VHL and HIF2a reprogram cancer metabolism: Opportunities for Therapeutic Targeting

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Significantly mutated genes
372 ccRCC tumor samples
Frequent VHL alterations
(91% copy, 55% mutation, 7% methylation)

Loss of VHL leads to HIFα activation
Normal Cell
Renal Cancer Cell

1

Preclinical validation
Clinical Trials
Direct targeting of HIF2a with small molecule inhibitors

TUMOR HYPOXIA

- EGFR
- HER2/Neu
- PI3K
- AKT
- mTOR
- EGFR
- EGLN
- SDH
- TSC1/2
- VHL

HIFα mRNA

HIFα

HIFα-ARNT

VEGF
PDGF
TGF
OTHER

Vhl<sup>−/−</sup> zebrafish recapitulates aspects of the human VHL disease

Germline mutations in vhl gene

HIF2α inhibitor ameliorates pathologic angiogenesis and abnormal hematopoiesis in vhl<sup>−/−</sup> embryos

HIF2α inhibitors suppress hypoxia induced erythrocytosis and angiogenic sprouting in vivo

Metelo et al JCI 2015
HIF2a inhibitor 76 improves cardiac contractility in vhl^{−/−} mutants and ameliorates early lethality

Ventricle Fractional shortening

Survival

Metelo et al JCI 2015

Reprogramming of metabolism by HIF2a: opportunities for synthetic lethality

Gameiro et al Cell Metabolism 2013

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

Phase 1a/1b CLINICAL TRIAL with oral GLS inhibitor CB-839

MASSACHUSETTS GENERAL HOSPITAL

Phase 1a  All solid tumors
Phase 1b  RCC
           SDH-related tumors (GIST, RCC, PG)
           FN
           TNBC
           NSCLC

Phase 0  Clinical pharmacology
Phase 1a  Single-agent dose escalation
Phase 1b  Randomized, blinded phase II trial
Phase 2a  Randomized, blinded phase II trial
Phase 2b  Randomized, blinded phase II trial
Phase 3  Randomized, blinded phase III trial
Phase 4  Open-label, non-blinded phase IV trial

Control

BPTES

0 100 200 300 400 500 600 700

Day 0 Day 2 Day 4 Day 6 Day 8 Day 10 Day 12 Day 14

Tumor size (mm)

Control

BPTES

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

Day 0 Day 2 Day 4 Day 6 Day 8 Day 10 Day 12 Day 14

Tumor weight (g)

0 100 200 300 400 500 600 700

Day 0 Day 2 Day 4 Day 6 Day 8 Day 10 Day 12 Day 14

Tumor size (mm)

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Tumor weight (g)
IV contrast-enhanced CT scans were performed at screening and Cycle 7/Day 1 in this patient with clear cell RCC. Almost complete regression of hilar lymphadenopathy had occurred by Cycle 7/Day 1, whereas a complex adrenal metastatic lesion was largely unchanged. The RECIST response is a Partial Response (PR) with a 32% reduction in target lesions.

GLS inhibition compromises the ability of VHL-deficient cells to produce Aspartate for de novo pyrimidine synthesis

De novo and Salvage Pathways for Pyrimidine biosynthesis
GLS1 Inhibition increases ROS in VHL-Deficient RCC Cells

GLS1 Inhibitor effect on VHL-Deficient RCC Cells can be rescued by downstream metabolites
GLS1 Inhibitor effect on VHL-Deficient RCC Cells can be rescued by nucleosides

Mechanisms of cell growth suppression by GLS1 inhibitors

- Apoptosis
- Senescence
- Autophagy
- Cell cycle arrest

GLS Inhibition Induces DNA Replication Stress in VHL-Deficient Cells

GLS Inhibition Induces DNA Replication Stress in VHL-Deficient Cells

Okazaki et al (Submitted)
GLS Inhibition Induces DNA Replication Stress in VHL-Deficient Cells

Treatment of VHL-Deficient Cells by combination of GLS Inhibitors with other drugs

Combination with olaparib (PARP inhibitor)
GLS Inhibitors synergize with Olaparib in killing VHL-Deficient Cells

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