VHL and HIF2α reprogram cancer metabolism: Opportunities for Therapeutic Targeting

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TCA metabolites link metabolism to HIF translation

Glucose is diverted to lactate in cancer (Warburg phenomenon) and hypoxic cells
Pathway tracing using $^{13}$C – enriched substrates

13C isotopes & GC-MS to determine metabolite enrichment

Tracing reductive glutamine metabolism using $^{13}$C isotopic tracers

Reductive carboxylation is the primary pathway for lipid synthesis under hypoxia conditions

Metallo CM et al Nature 2012
Glutamine becomes the main carbon source for lipid synthesis under hypoxia

VHL-deficient RCC cells rely on reductive carboxylation even under normoxia

Functional interaction between pVHL and HIF is necessary for inhibition of reductive lipogenesis

HIFs control the cellular response to hypoxia

TUMOR HYPOXIA

GLUCOSE-6P

LACTATE

GLUTAMINE

SUCCINIC
ACID

ACETYL
COA

GLUCOSE-6P

HK-1
LDH-A
PDK-1
PKM2

VHL (+)

VHL (-)

pVHL

HIFα

ROS

EGLN

Metallo CM et al Nature 2012

Metallo CM et al Nature 2012

Gameiro PA et al, Molecular Cell 2013
HIF is sufficient to induce reductive carboxylation from glutamine in RCC cells

Towards the mechanism: HIF does NOT effect the expression of glutamine-metabolizing enzymes

Testing the hypothesis
1. Feed acetate
2. Feed citrate
3. Knock-down of ACLY
4. Knock-down of PDK-1

Are RCC and/or hypoxic cancer cells “addicted” to Glutamine? Yes.
Reductive carboxylation from glutamine is active *in vivo*

![High-resolution 13C NMR spectra](image)

% M1 Glutamine

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<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
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<td>30%</td>
<td>10%</td>
<td>10%</td>
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Time (min)

- Tumor
- Kidney
- Plasma

Extract metabolites from:

- GC-MS analysis
- 13C NMR analysis

Loss of VHL renders RCC cells/tumors sensitive to glutaminase inhibition *in vivo*

![Graph showing change in tumor and kidney weight](image)

Control

BPTES

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Targeting cancer-specific metabolic dependences for therapy

![Diagram showing metabolic pathways](image)

- Proliferation
- Energy (ATP)
- Reducing power (NADPH)
- Biomass

GLUCOSE

GLUTAMINE

Adapted from: Douglas Hanahan and Robert A. Weinberg, Cell 144 (2011)
TCGA Mutations

RCC as metabolic disease

Analysis of Metabolic Pathways

GSEA

Preclinical validation

TCGA Mutations

RCC as metabolic disease

GSEA

Preclinical validation

Clinical Trials

Zebrafish Models of driver mutations

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VHL Alliance

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