Abstract

Glioblastoma (GBM) or the Grade IV malignant glioma is the most aggressive of brain tumors resulting in maximum morbidity and mortality. This thesis primarily explores a fusion protein ETV6-NTRK3 (EN) and temozolomide (TMZ) resistance in GBM and effective therapeutic interventions to overcome the same. Fusion proteins are oncogenic proteins formed due to the joining of two genes during chromosomal translocation. Here, GBM cell lines containing the EN fusion gene were developed. Further, to regulate the EN fusion in GBM a transcription factor RBPJ upstream of the ETV6 gene was identified. Since the EN fusion is also under the control of the ETV6 promoter/enhancer, RBPJ is seen to regulate the EN fusion. Next, Furamidine was established to be an inhibitor of RBPJ in GBM. Treatment with Furamidine was able to downregulate the EN downstream PI3K-Akt pathway and the epithelial to mesenchymal transition (EMT) pathway and induce apoptosis. Animal GBM models of both parental and EN fusion containing tumors also showed downregulation of EN pathway proteins after Furamidine treatment thus establishing it to be an effective inhibitor of RBPJ and thus of EN harboring fusions.

Temozolomide is the first chemotherapeutic drug that is administered to GBM patients. However, temozolomide resistance poses a common problem with 50% of patients not responding to TMZ. In this work, the role of Notch signaling pathway in the development of TMZ resistance was examined and a positive correlation was found. Next, the NICD(Notch1 Intracellular Domain) - RBPJ binding, an interaction that is crucial for the activation of the Notch pathway was targeted. This interaction can be inhibited by Nitric oxide (NO). Hence, Nicorandil, an NO donating compound was selected to modulate the Notch pathway and overcome TMZ resistance in GBM. Here it was shown that treatment with Nicorandil and TMZ was able to downregulate the Notch and EMT pathway and induce apoptosis in GBM and TMZ resistant GBM cell lines. The effect was found to be more significant in TMZ resistant cell lines, thus it was concluded that Nicorandil and TMZ when used as a combinatorial therapy has the potential to overcome TMZ resistance in GBM.

Keywords: Glioblastoma, ETV6-NTRK3 fusion, Furamidine, Temozolomide resistance, Therapeutic interventions, Nicorandil