Tumorigenic and non-neoplastic tissue injury occurs via the ischemic microenvironment defined by low oxygen, pH, and nutrients due to blood supply malfunction. Ischemic conditions exist within regions of pseudopalisading necrosis, a pathological hallmark of glioblastoma (GBM), the most common primary malignant brain tumor in adults. To recapitulate the physiologic microenvironment found in GBM tumors and tissue injury, Boyd et al., from Birmingham Alabama developed an in vitro ischemic model and identified chromodomain helicase DNA binding protein 7 (CHD7) as a novel ischemia-regulated gene. Point mutations in the CHD7 gene are causal in CHARGE syndrome, a CNS developmental disorder, and interrupt the epigenetic functions of CHD7 in regulating neural stem cell maintenance and development. Using this ischemic system, they observed microenvironment-mediated decreases in CHD7 expression in brain tumor initiating cells and neural stem cells. Validating the approach, CHD7 was suppressed in the perinecrotic niche of GBM patient and xenograft sections, and an interrogation of patient gene expression datasets determined correlations between low CHD7, increasing glioma grade and worse patient outcomes. Segregation of GBM by molecular subtype revealed a novel observation that CHD7 expression is elevated in proneural vs mesenchymal glioblastoma. Genetic targeting of CHD7 and subsequent gene ontology analysis of RNA sequencing data indicated angiogenesis as a primary biological function affected by CHD7 expression changes. They validated this finding in tube formation assays and vessel formation in orthotopic GBM models. Together, this data provide further understanding of molecular responses to ischemia and a novel function of CHD7 in regulating angiogenesis in both neoplastic and non-neoplastic systems.

Inactivating mutations in the epigenetic modifier chromodomain helicase DNA binding protein 7 (CHD7) are associated with CHARGE syndrome, a disorder causing Coloboma, Heart defects, Atresia choanae, growth Retardation, Genital abnormalities, and Ear abnormalities.

They find for the first time that ischemic microenvironments repress CHD7 levels in neural progenitors and brain tumor initiating cells/cancer stem cells. This novel results also demonstrate that reduced levels of CHD7 in neural progenitors or brain tumor initiating cells increase angiogenesis. They believed that this data may have important implications for development, stem cells, and cancer [1].

1)
Boyd NH, Walker K, Ayokanmbi A, Gordon ER, Whetsel J, Smith CM, Sanchez RG, Lubin F, Chakraborty A, Tran AN, Herting C, Hambardzumyan D, Yancey Gillespie G, Hackney JR, Cooper SJ, Jiao K, Hjelmeland AB. CHD7 is Suppressed in the Perinecrotic/Ischemic Microenvironment and is a Novel Regulator of Glioblastoma Angiogenesis. Stem Cells. 2019 Jan 10. doi: 10.1002/stem.2969. [Epub ahead of print] PubMed PMID: 30629778.