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Atypical cell cycle control over neural cell fate

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Neuroblastoma is an aggressive pediatric cancer fuelled by inappropriate differentiation of immature cells within the ganglionic lineage. The heterogeneity of the disease, as most cancers, complicates diagnosis and treatment. In neuroblastoma this heterogeneity is well represented in both primary tumors and derived cell lines, and mirrors neural crest plasticity. Multiple studies over the years have attempted to elucidate the molecular basis driving the expansion of the stem-like population within aggressive neuroblastoma; however no study has adequately addressed the role of the core cell cycle machinery. This was the focus of our recent publication in Oncoscience.[1]

Decreases in activity of the G1/S cyclin dependent kinase (Cdk) Cdk2 and accumulation of the Cdk inhibitor $p27^{Kip1}$ supports functional differentiation. Indeed, Cdk2 inhibition is synthetic lethal in MYCN overexpressing neuroblastoma.[2] Adult stem cells carefully balance inhibition of the cell cycle with limited expansion *in vivo* to enable development and regeneration while preventing pathogenesis. The Speedy/RINGO family of 'cyclin-like' proteins are capable of binding to and activating the Cdks via a unique mechanism to drive cell growth. Spy1-bound Cdks are not dependent on the classically defined post-translational modifications for activation, nor are they sensitive to suppression by the Cdk inhibitors, quite contrary they can actually promote the degradation of the Cdk inhibitor $p27^{Kip1}$ [3]. Consistent with this guise our group and others have shown that elevated Spy1 levels are capable of overriding numerous forms of senescence.[4-6] Why would a cell evolve such a mechanism? We hypothesize that endogenously this may enable expansion of select stem cell populations during development and regeneration, as well as allowing for recovery of a variety of cell types from checkpoint responses. In support of this model, Spy1 has demonstrated roles in spinal cord regeneration and was found to possess stem-like qualities in the developing mammary gland, supporting a general role for Spy1 in select populations of adult stem or progenitor cells.[4,7] More recently pathological levels of Spy1 have been implicated in supporting the symmetric expansion of the CD133+ population in human glioma.[6] In one of the inaugural issues of Oncoscience we show that Spy1 supports prolonged clonal tumorsphere formation in neuroblastoma cell lines and expands cell populations enriched for markers of multipotency. We find that endogenous Spy1 levels are reduced during guided differentiation of the stem-like population in neuroblastoma and that preventing this downregulation leads to resistance to 13-*cis*-Retinoic Acid (RA)-induced differentiation. In the mammary gland we have previously reported that Spy1 expression is regulated downstream of c-Myc during normal development. In neuroblastoma we find that c-Myc protein levels correlate with that of Spy1 in all cell lines tested, the relevance for these observations in neuroblastoma pathogenesis remain to be tested. Forced silencing of Spy1 levels in neuroblastoma resulted in a decrease in tumorsphere number, and a reduction in the CD133+ population. Hence, our data supports a novel fundamental role for an atypical cell cycle mechanism in driving expansion of the neural crest stem cells that define the aggressive, drug resistant population in subsets of neuroblastoma. This discovery may represent an important opportunity to design Cdk inhibitor drugs to uniquely target subpopulations of cells within these aggressive neural tumors.

References

1. Lubanska D, Porter LA. Oncoscience 2014; 1:336-48; www.impactjournals.com/oncoscience
2. Molenaar JJ, et al. Proc Natl Acad Sci U S A 2009; 106:12968-73; PMID:19525400; http://dx.doi.org/10.1073/pnas.0901418106
3. McAndrew CW, et al. Cell Cycle 2009; 8:66-75; PMID:19106603; http://dx.doi.org/10.4161/cc.8.1.7451
4. Huang Y, et al. Cell Mol Neurobiol 2009; 29:403-11; PMID:19082704; http://dx.doi.org/10.1007/s10571-008-9332-8
5. Barnes EA, et al. Cancer Res 2003; 63:3701-7; PMID:12839962
6. Lubanska D, et al. Cancer Cell 2014; 25:64-76; PMID:24434210; http://dx.doi.org/10.1016/j.ccr.2013.12.006
7. Golipour A, et al. Cancer Res 2008; 68:3591-600; PMID:18483240; http://dx.doi.org/10.1158/0008-5472.CAN-07-6453

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