

p38 mitogen-activated protein kinases are a class of mitogen-activated protein kinases (MAPKs) that are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation, apoptosis and autophagy.

Differentiation therapy has been proposed as an alternative for glioblastoma treatment, with the aim of bringing cancer cells into a post-mitotic/differentiated state, ultimately limiting tumor growth. As an integral component of cancer development and regulation of differentiation processes, kinases are potential targets of differentiation therapies.

Lane et al. in a study describe how the screening of a panel of kinase inhibitors (KIs) identified PDGF-R α/β inhibitor CP-673451 as a potential differentiation agent in glioblastoma. They show that targeting PDGF-R α/β with CP-673451 in vitro triggers the outgrowth of neurite-like processes in glioblastoma cell lines and glioblastoma stem cells (GSCs), suggesting differentiation into neural-like cells while reducing proliferation and invasion in 3D hyaluronic acid hydrogels. In addition, they report that treatment with CP-673451 improves the anti-tumor effects of temozolomide in vivo using a subcutaneous xenograft mouse model. RNA sequencing and follow-up proteomics revealed that upregulation of phosphatase DUSP1 and consecutive downregulation of phosphorylated-p38 mitogen-activated protein kinases can underlie the pro-differentiation effect of CP-673451 on Glioblastoma cells. Overall, the present study identifies a potential novel therapeutic option that could benefit Glioblastoma patients in the future, through differentiation of residual GSCs post-surgery, with the aim to limit glioblastoma recurrence and improve quality of life ¹⁾.

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Lane R, Cilibrasi C, Chen J, Shah K, Messuti E, Mazarakis NK, Stebbing J, Critchley G, Song E, Simon T, Giamas G. PDGF-R inhibition induces glioblastoma cell differentiation via DUSP1/p38MAPK signaling. Oncogene. 2022 Apr 7. doi: 10.1038/s41388-022-02294-x. Epub ahead of print. PMID: 35393545.

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