRAF V600E melanoma?

Novel shRNA library targeting the majority of metabolism-related proteins in human genome

6,872 lentiviral shRNA constructs (each target gene has 1-5 shRNA)

Individual lentivirus

Loss-of-function RNAi screens

8 candidates
HMGCL
HMGCS1
CYP39A1
CYP2C9
CYP2E1
CYP2J2
CYP2S1

Chondroitin sulfates

Chondroitin sulfate
• important structural component of cartilage;
• widely used dietary supplement for treatment of osteoarthritis and joint pain

Chondroitin sulfate biosynthesis

Chondroitin sulfate glucuronyltransferase

UDP-GlcUA
UDP

n

Chain elongation

Repeat unit

Xyl
Gal
Gal
GlcA
GalNAc
GlcA
GalNAc

Chondroitin-4-sulfate (CHSA)

Chondroitin-6-sulfate (CHSC)
CHSA selectively promotes BRAF V600E melanoma PDX tumor growth and confer drug resistance, which requires PTEN.
得不偿失 (More Harm than Good):
Oncogene-specific pro-tumor effects of dietary supplements

Circulating “blood chemicals” have intracellular signaling functions
Mechanism-driven dietary advice with low cancer risk and “Precision Diet”

- Our findings are informative to not only allow physicians or pharmacists to consider individual’s genetic background when advising dietary supplements with low cancer risk, but also educate people to seek professional advice because unlike drugs, many people currently “self-prescribe” dietary supplements.

- BRAF V600E positive cancer patients should watch their dietary fat intake and monitor their circulating acetoacetate levels, and consider lipid lowering agents such as statin as supplemental treatment.

- BRAF V600E patients with PTEN WT should also avoid chondroitin sulfate as a diet supplement, which may commonly increase cancer risk and/or confer drug resistance through PTEN inhibition.
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