Isocitrate dehydrogenase-1 (IDH1) R132 mutations occur in glioma, but their physiological significance is unknown. Here we describe the generation and characterization of brain-specific Idh1 R132H conditional knock-in (KI) mice. Idh1 mutation results in hemorrhage and perinatal lethality. Surprisingly, intracellular reactive oxygen species (ROS) are attenuated in Idh1-KI brain cells despite an apparent increase in the NADP(+)/NADPH ratio. Idh1-KI cells also show high levels of D-2-hydroxyglutarate (D2HG) that are associated with inhibited prolyl-hydroxylation of hypoxia-inducible transcription factor-1α (Hif1α) and up-regulated Hif1α target gene transcription. Intriguingly, D2HG also blocks prolyl-hydroxylation of collagen, causing a defect in collagen protein maturation. An endoplasmic reticulum (ER) stress response induced by the accumulation of immature collagens may account for the embryonic lethality of these mutants. Importantly, D2HG-mediated impairment of collagen maturation also led to basement membrane (BM) aberrations that could play a part in glioma progression. Our study presents strong in vivo evidence that the D2HG produced by the mutant Idh1 enzyme is responsible for the above effects [1)].

1)

Sasaki M, Knobbe CB, Itsumi M, Elia AJ, Harris IS, Chio II, Cairns RA, McCracken S, Wakeham A, Haight J, Ten AY, Snow B, Ueda T, Inoue S, Yamamoto K, Ko M, Rao A, Yen KE, Su SM, Mak TW. D-2-hydroxyglutarate produced by mutant IDH1 perturbs collagen maturation and basement membrane function. Genes Dev. 2012 Sep 15;26(18):2038-49. doi: 10.1101/gad.198200.112. Epub 2012 Aug 27. PubMed PMID: 22925884; PubMed Central PMCID: PMC3444730.