New insight into aggressive childhood cancer

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A new study reveals critical molecular mechanisms associated with the development and progression of human neuroblastoma, the most common cancer in young children. The research, published by Cell Press in the January 6th issue of the journal *Cancer Cell*, may lead to development of future strategies for treatment of this aggressive and unpredictable cancer.

Neuroblastoma cells are derived from migratory neural crest cells that give rise to the peripheral sympathetic nervous system. During normal development, neural crest cells stop dividing and differentiate. However, neuroblastoma cells seem to have lost this capacity. Previous work has shown that amplification of the MYCN gene, which disrupts control of cell division and differentiation, is a strong predictor of poor prognosis in neuroblastoma.

"We speculated that genes that are expressed in a MYCN-dependent manner might be required specifically for the growth of MYCN-amplified neuroblastomas and that MYCN-amplified neuroblastomas might depend not only on N-Myc itself, but also on upstream regulatory factors or downstream target genes," explains senior study author, Dr. Martin Eilers, from the University of Wurzburg in Germany.

Dr. Eilers and colleagues performed a genetic screen of nearly 200 genes that are dependent on amplified MYCN in human neuroblastoma or are direct targets of Myc. The researchers found that the oncogene AURKA is required for growth of MYCN-amplified neuroblastoma cells, but not cells lacking amplified MYCN.

AURKA encodes the kinase Aurora A which is dysregulated in multiple types of cancer cells. Interestingly, Aurora A kinase activity was not required for N-Myc stabilization. Instead, elevated Aurora A levels in MYCN-amplified neuroblastoma cells interfered with the PI3-kinase-dependent and mitosis-specific degradation of N-Myc. This suggests that small molecule inhibitors of Aurora A kinase may not be effective at inhibiting the oncogenic functions of Aurora A.

"Our results show that stabilization of N-Myc is a critical oncogenic function of Aurora A in childhood neuroblastoma; the challenge will now be to find ways to interfere with this function in order to find new approaches for the therapy of these tumors," says Dr. Eilers. "The findings also suggest that the current views about why Aurora A is oncogenic may need to be re-evaluated."

Source: Cell Press