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CANCER RESEARCH

FOXR2 targets LHX6+/DLX+ neural lineages to drive CNS neuroblastoma

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Central nervous system neuroblastoma with FOXR2 activation (NB-FOXR2) is a high-grade tumor of the brain hemispheres and a newly identified molecular entity. Tumors express dual neuronal and glial markers, leading to frequent misdiagnoses, and limited information exists on the role of FOXR2 in their genesis.

To identify their cellular origins, we profiled the transcriptomes of NB-FOXR2 tumors at the bulk and single-cell levels and integrated these profiles with large single-cell references of the normal brain. NB-FOXR2 tumors mapped to LHX6+/DLX+ lineages derived from the medial ganglionic eminence, a progenitor domain in the ventral telencephalon. In vivo prenatal Foxr2 targeting to the ganglionic eminences in mice induced postnatal cortical tumors recapitulating human NB-FOXR2 specific molecular signatures. Profiling of Foxr2 binding on chromatin in murine models revealed an association with ETS transcriptional networks, as well as direct binding of Foxr2 at key transcription factors that coordinate initiation of gliogenesis.

These data indicate that NB-FOXR2 originate from LHX6+/DLX+ interneuron lineages, a lineage-of-origin distinct from that of other FOXR2-driven brain tumors, highlight the susceptibility of ventral telencephalon-derived interneurons to FOXR2-driven oncogenesis, and suggest that FOXR2-induced activation of glial programs may explain the mixed neuronal and oligodendroglial features in these tumors.

This study adds to a growing body of evidence for the involvement of interneurons in brain pathologies. More broadly, it underscores systematic profiling of brain development as an efficient approach to orient oncogenic targeting for in vivo modeling, critical for the study of rare tumors and development of therapeutics.

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