PNR-08 NEWLY DISCOVERED ONCOGENES DRIVING AND MAINTAINING CHOROID PLEXUS CARCINOMA PROVIDE POTENTIALLY DRUGGABLE TARGETS

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Choroid plexus carcinomas (CPCs) are poorly understood and frequently lethal brain tumours with few treatment options. The role of surgical treatment is well established, but the benefit of either chemotherapy or radiotherapy remains controversial. There is a great need for new, effective and non-toxic treatments. Using a mouse model of the disease and a large cohort of human CPCs, we performed a cross-species, genome-wide search for oncogenes within syntenic regions of chromosome gain. Our data identified a group of concurrently gained oncogenes, TAF12, NFYC, and RAD54L that cooperate in the formation and progression of CPC and reveal potential avenues for therapy. These oncogenes are co-located on human chromosome 1p32-35.3 and mouse chromosome 4qD1-D3 and were amplified in tumours of both species. TAF12 and NFYC are transcription factors that regulate the epigenome, whereas RAD54L plays a central role in DNA repair. Early in postnatal life, aberrantly proliferating choroid plexus epithelium cells develop increasingly abnormal genomes leading to genotoxic crisis. While most of these cells undergo cell death, presumably through TP53-independent mechanisms, a fraction acquire aberrant DNA repair and epigenome remodeling capacity, including amplification of TAF12, NFYC, and RAD54L. This enables them to tolerate an aberrant but stable genome and drive further transformation. Validation of aberrant DNA repair as a requirement for CPC formation and maintenance could lead to new therapies, as inhibition of DNA repair enzymes should result in intolerable DNA damage. To test this hypothesis we will utilize compounds inhibiting RAD54/ATR/ATM-driven homologous recombination up-regulation at a crucial stage of tumour development.