IDH1 R132H mutation

IDH1 R132H is a heterozygous point mutation in IDH1 producing gene, which affects the amino acid arginine at position 132, however, the metabolic importance of this mutation in tumor cell growth remains to be elucidated.

Mutations in the isocitrate dehydrogenase 1 (IDH1) gene commonly occur in gliomas. Remarkably, the R132H mutation in IDH1 (IDH1-R132H) is associated with better prognosis and increased survival than patients lacking this mutation. The molecular mechanism underlying this phenomenon is largely unknown. In this study, we investigated potential cross-talk between IDH1-R132H and Wnt/β-catenin signaling in regulating the cellular properties of human glioma. Although aberrant nuclear accumulation of β-catenin is linked to the malignant progression of gliomas, its association with IDH1 remains unknown. We identified an inverse correlation between IDH1-R132H and the expression and activity of β-catenin in human gliomas. In addition, overexpression of IDH1-R132H in glioblastoma cell lines U87 and U251 led to reduced cell proliferation, migration and invasion, accompanied by increased apoptosis. At the molecular level, we detected a significant reduction in the expression, nuclear accumulation and activity of β-catenin following overexpression of IDH1-R132H. A microarray-based comparison of gene expression indicated that several mediators, effectors and targets of Wnt/β-catenin signaling are downregulated, while negative regulators are upregulated in IDH1-R132H gliomas. Further, overexpression of β-catenin in IDH1-R132H glioma cells restored the cellular phenotype induced by this mutation. Specifically, β-catenin abrogated the decrease in proliferation, invasion and migration, and the increase in apoptosis, triggered by overexpression of IDH1-R132H. Finally, we demonstrate that xenografts of IDH1-R132H overexpressing U87 cells can significantly decrease the growth of tumors in vivo. Altogether, our results strongly suggest that the R132H mutation in IDH1 serves a tumor suppressor function in human glioma by negatively regulating Wnt/β-catenin signaling [1)].

A172 glioma cell lines stably overexpressing either wild-type IDH1 or IDH1 R132H were produced. The results demonstrated that the IDH1 R132H mutation enhanced the proliferation of the A172 glioma cells in vitro. Furthermore, IDH1 R132H performed this function by elevating the expression levels of hypoxia inducible factor-1α, leading to an increase in the expression levels of the key glycolytic enzymes, glucose transporter 1 and hexokinase 2. Therefore, the metabolism was shifted towards aerobic glycolysis, leading to an increase in glucose uptake and lactate production. These findings demonstrated that the IDH1R132H molecular target was involved in orchestrating the Warburg effect in mutant IDH1R132H glioma cells [2)].

1)
Cui D, Ren J, Shi J, Feng L, Wang K, Zeng T, Jin Y, Gao L. R132H mutation in IDH1 gene reduces proliferation, cell survival and invasion of human glioma by downregulating Wnt/β-catenin signaling. Int J Biochem Cell Biol. 2016 Apr;73:72-81. doi: 10.1016/j.biocel.2016.02.007. PubMed PMID: 26860959.
2)
Nie Q, Guo P, Guo L, Lan J, Lin Y, Guo F, Zhou S, Ge J, Mao Q, Li X, Qiu Y. Overexpression of isocitrate dehydrogenase-1R132H enhances the proliferation of A172 glioma cells via aerobic glycolysis. Mol Med Rep. 2015 Jan 13. doi: 10.3892/mmr.2015.3187. [Epub ahead of print] PubMed PMID: 25586175.