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Role of Myc in Choroid Plexus Tumour Pathogenesis

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Introduction: Choroid plexus tumours (CPT) constitute 2-5% of all paediatric brain tumours. They can spread along the neuraxis and are known to recur after treatment. Understanding the molecular mechanisms underlying their formation will be important to devise more efficient therapeutic strategies. c-Myc is a proto-oncogene deregulated in various malignancies, including paediatric brain tumours. Here, we test the hypothesis that deregulation of c-Myc expression plays a role in human CPTs.

Methods: The brains of RosaMycI^{B12};Nestin Cre mice, overexpressing c-Myc in neural progenitor cells, were examined at 20 months of age. 42 human CPT samples obtained from the BRAIN UK Network and CCLG were tested for c-Myc expression and amplification by immunohistochemistry and fluorescence in-situ hybridisation. Publicly available gene expression microarrays [GEO GSE60886] for 40 CPT cases were screened for correlation with c-Myc probes using R software. Heatmap and pathway analysis was performed using DAVID Bioinformatics Resources and KEGG.

Results: CPT developed in 84% of transgenic mice with activated c-Myc construct. A total of 43% human CPT cases expressed c-Myc on IHC. None of the 16 C-MYC+ tumours examined showed amplification. From bioinformatics analysis of the published database, we identified 212 genes, the expression of which correlated with c-Myc expression. Among the canonical pathways associated with high c-Myc expression, were TNF and Cytokine-Cytokine receptor pathway. Furthermore average CD3+ T-lymphocyte infiltrate count/HPF in our cohort was 12.3 vs 3.8 ($p < 0.05$) for c-Myc positive vs negative tumours.

Conclusions: Overexpression of c-Myc in neural progenitor cells leads to CPT development in a high proportion of the mutant mice. More than a third of the human CPT tested express c-Myc, although this was not caused by gene amplification. Analysis of published dataset suggests that c-Myc may influence CPT pathogenesis via inflammatory mediated pathways.