EZH2

EZH2 is thought to promote tumor progression by silencing tumor suppressor genes. Hence pharmacological disruption of the PRC2 is an attractive therapeutic strategy for cancer treatment.

Ott et al. showed that EZH2 is expressed in human glioma and correlates with malignancy. Silencing of EZH2 reduced glioma cell proliferation and invasiveness. While they did not observe induction of cell cycle-associated tumor suppressor genes by silencing or pharmacological inhibition of EZH2, microarray analyses demonstrated a strong transcriptional reduction of the AXL receptor tyrosine kinase. Neither histone nor DNA methylation appeared to be involved in the positive regulation of AXL by EZH2. Silencing AXL mimicked the antiinvasive effects of EZH2 knockdown. Finally, AXL expression is found in human gliomas with high EZH2 expression. Collectively these data suggest that EZH2 drives glioma invasiveness via transcriptional control of AXL independent of histone or DNA methylation [1].

EZH2 is a potential prognostic marker for poor overall survival (OS), progression free survival (PFS) and lower KPS score in glioma patients.

Histone-lysine N-methyltransferase EZH2 is a Histone methyltransferase enzyme that in humans is encoded by the EZH2 gene.

EZH2 encodes a member of the Polycomb-group (PcG) family, which forms multimeric protein complexes and is involved in maintaining the transcriptional repressive state of genes over successive cell generations. A study suggested that the EZH2-exerted transcription repression involves a mechanism that directly controls DNA methylation.

Two transcript variants encoding distinct isoforms have been identified for this gene.

Recent data have shown the potential oncogenic role and prognostic significance of EZH2 in several human cancers. However, the clinical signature and further mechanisms of EZH2 function in gliomagenesis are still poorly understood [2].

Increased EZH2 expression was associated with tumor grade. High expression of EZH2 in glioblastoma (Glioblastoma) was determined to be a strong and independent predictor of short overall survival. Further, Zhang et al. screened EZH2 targets and associated genes in Glioblastoma. Repression of EZH2 induced cell cycle arrest and inhibited tumor growth in vivo. This event represents a positive feedback loop with beta-catenin/TCF4 and STAT3 signaling. Taken together, EZH2 could be an independent prognostic factor and potential therapeutic target for Glioblastoma [3].

There is an interaction of Long non-coding RNA (lncRNAs) with signaling pathways in gliomas with EZH2 [4].

The findings suggest that EZH2 plays an important part in the development of multidrug resistance and may represent a novel therapeutic target for multidrug-resistant glioblastoma [5].

NIMA-related kinase 2 (NEK2) as a functional binding protein of enhancer of zeste homolog 2 (EZH2) that plays a critical role in the posttranslational regulation of EZH2 protein in glioma stem cells (GSCs). NEK2 was among the most differentially expressed kinase-encoding genes in GSC-containing

cultures (glioma spheres), and it was required for in vitro clonogenicity, in vivo tumor propagation, and radioresistance. Mechanistically, the formation of a protein complex comprising NEK2 and EZH2 in glioma spheres phosphorylated and then protected EZH2 from ubiquitination-dependent protein degradation in a NEK2 kinase activity-dependent manner. Clinically, NEK2 expression in patients with glioma was closely associated with EZH2 expression and correlated with a poor prognosis. NEK2 expression was also substantially elevated in recurrent tumors after therapeutic failure compared with primary untreated tumors in matched Glioblastoma patients. We designed a NEK2 kinase inhibitor, compound 3a (CMP3a), which efficiently attenuated Glioblastoma growth in a mouse model and exhibited a synergistic effect with radiotherapy. These data demonstrate a key role for NEK2 in maintaining GSCs in Glioblastoma by stabilizing the EZH2 protein and introduce the small-molecule inhibitor CMP3a as a potential therapeutic agent for Glioblastoma [6].

1)
Ott M, Litzenburger UM, Sahm F, Rauschenbach KJ, Tudoran R, Hartmann C, Marquez VE, von Deimling A, Wick W, Platten M. Promotion of glioblastoma cell motility by enhancer of zeste homolog 2 (EZH2) is mediated by AXL receptor kinase. PLoS One. 2012;7(10):e47663. doi: 10.1371/journal.pone.0047663. Epub 2012 Oct 15. PubMed PMID: 23077658; PubMed Central PMCID: PMC3471855.
2)
Bian EB, Li J, He XJ, Zong G, Jiang T, Li J, Zhao B. Epigenetic modification in gliomas: role of the histone methyltransferase EZH2. Expert Opin Ther Targets. 2014 Oct;18(10):1197-206. doi: 10.1517/14728222.2014.941807. Epub 2014 Jul 21. PubMed PMID: 25046371.
3)
Zhang J, Chen L, Han L, Shi Z, Zhang J, Pu P, Kang C. EZH2 is a negative prognostic factor and exhibits pro-oncogenic activity in glioblastoma. Cancer Lett. 2015 Jan 28;356(2 Pt B):929-36. doi: 10.1016/j.canlet.2014.11.003. Epub 2014 Nov 11. PubMed PMID: 25444902.
4)
Bian EB, Li J, Xie YS, Zong G, Li J, Zhao B. LncRNAs: New Players in Gliomas, With Special Emphasis on the Interaction of lncRNAs With EZH2. J Cell Physiol. 2015 Mar;230(3):496-503. doi: 10.1002/jcp.24549. PubMed PMID: 24403021.
5)
Fan TY, Wang H, Xiang P, Liu YW, Li HZ, Lei BX, Yu M, Qi ST. Inhibition of EZH2 reverses chemotherapeutic drug TMZ chemosensitivity in glioblastoma. Int J Clin Exp Pathol. 2014 Sep 15;7(10):6662-70. eCollection 2014. PubMed PMID: 25400745; PubMed Central PMCID: PMC4230130.
6)
Wang J, Cheng P, Pavlyukov MS, Yu H, Zhang Z, Kim SH, Minata M, Mohyeldin A, Xie W, Chen D, Goidts V, Frett B, Hu W, Li H, Shin YJ, Lee Y, Nam DH, Kornblum HI, Wang M, Nakano I. Targeting NEK2 attenuates glioblastoma growth and radioresistance by destabilizing histone methyltransferase EZH2. J Clin Invest. 2017 Jul 24. pii: 89092. doi: 10.1172/JCI89092. [Epub ahead of print] PubMed PMID: 28737508.