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Unholy Matrimony: Aurora A and N-Myc as Malignant Partners in Neuroblastoma

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Aurora A is a mitotic kinase that is essential for regulation of the G2/M checkpoint. In this issue of *Cancer Cell*, Otto et al. report that Aurora A interacts with *MYCN*, a potent oncogene in human neuroblastoma, and sequesters it from proteolytic degradation. This surprising finding further enhances Aurora A's potential as a therapeutic target.

The Aurora kinases have attracted intense scrutiny in recent years due to accumulating evidence that they often act as oncogenic drivers in many human cancers (Gautschi et al., 2008). The Aurora family consists of three known gene paralogs (*AURKA*, *AURKB*, and *AURKC*) that are key regulators of mitosis. The genes each encode serine/threonine kinases with a significant degree of homology in the C-terminal catalytic domain, suggesting that the divergent N-terminal domains distinguish their diverse effects on the cell cycle and mitosis. While little is known about Aurora C, and Aurora B appears to play a regulatory role throughout mitosis, recent evidence strongly suggests that Aurora A has a more restricted role in the cell cycle and is absolutely required for the G2/M transition via phosphorylation of polo-like kinase 1 in concert with the cofactor Bora (Macurek et al., 2008; Sasai et al., 2008). In addition, Aurora A is critical for mitotic spindle assembly and stability, as well as regulation of centrosomal and kinetochore formation (Marumoto et al., 2005). It is therefore not surprising that Aurora A expression is tightly regulated throughout normal development and the cell cycle and that engineered *Aurka* deficiency in mice is early embryonic lethal (Sasai et al., 2008). Finally, *AURKA* amplification/overexpression is commonly seen in a variety of human neoplasms, and there has been interest in leveraging this fact therapeutically (Gautschi et al., 2008).

Likewise, the Myc family of transcription factors is commonly deregulated in cancer, via chromosomal translocation events, gene amplification, and interference with normal protein degradative pathways. In the childhood cancer neuroblastoma, *MYCN* is highly amplified in about 20% of cases, and these are uniformly very aggressive neoplasms with patients showing a poor survival probability. Importantly, there are another 20%–30% of cases that behave in an equally aggressive fashion but in which the tumors do not harbor amplification of the *MYCN* locus or other mechanisms for *MYCN* overexpression. Strikingly, these tumors typically overexpress *MYC* via mechanisms yet to be determined (Liu et al., 2008). While both the Aurora and Myc gene families seem to be obvious candidates for anticancer drug development, the Auroras theoretically provide a much more tractable therapeutic target since kinases are currently more easily druggable, especially compared to promiscuous and weak transcription factors like Myc and N-Myc.

In this issue of *Cancer Cell*, Otto et al. (2009) identify Aurora A and N-Myc as oncogenic partners in neuroblastoma, with Aurora A functioning to sequester N-Myc away from ubiquitin-mediated proteolytic degradation. Using a synthetic-lethal screening strategy in neuroblastoma cell line models, the investigators knocked down 194 separate genes selected to be candidates for allowing neural progenitor cells to survive deregulated *MYCN* (forced overexpression of *MYCN* in neural progenitor cell models or *MYCN*-nonamplified neuroblastomas results in immediate induction of programmed cell death). These were genes overexpressed in *MYCN*-amplified tumors and/or genes with direct evidence for being a Myc target. *AURKA* was one of 17 genes that showed selective antiproliferative effects in the *MYCN*-amplified cells when the protein was knocked down. In a series of elegant and well-controlled experiments, Otto and colleagues demonstrated that Aurora A stabilizes the N-Myc protein through a direct physical interaction and interferes

with ubiquitin-mediated degradation in a kinase-independent manner. The authors caution that small-molecule inhibitors of Aurora A kinase activity currently in development may fail to interfere with the critical oncogenic function of Aurora A in mediating N-Myc stabilization.

Since one of the major functions of Aurora A is to stabilize microtubular assembly in the mitotic spindle, it perhaps should not be too surprising that it can also bind to and protect a critical transcription factor from proteasomal degradation, but this is a novel and important observation. It will be interesting to determine whether Aurora A also stabilizes Myc, but the data presented by Otto et al. suggest that this is not likely, since Myc is overexpressed in the *MYCN*-nonamplified cell lines used in their experiments. Regardless, the work of Otto et al. extends an already impressive resume of protein partners of Aurora A and further expands its central and pleiotropic role in cell-cycle regulation. It will be important to understand the cellular context necessary for this interaction and whether the potential oncogenic association of these proteins occurs only in neurally derived cancers.

What does this mean for neuroblastoma, especially in terms of developmental therapeutics? The first curious fact is that the *AURKA* locus is very seldomly, if ever, amplified in human neuroblastoma primary tumors. We have recently screened over 600 primary neuroblastomas on a high-density SNP array and detected amplification in fewer than 1% of cases (unpublished data), and this is consistent with other published comparative genomics hybridization studies. In addition, a variety of expression profiling studies in neuroblastoma show, as do Otto et al., that overexpression of *AURKA* is not restricted solely to *MYCN*-amplified neuroblastomas. *AURKA* is also highly expressed in the majority of high-risk neuroblastomas without *MYCN* amplification, whereas low-risk cases, which almost never show *MYCN* amplification, generally have low expression of *AURKA*. Finally, the Pediatric Preclinical Testing Program (PPTP; http://pptp.stjude.org/) has been performing unbiased cell line and murine xenograft-based screens of new drugs in development. The Aurora A kinase inhibitor MLN8237 demonstrated broad and unprecedented robust antitumor activity in all neuroblastomas studied in a *MYCN*-independent manner (http://pptp.stjude.org/doc/meetingPresentations/MLN8237%20AACR%202008.pdf). In fact, its activity in the mouse setting was so impressive that a phase I trial in children with refractory neuroblastoma was fast tracked and is currently enrolling patients (http://clinicaltrials.gov/; identifier NCT00739427). While the human study will prove whether this is an active agent for refractory neuroblastoma, the PPTP data seem to obviate a major concern of Otto et al., that since kinase activity is not required for N-Myc stabilization, kinase inhibition strategies may be ineffective. Regardless, *AURKA* has rapidly emerged as a critical oncogene in neuroblastoma, and ongoing work will determine whether interference with N-Myc stabilization, inhibition of kinase-mediated effects on cellular proliferation, or both should be the focus of therapeutic intervention strategies. Coupled with the recent discovery of *ALK* as a mutated therapeutic target in neuroblastoma (Chen et al., 2008; George et al., 2008; Janoueix-Lerosey et al., 2008; Mosse et al., 2008), investigators are now tasked with rapidly translating these seminal advances into thoughtfully designed clinical trials for a disease that still exacts significant morbidity and mortality.

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