Industry Day Theme # Sustainable Medical Technologies

Targeting Genetic Abnormalities for Cancer Therapy

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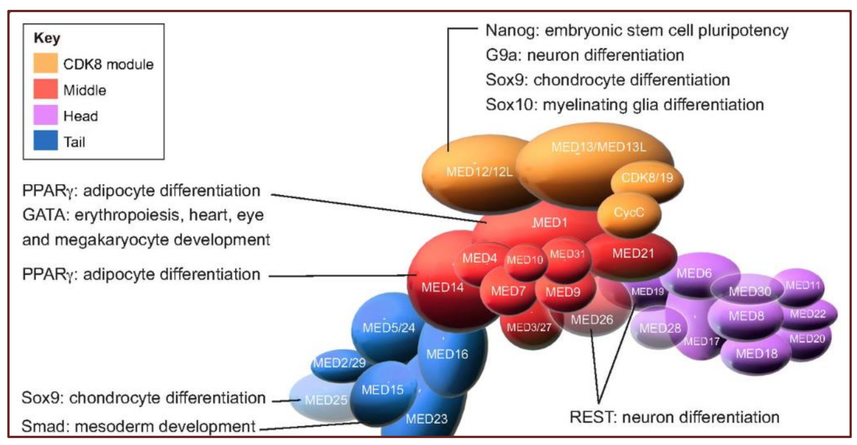
Abstract

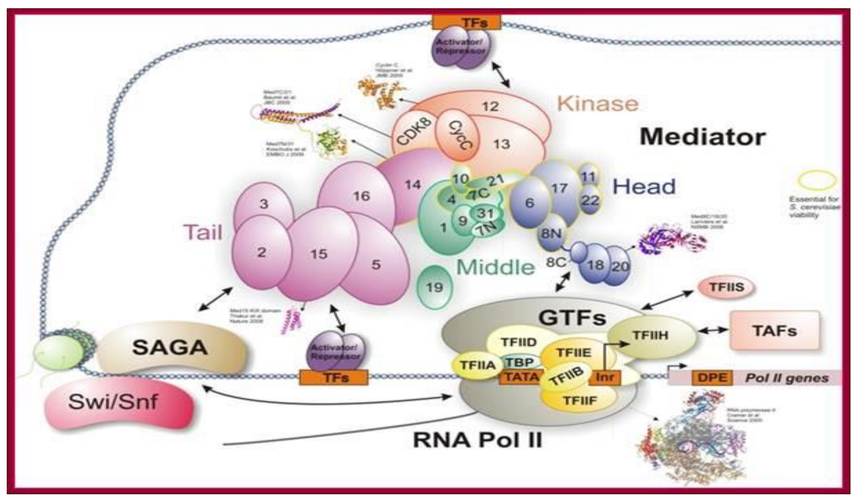
Cancer heterogeneity is a major obstacle in designing new treatment modalities and leads to therapy resistance. Thus, targeting specific biochemical pathways central to a particular cancer type might lead to better therapeutic outcome and increase patient survival. Glioblastoma (GBM) is the most common primary brain tumor in humans, with a poor prognosis. The malignant transformation of the cells has been linked to aberrant gene expression that may be attributed to a fault in transcriptional machinery. The mediator (MED) complex is a set of proteins that are essential for eukaryotic gene expression. Abnormal expression of MED genes has been associated with progression of various cancers. However, its role and status in GBM remains largely unknown so far. Our work shows that a key mediator subunit, MED-X (belonging to the Kinase module of mediator complex) is over-expressed in GBM patients and cell lines. Further, high expression of MED-X was found to be correlated with a poor overall survival in GBM patients. Functional characterization of MED-X gene revealed that it significantly promotes cellular proliferation and migration in vitro. Whole transcriptome analysis post MED-X knockdown revealed Interferon alpha/beta signalling, VEGFA-VEGFR2 Signalling Pathway, RIG-I-like receptor signalling pathway, Vitamin D receptor pathway to be key pathways affected by MED-X in GBM. Overall, our work suggests that MED-X downregulation may be a novel option for treatment of GBM patients

Introduction

MEDIATOR COMPLEX SUBUNITS

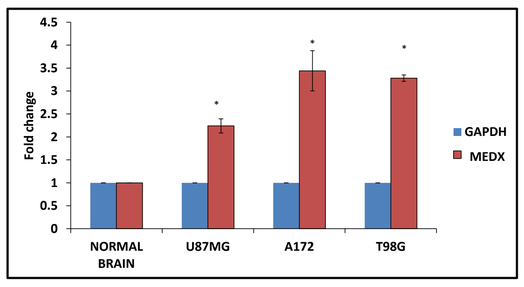


MEDIATOR FUNCTIONS

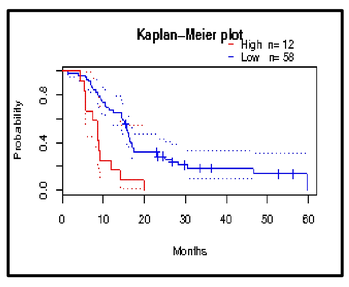


Results:

MED-X IS OVER-EXPRESSED IN GBM CELLS & IS ASSOCIATED WITH POOR OVER-ALL SURVIVAL



Transcript levels of MEDX in different GBM cell lines



Co-relation between prognosis and expression of MEDX in GBM patients

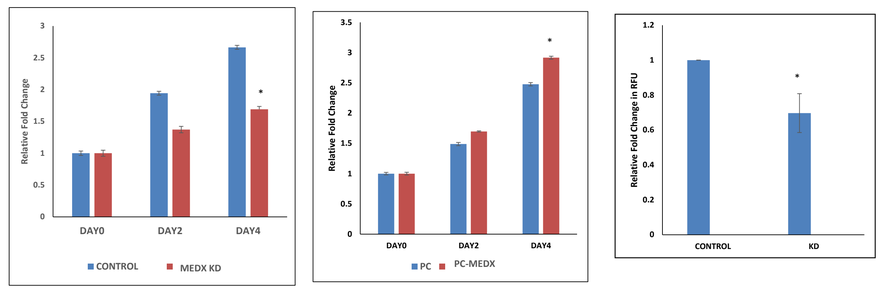
Conclusions and Industrial Significance:

One of the most important hallmarks of GBM is tumor heterogeneity. Molecular heterogeneity in GBM and its role in therapy resistance prompt us to study molecular mechanisms leading to GBM pathogenesis in more detail. Malignant transformation of cells has been linked to aberrant gene expression that may be attributed to a fault in transcriptional machinery.

We identify MED-X, a key subunit of kinase domain, as a novel oncogene promoting cancer cell proliferation and migration. Transcriptome analysis post MED-X, knockdown gave important insights into pathways affected by MED-X in GBM.

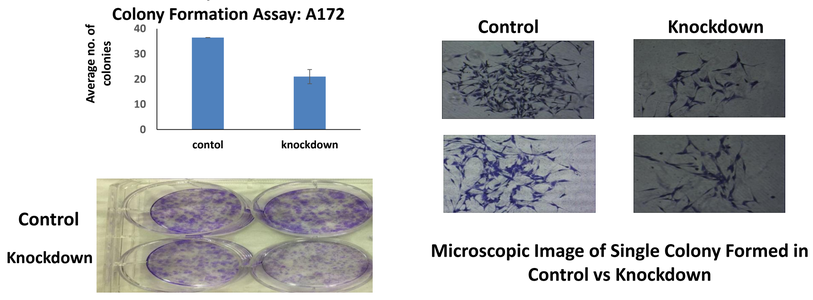
Development of targeted molecular therapy for personalized medicine is currently the focus of cancer research. The industrial significance is apparent from the fact that many of such therapies are approved by FDA and many are being extensively studied in clinical trails.

MED-X PROMOTES CANCER CELL PROLIFERATION



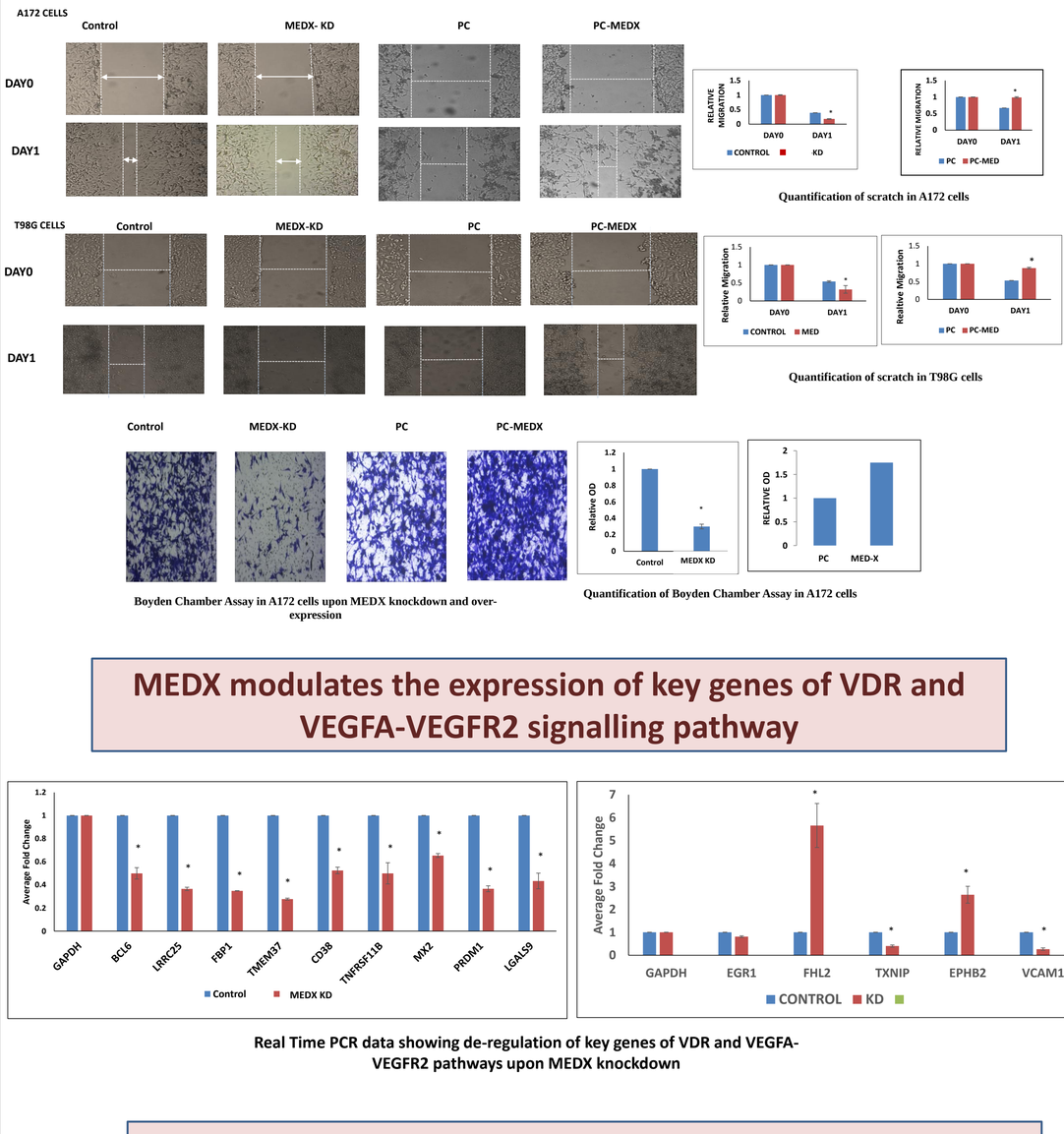
MTT Assay in A172 cells upon MEDX knockdown and over-expression

Cyquant Cell Proliferation Assay in A172 cells upon MEDX knockdown



Microscopic Image of Single Colony Formed in Control vs Knockdown

MED-X PROMOTES CELL MIGRATION IN GBM



Quantification of scratch in A172 cells

Quantification of scratch in T98G cells

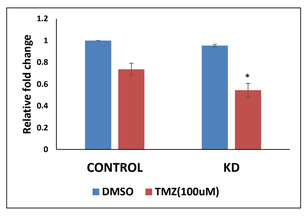
Boyden Chamber Assay in A172 cells upon MEDX knockdown and over-expression

Quantification of Boyden Chamber Assay in A172 cells

MEDX modulates the expression of key genes of VDR and VEGFA-VEGFR2 signalling pathway

Real Time PCR data showing de-regulation of key genes of VDR and VEGFA-VEGFR2 pathways upon MEDX knockdown

MEDX promotes temozolomide resistance



MTT assay after TMZ treatment post 72 hours

References:

Benjamin, L.Allen and Dylan, J.Taatjes.(2015).The mediator complex: a central integrator of transcription. *NatReviewMolecular cell Biology.* **16,**155-166**.**

Acknowledgements:

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