Cathepsin L

Cathepsin L is a lysosomal cysteine protease that plays important roles in cancer tumorigenesis, proliferation and chemotherapy resistance.

It is exclusively elevated in a variety of malignancies, including gliomas.

Cathepsin L acts as an upstream regulator of NF-κB activation in human glioma cells and contributes to their sensitivity to ionizing radiation (IR) in vitro. Inhibition of cathepsin L can sensitize the cells to IR [1].

Cathepsin L is involved in modulation of radiosensitivity in human glioma U251 cells (harboring the mutant type p53 gene) in vitro [2].

A study assessed whether knockdown of Cathepsin L can influence GSC growth, tumor radiosensitivity, and clinical outcome. Protein levels of Cathepsin L and stem cell markers (CD133 and Nestin) were analyzed in samples from 90 gliomas of different WHO grades and 6 normal brain tissues by immunohistochemistry. Two glioma stem cell lines with overexpressed Cathepsin L were stably transfected with Cathepsin L small hairpin RNA expression vectors. The effect of Cathepsin L inhibition on radiosensitivity, self-renewal, stemness, DNA damage, and apoptosis were evaluated. In addition, an intracranial animal model and subcutaneous tumor xenografts in nude mice were used to assess tumor response to Cathepsin L inhibition in vivo.

The results proved that expression of Cathepsin L and CD133, but not of Nestin, correlated with malignant grades of glioma tissues. GSCs with high Cathepsin L and CD133 co-expression were extraordinarily radioresistant. Cathepsin L inhibition with radiotherapy significantly reduced GSC growth, promoted apoptosis, and improved radiosensitivity. Knockdown of Cathepsin L resulted in a dramatic reduction of CD133 expression, as well as the decreased phosphorylation of DNA repair checkpoint proteins (ATM and DNA-PKcs). Furthermore, combination of Cathepsin L inhibition and radiotherapy potently blocked tumor growth and decreased blood vessel formation in vivo. Taken together, these findings suggest the Cathepsin L as a promising therapeutic target for clinical therapy in GBM patients [3].

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Yang N, Wang P, Wang WJ, Song YZ, Liang ZQ. Inhibition of cathepsin L sensitizes human glioma cells to ionizing radiation in vitro through NF-κB signaling pathway. Acta Pharmacol Sin. 2015 Mar;36(3):400-10. doi: 10.1038/aps.2014.148. Epub 2015 Feb 9. PubMed PMID: 25661319; PubMed Central PMCID: PMC4349927.
2)
Zhang QQ, Wang WJ, Li J, Yang N, Chen G, Wang Z, Liang ZQ. Cathepsin L suppression increases the radiosensitivity of human glioma U251 cells via G2/M cell cycle arrest and DNA damage. Acta Pharmacol Sin. 2015 Sep;36(9):1113-25. doi: 10.1038/aps.2015.36. Epub 2015 Jun 22. PubMed PMID: 26095040; PubMed Central PMCID: PMC4561966.
3)
Wang W, Long L, Wang L, Tan C, Fei X, Chen L, Huang Q, Liang Z. Knockdown of Cathepsin L promotes radiosensitivity of glioma stem cells both in vivo and in vitro. Cancer Lett. 2015 Dec 16. pii: S0304-3835(15)00753-3. doi: 10.1016/j.canlet.2015.12.012. [Epub ahead of print] PubMed PMID: 26706414.