Neuroblastoma and Glioblastoma Differentiation by Retinoic Acid: Epigenetic and Transcriptional Changes

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Purpose: Neuroblastoma and glioblastoma are highly aggressive malignant neural tumors affecting pediatric and adult populations respectively. Both are associated with very poor prognoses despite multimodality treatment. All Trans Retinoic Acid (RA), a vitamin A derivative, promotes cellular differentiation; however, its effects on malignant neuroblastoma stem cells (NSC) and glioblastoma stem cells (GSC) and underlying molecular mechanisms remain unknown. Methods: SH-SY5Y NSCs and U87-MG GSCs were treated with increasing concentrations of RA (1, 2.5, 5,10, and 20 μM) in growth media containing 10% fetal bovine serum. Control groups were incubated without RA. Neuronal differentiation was evaluated using immunofluorescence staining for the neuron-specific marker TUJ1. Single-cell microarray gene expression analysis was performed to analyze transcriptional profiles in treated NSCs and GSCs. Results: RA at 5 μM induced differentiation in SH-SY5Y NSCs and U87-MG GSCs while concentrations =10 μM resulted in cytotoxicity. Microarray RNA analysis demonstrated statistically significant downregulation of EGFR and PI3K/AKT/mTOR signaling pathway components in U87-MG GSCs treated with RA. Similarly, MYCN downregulation was seen in SH-SY5Y NSCs following RA treatment, determined by one-way ANOVA with post-hoc analysis ($p<0.05$). Conclusion: RA at 5 μM effectively induces differentiation in malignant GSCs and NSCs. The observed downregulation of EGFR and PI3K/AKT/mTOR signaling in glioblastoma cells, as well as MYCN suppression in neuroblastoma cells, suggests that RA-mediated differentiation involves multiple molecular mechanisms targeting oncogenic pathways. These findings support further investigation of RA-based differentiation therapy for neuroblastoma and glioblastoma.

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