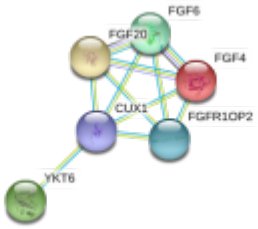
CUX1



Cut Like homeobox 1 (CUX1), which encodes an auxiliary factor in base excision repair, resides on 7q22.1, the most frequently and highly amplified chromosomal region in glioblastomas.

It is expressed in the upper layer of the cortex and participates in DNA replication, cell cycle control, and DNA repair. It has been shown to be involved in the proliferation of various types of solid tumors.

The aims of a study of Wu et al. from the Linyi People's Hospital, Qingdao University, Weifang Medical University, Taishan Medical University, Binzhou Medical University, were to explore the relationship between CUX1 expression and the glioma outcome by performing a series of functional experiments and bioinformatics. Firstly, they found that CUX1 expression levels differed among patients with different grades of gliomas, and they were significantly correlated with the prognosis of glioma patients according to an analysis of data from a public database. qRT-PCR, western blotting, and immunohistochemical analysis of CUX1 were performed to demonstrate that the expression of CUX1 was positively correlated with the glioma WHO grade ($P < 0.05$) and several malignant clinical pathological parameters, including Ki67 and P53mut. In addition, the multivariate Cox regression and Kaplan-Meier curves showed that CUX1 expression exerted predictive value for overall survival. Finally, to further investigate the functions of CUX1, they identified CUX1-associated genes and, though GO/KEGG analysis, their associated biological functions and signaling pathways; the results suggested that the activity of CUX1 might be exerted via the JAK-STAT signaling pathway or other key regulators of the cell cycle to promote proliferation, inflammation, and chemotherapy resistance in glioma. Taken together, these results indicate that CUX1 is a potential biomarker of malignancy and prognosis and may serve as a potential therapeutic target for glioma patients. [1)].

To monitor the effect of CUX1 and its CUT domains on APE1 activity, DNA repair assays were performed with purified proteins and cell extracts. CUX1 protein expression was analyzed by immunohistochemistry using a tumor microarray of 150 glioblastoma samples. The effect of CUX1 knockdown and overexpression on the resistance of glioblastoma cell lines to temozolomide was investigated.

Kaur et al. showed that CUT domains stimulate APE1 activity. In agreement with these findings, CUX1 knockdown causes an increase in the number of abasic sites in genomic DNA and a decrease in APE1 activity as measured in cell extracts. Conversely, ectopic CUX1 expression increases APE1 activity and lowers the number of abasic sites. Having established that CUX1 is expressed at high levels in most glioblastomas, we next show that the resistance of glioblastoma cells to temozolomide and to a combined treatment of temozolomide and ionizing radiation is reduced following CUX1 knockdown, but increased by overexpression of CUX1 or a short protein containing only 2 CUT domains, which is active in DNA repair but devoid of transcriptional activity.

These findings indicate that CUX1 expression level impacts on the response of glioblastoma cells to treatment and identifies the CUT domains as potential therapeutic targets. [2].

References

[1]
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[2]
Kaur S, Ramdzan ZM, Guiot MC, Li L, Leduy L, Ramotar D, Sabri S, Abdulkarim B, Nepveu A. CUX1 stimulates APE1 enzymatic activity and increases the resistance of glioblastoma cells to the mono-alkylating agent temozolomide. Neuro Oncol. 2018 Mar 27;20(4):484-493. doi: 10.1093/neuonc/nox178. PubMed PMID: 29036362; PubMed Central PMCID: PMC5909652.