CHD7

Chromodomain-helicase-DNA-binding protein 7 also known as ATP-dependent helicase CHD7 is an enzyme that in humans is encoded by the CHD7 gene.

CHD7 is an ATP-dependent chromatin remodeler homologous to the Drosophila trithorax-group protein Kismet.Mutations in CHD7 are associated with CHARGE syndrome

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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)].

Badodi et al., described molecular convergence between BMI1 and CHD7 in the initiation of medulloblastoma. Identified in a functional genomic screen in mouse models, a BMI1High;CHD7Low expression signature within medulloblastoma characterizes patients with poor overall survival.

They showed that BMI1-mediated repression of the ERK1/2 pathway leads to increased proliferation and tumor burden in primary human MB cells and in a xenograft model, respectively. They provided evidence that repression of the ERK inhibitor DUSP4 by BMI1 is dependent on a more accessible chromatin configuration in G4 MB cells with low CHD7 expression. These findings extend current knowledge of the role of BMI1 and CHD7 in medulloblastoma pathogenesis, and they raise the

possibility that pharmacological targeting of BMI1 or ERK may be particularly indicated in a subgroup of MB with low expression levels of CHD7 [2].

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2)
Badodi S, Dubuc A, Zhang X, Rosser G, Da Cunha Jaeger M, Kameda-Smith MM, Morrissy AS, Guilhamon P, Suetterlin P, Li XN, Guglielmi L, Merve A, Farooq H, Lupien M, Singh SK, Basson MA, Taylor MD, Marino S. Convergence of BMI1 and CHD7 on ERK Signaling in Medulloblastoma. Cell Rep. 2017 Dec 5;21(10):2772-2784. doi: 10.1016/j.celrep.2017.11.021. PubMed PMID: 29212025; PubMed Central PMCID: PMC5732319.