Industry Day Theme # Sustainable Medical Technologies

Prospective role of Neuronal Differentiation Factors in Glioblastoma Treatment

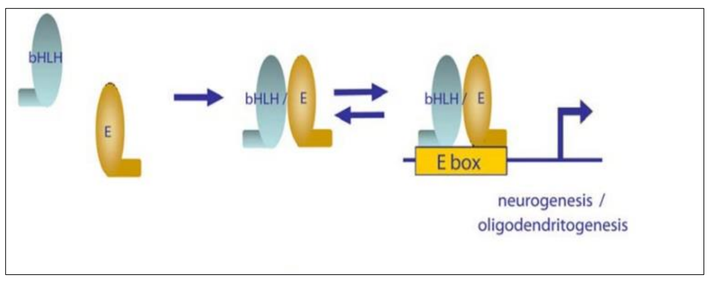
Anirban Jana, Rahul Agrawal, Ritu Kulshreshtha*.

Biochemical Engineering and Biotechnology, IIT Delhi

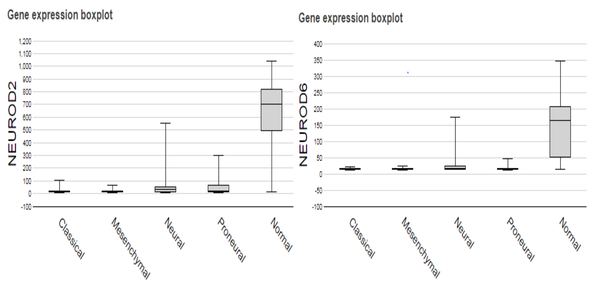
Abstract
Neural differentiation factors are a class of bHLH transcription factors that have been recently shown to play a role in various cancers. However, their functions in glioblastoma (GBM) remain unstudied so far. Our study demonstrates significant downregulation of neuronal differentiation factors, NeuroD2 and NeuroD6 in GBM patients and cell lines. Low levels of NeuroD2 and NeuroD6 were found to be correlated with overall poor survival of GBM patients. Functional characterization of NeuroD2 and NeuroD6 demonstrate their function as tumor suppressors in GBM by bringing about inhibition of cell proliferation, migration and tumor formation ability in GBM cell lines T98G and A172. Our study also reveals that both NeuroD2 and NeuroD6 are transcriptionally induced by p53. NeuroD2 gene-signature was found to be enriched in pathways belonging to cytokine-cytokine receptor interaction, TNF-signaling, PI3K-AKT signaling, focal adhesion and ECM-receptor interaction. Overall, our work reveals that NeuroD factors may function as diagnostic and prognostic biomarkers for GBM treatment. Further, overexpression of NeuroD factors may be an attractive option for GBM treatment.

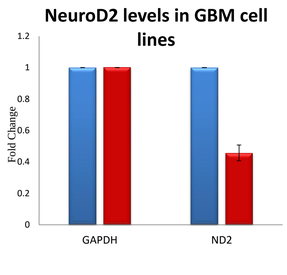
Regulation of bHLH-NeuroD2 and NeuroD6

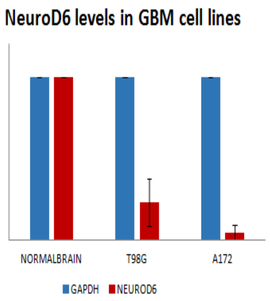
a) Neuronal Differentiation factors



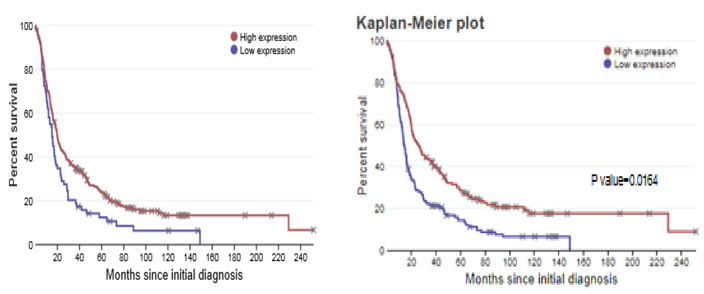
b) NeuroD2 and NeuroD6 downregulated in GBM



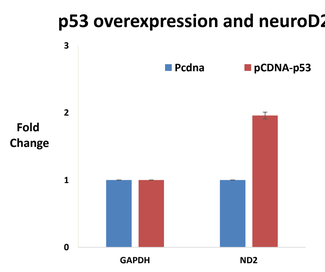


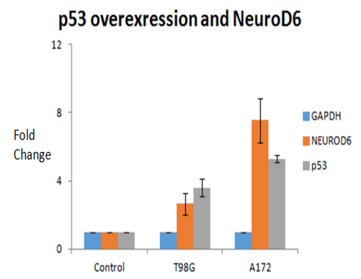


c) Low levels of NeuroD2 and NeuroD6- correlation with poor survival of GBM patients



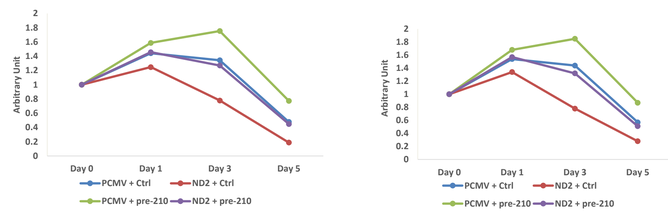
d) NeuroD2 and NeuroD6 both regulated by p53



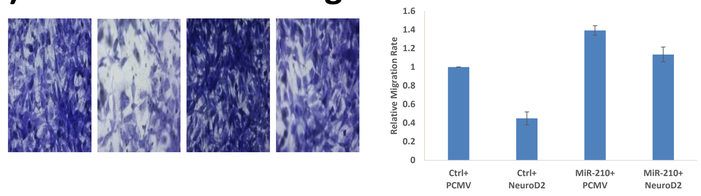


NeuroD functions as a tumor suppressor in GBM

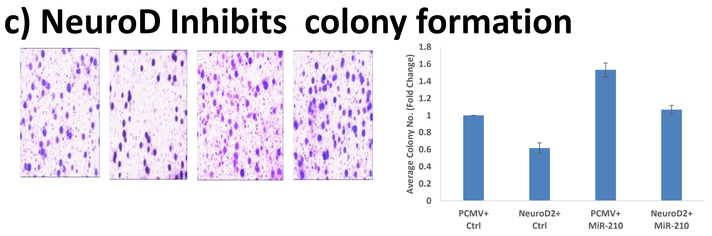
a) NeuroD Inhibits cell proliferation



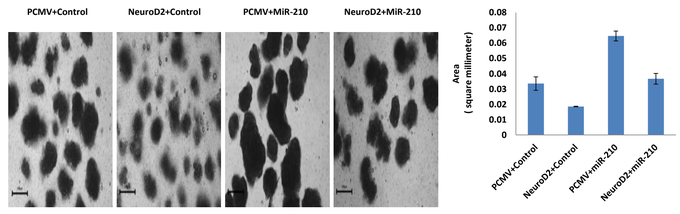
b) NeuroD Inhibits migration



c) NeuroD Inhibits colony formation

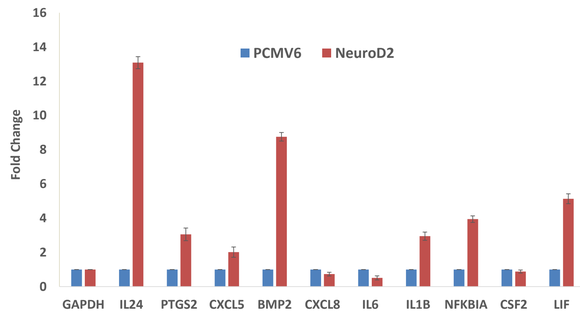


d) NeuroD Inhibits spheroid formation



NeuroD2 target analysis

Upregulated pathways	Downregulated pathways
TNF signaling pathways	Antigen processing and presentation
Cytokine-cytokine receptor interaction	TGFB pathway
MAPK signaling pathway	PI3K-Akt signaling pathway
Toll like receptor signaling pathways	ECM-receptor interaction
Hematopoietic cell lineage	Focal adhesion



Conclusions

Our work shows significant downregulation of specific Neuronal differentiation factors, NeuroD2 and NeuroD6, in glioblastoma. Overexpression of NeuroD2 and NeuroD6 bring about inhibition of cellular proliferation, migration and colony formation abilities in GBM suggesting their tumor suppressive role. NeuroD2 is a direct target of oncogenic miR210 and is involved in regulating different cancer pathways. Overall, neuronal differentiation factors may have a potential therapeutic role in GBM

Industrial Significance

Though understanding the GBM regulatory networks improved, but still side effects, drug resistance, drug-induced toxicity and cancer recurrence are still the main obstacles.

Alteration in levels of NeuroDs has been correlated with GBM diagnosis, prognosis and this therapy provides a promising approach for cancer therapy and can simultaneously regulate multiple genes and pathways.

Development of novel therapeutic strategies have immense industrial significance as can be evaluated from the promising current clinical trials involving NeuroD factors.

Technology Readiness Level

In-vitro experiments showed very convincing results. After in vivo analysis, clinical trials can be done. This can be a new strategy to treat GBM.

References

Agrawal R, Garg A, Benny Malgulwar P, Sharma V, Sarkar C, Kulshreshtha R2017 p53 and miR-210 regulated NeuroD2, a neuronal basic helix-loop-helix transcription factor, is downregulated in glioblastoma patients and functions as a tumor suppressor under hypoxic microenvironment. Int J Cancer. December 11; 15:686

Acknowledgement

AJ thanks Ministry of Human Resource Development, Govt. of India for Junior Research Fellowship. RA thanks DST-UKIERI programme for the financial support. RA thanks Department of Biotechnology for Senior Research Fellowship. RK thanks DBT for funding.