IKBKE

Inhibitor of nuclear factor kappa-B kinase subunit epsilon also known as I-kappa-B kinase epsilon or IKK-epsilon is an enzyme that in humans is encoded by the IKBKE gene.

It is a major oncogenic protein in tumors and can inhibit glioblastoma cell proliferation, migration, and tumorigenesis.

Guo et al. aimed to investigate the mechanism of IKBKE enhancing the resistance of glioma cells to temozolomide.

For the in vitro experiments, LN18 and U118 glioblastoma cells were treated with a combination of sh/oe-IKBKE lentivirus and TMZ. Cell proliferation was determined by the EdU assay and colony formation assays. Apoptosis was analyzed by the TUNEL assay. In vivo, LN18 NC and LN18 sh-IKBKE cells were implanted into the cerebrums of nude mice to detect the effect of combination therapy. The protein and mRNA levels were assayed by western blot, immunohistochemistry, and qRT-PCR.

They demonstrated that IKBKE enhances the resistance of glioblastoma cells to temozolomide (TMZ) by activating the AKT/NF-κB signaling pathway to upregulate the expression of the DNA repair enzyme o6-methylguanine-dna methyltransferase (MGMT). In glioblastoma cells, IKBKE knockdown enhances apoptosis and suppresses cell proliferation, clone formation, and tumor development in vivo induced by TMZ. However, overexpression of IKBKE reduces the effects of TMZ.

This study suggest that inhibition of IKBKE can enhance the therapeutic effect of TMZ on GBM in vitro and in vivo, providing new research directions and therapeutic targets for the treatment of GBM [1)].

The Serine/threonine-specific protein kinase IKBKE is frequently overexpressed or activated in a variety of human cancers. Ectopic expression of IKBKE induces malignant transformation, cell migration, invasion and chemoresistance. Thus, IKBKE is an attractive target for anti-cancer drug development.

By screening of NCI Diversity Set and Clinical Collection I and II compound libraries using cell-based assay, we identified several candidates of IKBKE inhibitors, which directly inhibited IKBKE kinase activity in vitro and in vivo. One of them, malachite green oxalate (MCCK1), was further characterized. The mechanism was examined by western blot, immunoprecipitation (IP) and Immunofluorescence. We also evaluated in a mouse xenograft model. In vitro kinase assay and luciferase reporter assay were also performed in our experiments.

MCCK1 inhibits IKBKE kinase as well as its downstream targets such as IκBα, p65 and IRF3. MCCK1 is a selective inhibitor for IKBKE, with moderate effect on TBK1, but does not inhibit the activation of IKKα/β, STAT3, Erk-1/2, p38 or JNK. The inhibition of IKBKE by MCCK1 resulted in induction of cell growth arrest and apoptosis selectively in human cancer cells that harbor aberrant expression of IKBKE. Furthermore, MCCK1 inhibits tumor growth in nude mice of human cancer cells in which IKBKE is elevated but not of those cancer cells in which it is not.

These data indicate that MCCK1 is an IKBKE inhibitor with anti-tumor activity in vitro and in vivo and could be a potential anti-cancer agent for patients with tumors over expressing IKBKE [2)].

1)
Guo G, Sun Y, Hong R, Xiong J, Lu Y, Liu Y, Lu J, Zhang Z, Guo C, Nan Y, Huang Q. IKBKE enhances TMZ-chemoresistance through upregulation of MGMT expression in glioblastoma. Clin Transl Oncol. 2019 Dec 21. doi: 10.1007/s12094-019-02251-3. [Epub ahead of print] PubMed PMID: 31865606.
2)
Liu T, Gao X, Xin Y. Identification of an IKBKE inhibitor with antitumor activity in cancer cells overexpressing IKBKE. Cytokine. 2019 Jan 24;116:78-87. doi: 10.1016/j.cyto.2019.01.005. [Epub ahead of print] PubMed PMID: 30685606.