IDH1-R132H tumor cells are not robustly sensitive to PARP inhibition in a 2-HG–dependent manner

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BACKGROUND
- IDH1 mutations accelerate carcinogenesis in several tumor types, including CHOL, LGG, GBM, and AML. Metabolic consequences include elevated intracellular 2-HG, a direct DNA damaging agent.
- Preclinical and clinical studies have shown IDH1-R132H is sensitive to PARP inhibition, suggesting 2-HG-driven HRD loss of function (LOF) is a mechanism of resistance.

OBJECTIVES
- To evaluate response to PARP inhibition in IDH1-R132H cell lines with 2-HG-driven HRD LOF.
- To investigate the relationship between 2-HG and DNA damage and DNA repair.

METHODS
- Two IDH1-R132H-mutant AML PDX cell lines were selected for study.
- Cell lines were grown as xenografts in NOD/SCID-γc mice.
- Tumors were treated with PARP inhibitors and 2-HG in vitro and in vivo.

RESULTS
- IDH1-R132H cells show increased basal DNA damage.
- Treatment of IDH1-R132H cells with 2-HG fails to reduce DNA damage.
- PARP inhibition with OLA or IVO did not reduce 2-HG-driven DNA damage.
- Combination of PARP inhibition and 2-HG did not improve outcome compared to PARP inhibition alone.

CONCLUSIONS
- IDH1-R132H cells are not robustly sensitive to PARP inhibition in a 2-HG–dependent manner.
- PARP inhibition is not a useful strategy for treating 2-HG-driven IDH1-R132H tumors.
- Further studies are needed to identify alternative therapeutic strategies for these tumors.