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Abstracts

PNR-12. GENOME-WIDE PROFILING OF EMBRYONAL TUMORS WITH MULTILAYERED ROSETTES (ETMR)

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ETMRs are rare pediatric brain tumors with a dismal prognosis and largely unknown mechanisms driving the tumors. Characteristic to ETMR tumors are high expression of LIN28A/B and fusion of a Chr19 microRNA cluster (C19MC) to TTYH1 coupled with amplification of the cluster. Our goal is to understand the mechanisms that play a role in tumorigenesis and possibly identify new treatment strategies. We generated genomic data from 23 ETMRs, including three that lack the C19MC amplification, to understand their genome, transcriptome and epigenome. Whole genome sequencing identified no other recurrent genetic events than the fusion and C19MC amplification, frequently accompanied by other complex rearrangements. Interestingly, gene and miRNA expression profiles of ETMRs w/o C19MC amplification were very similar. Analysis of whole genome bisulfite sequencing data supported this similarity, demonstrating large overlapping regions of strong hypomethylation between tumors. Additionally, we generated genome-wide chromatin maps for the major (ENCODE) histone marks. The resulting enhancer landscape, combined with gene and miRNA expression, revealed high similarity with neural tube cells in the forebrain lineage. miRNA target prediction algorithms predicted that NFI transcription factors, highly downregulated in ETMRs, are targeted by multiple miRNAs in C19MC, suggesting a role for NFI genes in ETMR tumorigenesis. Inhibition of NFI protein function in the mouse brain indeed resulted in formation of ectopic rosette-like structures in the forebrain and an increased size of the ventricular zone, but the mice died before tumors could eventually develop. Together our data provides many novel insights into (epi)genetic aberrations and transcriptional networks driving ETMRs.