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A novel multimodal strategy combining miRNA modulation and tyrosine kinase inhibitors to enhance glioblastoma cell sensitivity to therapeutics

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Glioblastoma Multiforme (GBM) is the most hostile and lethal form of human brain cancer; the patients usually survive for only up to one year under treatment. Current treatments for GBM have been insufficient, with a high recurrence after surgery, radiation, or chemotherapy, primarily because of the resistance of tumor cells to chemotherapy drugs. Studies have shown that dysregulation of PI3K and MAPK pathways has been one of the underlying causes of uncontrolled cell proliferation, apoptotic inhibition and metastasis for glioblastoma, but individual targeting of these pathways using kinase inhibitors has been insufficient due to the existence of cross-talks between parallel cascades. Micro RNAs (miRNAs), known to directly target a network of genes such as *PTEN, EGFR, TP53* also facilitate simultaneous repression of PI3K and MAPK pathways. miRNAs can act as tumor suppressors or oncogenes and have been identified as promising tumor biomarkers. This research study was on glioblastoma focuses on a multimodal strategy, combining the impact of Tyrosine Kinase Inhibitors (TKIs) along with miRNA inhibitors on up-regulated miRNAs to modulate the expressions of tumor suppressing genes and target aberrant cellular pathways (PI(3)K and MAPK). Patient data from The Cancer Genome Atlas (TCGA) demonstrated that overexpressed EGFR and mutated PTEN play a significant role in GBM. MiRNA-gene analysis along with a structure-based drug discovery approach was used to compare the stability of miRNAs+Small molecule inhibitors of miRNAs (SMIRs)+Erlotinib (TKI) followed by Temozolomide (TMZ) vs. EGFR+TMZ. The simulation results of a myriad of SMIR combinations from PubChem were analyzed using AutoDock software through the energy scores and binding affinity values. The high throughput virtual screening approach used highlighted the synergistic effects of horizontal inhibition of signaling pathways through TKIs and vertical inhibition of downstream signaling pathways with miRNA inhibitors as a promising approach towards decreasing GBM cell viability. This is in contrast to any significant effect observed by using TMZ, a commercial drug on an amplified and overexpressed EGFR.

Biography

Viraj Mehta is a junior at Basis Scottsdale, school in the U.S. He has been doing independent computational research on glioblastoma multiforme for two years and has discovered ways to identify small molecule inhibitors of miRNAs in order to enhance glioblastoma cell susceptibility to tyrosine kinase inhibitors.

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