MDB-52. MYC-DRIVEN PEDIATRIC BRAIN TUMORS SHARE A COMMON PHOTORECEPTOR IDENTITY
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Mouse models serve as invaluable tools for improving the understanding and treatment of pediatric brain tumors. We recently published a highly
aggressive MYC-driven brain tumor model (GMYC), which exhibits approximately 70% penetrance. Our transcription profiling indicates that GMYC tumors accurately resemble human Group 3 medulloblastoma (MB-G3). Interestingly, a strong photoreceptor program was activated in the tumor model. This is commonly upregulated in MB-G3 but also in pineoblastoma (PB), another malignant pediatric brain tumor. CRX, a transcription factor critical for photoreceptor cell development is also a master regulator for MB-G3 maintenance. By studying early tumor initiation using Crx-lineage tracing and scRNA-seq, we confirmed that GMYC tumors originate from early pinealocytes. Exome sequencing of GMYC tumors further confirmed mutations of epigenetic regulators commonly reported in either PB or MB. To investigate tumor development from photoreceptor-positive progenitors in the developing brain, we performed Crx-lineage tracing with tamoxifen injections, confirming that Crx-positive cells exist in pineal gland progenitors. However, Crx-traced cells also marked granule neurons in the flocculonodular lobe of the cerebellum, which is the suggested site of MB-G3 origin arising from the developing rhombic lip. To investigate if the Myc oncogene can generate different types of pediatric brain tumors in Crx-positive cells, an XMYC{TSA}-Tomato mouse model was established by crossing Crx-CreERT2; LSL-MycT58A and Rosa26/LSL-tdTomato strains. Here, MycT58A was turned on with tamoxifen injection after birth and tumor development followed using the tdTomato reporter. XMYC{TSA}-Tomato mice developed brain tumors from both the pineal gland and cerebellum after 2-6 months. Histologically, tumors were non-glial (GFAP, Olig2-), showed neuronal activity (NeuroD1+), and stained positive for photoreceptor identity markers (CRX+, OTX2+) similar to both MB-G3 and PB-MYC. Collectively, our data suggest that both MYC-driven MB-G3 and PB-MYC originate from photoreceptor-positive cells, which has implications for developing novel treatments targeting these devastating childhood malignancies.