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Cytotoxic Synergy in Dual Inhibition of Nek2 and EGFR Kinases in Glioblastoma Cells

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Glioblastoma (GBM), also known as Grade IV astrocytoma, is an aggressive form of brain tumor which shows strong resistance to chemotherapy and radiotherapy. The median survival time is only 12-15months with the current treatment options. Therefore, there is an unmet need to identify novel druggable targets associated with glioblastoma progression. The Never-In-Mitosis-A-related kinase (Nek) family in mammals is comprised of eleven genes (Nek1-11), a prominent member of which is Nek2 kinase. Nek2 primarily localizes at centrosomes and has been shown to play critical roles in centrosome separation and bipolar spindle formation. Many malignant tumors including lung cancer and GBM show overexpression of Nek2 kinase. Furthermore, Nek2 knockdown is known to reduce malignancy of GBM. Many highly invasive cancers, including GBM, also overexpress EGFR, a growth factor receptor tyrosine kinase. Our research hypothesis is aimed at developing dual-action single molecule inhibitor of both Nek2 and EGFR kinases that would impart enhanced anti-cancer properties in GBM cells. To check the merit of our working hypothesis that dual inhibition of Nek2 and EGFR kinases by a single agent will provide superior anti-cancer effects, we first used the following commercially available inhibitors- Rac (Nek2 kinase inhibitor), Lap (Lapatinib, EGFR kinase inhibitor), Erl (Erlotinib, EGFR kinase inhibitor) and investigated their synergistic effects on cell viability assay on a lung cancer cell line, A549. Our findings show that simultaneous inhibition of both Nek2 and EGFR kinases by small molecules, Rac with Lap and Rac with Erl, yielded net signaling output that results in synergistic cell death of A549 cells. Our present work is focused on inhibiting Nek2 and EGFR kinases in glioblastoma cell lines, namely A172 and C6, which are known to overexpress both Nek2 and EGFR kinases. Preliminary data shows that simultaneous dual inhibition also decreases the cell viability of glioblastoma cells. A recent publication suggested that Nek2-NF-kB could be a potential axis for targeting GBM tumors; Nek2 activated the non-canonical NF-kB signaling by interacting with NIK by posttranslational modification. Present effort of the lab is directed towards investigating the phosphorylation status of NIK, as a potential downstream target of Nek2 kinase after treatment with commercially available dual action inhibitors.

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