Poster Number 52

Abstract 0240_0346_000094

The contribution of PAX genes as novel tumor suppressors in Group 3 medulloblastoma

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Background:

Medulloblastoma (MB) is the most common malignant primary pediatric brain tumor with the Group 3 MB subgroup exhibiting the worst overall prognosis. OTX2 is a transcription factor overexpressed/amplified in 80% of Group 3 MB, where it contributes to increased self-renewal and reduced neuronal differentiation**.**

Objective:

We sought to **identify novel tumor suppressor genes associated with the OTX2 gene regulatory network in Group 3 MB.**

Methods:

We mapped changes in active and repressive histone modifications following OTX2 silencing in Group 3 MB tumorspheres by ChIP-sequencing to identify novel tumor suppressor genes. Changes in candidate gene expression were validated in Group 3 cell lines and a cohort of 763 MB patient samples. Tumor suppressive properties of candidate genes were examined by gain-of-function studies both *in vitro* and *in vivo.*

Results:

ChIP sequencing demonstrated that cell cycle genes were associated with changes in active histone modifications while neural differentiation genes were associated with changes in repressive histone modifications. Specifically, transcription factors were associated with changes in repressive histone marks, indicating an overall de-repression of transcription factor expression following OTX2 silencing. PAX family genes were among the transcription factors de-repressed and their role in MB progression is unknown. Expression analysis in a 763 patient cohort demonstrated that *PAX3* and *PAX6* expression is significantly lower in Group 3 MB and correlated with a reduction in overall patient survival. In addition, OTX2 knockdown in Group 3 MB cell lines resulted in significant increases in *PAX3* and *PAX6* expression. Over-expression of PAX3 and PAX6 significantly reduced self-renewal while increasing differentiation *in vitro*; however, only PAX3 enhanced survival of NOD SCID mice transplanted with Group 3 MB cells *in vivo.*

Conclusion:

Taken together, examination of the OTX2 regulatory network and identification of novel tumor suppressors could lead to the development of targeted therapies that aim to differentiate MB cells.