TITLE: IDH1R132H Is Intrinsically Tumor-Suppressive but Functionally Attenuated by the Glutamate-Rich Cerebral Environment.

SPEAKER: L. ERIC HUANG, M.D., PH.D. CITY/STATE: Salt Lake City, UT

AUTHORS: Patricia D. B. Tiburcio, Ph.D.1,2, David L. Gillespie, Ph.D.1, Randy L. Jensen, M.D., Ph.D.1 and L. Eric Huang, M.D., Ph.D.1,2

ABSTRACT:

Introduction
Recurrent heterozygous mutation of isocitrate dehydrogenase 1 gene (IDH1), predominantly resulting in histidine substitution at arginine 132, was first identified in glioma. The biological significance of IDH1R132H, however, has been controversial, and its prevalent association with glioma remains enigmatic. Although recent studies indicate that IDH1R132H is nonessential to tumor growth or even anti-tumor growth, whether IDH1R132H initiates gliomagenesis remains obscure.

Methods
RCAS/tva glioma models as well as subcutaneous and orthotopic transplantation were used to investigate platelet-derived growth factor B (PDGFB)-driven glioma genesis and growth. IDH1R132H and PDGFB transgenes were engineered to be expressed from either same or different transcripts. Neurosphere culture was used for in vitro studies. Glioma genesis and growth were determined by immunohistochemistry, immunofluorescent microscopy, and survival.

Results
We observed that IDH1R132H was highly suppressive of PDGFB-driven subcutaneous tumor growth, but in orthotopic models IDH1R132H tumor growth and glioma penetrance were virtually indistinguishable from those of IDH1-wildtype tumors. In vitro, addition of glutamate compromised IDH1R132H inhibition of neurosphere genesis, indicating glutamate promotion of oncogenic dominance. Furthermore, IDH1R132H expression was markedly decreased in tumors, indicating tumor antagonism toward IDH1R132H expression, but became more permissible upon the deletion of tumor-suppressor gene Cdkn2a. To provide direct evidence for the opposing effect of IDH1R132H on PDGFB-driven glioma development, we explored tandem expression of the two molecules from a single transcript to preclude selection against IDH1R132H expression. When juxtaposed with oncogenic PDGFB, IDH1R132H overrode the oncogenic activity and obliterated neurosphere genesis and gliomagenesis even in the glutamate-rich microenvironment.

Conclusion
IDH1R132H is intrinsically suppressive of glioma initiation and growth but such tumor-suppressive activity is compromised by the glutamate-rich cerebral cortex. Our findings offer a unifying hypothesis for the perplexing role of IDH1R132H in glioma initiation and growth.