Posterior Fossa Ependymomas: A Tale of Two Subtypes

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Ependymomas are common childhood brain tumors, but little is known about their underlying biology. In this issue of *Cancer Cell*, Witt et al. present that posterior fossa ependymomas comprise two distinct molecular subtypes, each with unique gene expression signatures, different levels of genomic instability, and different prognosis.

Although more common in children, ependymomas occur in both children and adults. They arise in supratentorial, posterior fossa, or spinal levels of the neuraxis from ependymal cells that line the walls of the ventricles. As remnants of the proliferative ventricular zone, ependymal cells are hypothesized to be an adult multipotent stem cell (Pevny and Rao, 2003). This is corroborated by evidence that ependymomas express both neuronal and glial markers (Pevny and Rao, 2003). It is hypothesized that since ependymal cells are maintained as proliferating neural progenitors beyond the postnatal period, this leaves them susceptible to oncogenic transformation.

Clinically, ependymomas remain an enigma to neuro-oncologists and neurosurgeons. As chemotherapy has yet to demonstrate any improvement in overall survival from this disease, maximal surgical removal followed in some cases by external beam radiation is the current standard of care. The clinical outcome is quite variable for patients diagnosed with ependymoma, but approximately 50% of patients do not survive more than five years (Dubuc et al., 2010).

One major barrier to improving patient outcome has been our inability to predict the clinical behavior of the tumors and thus determine which patients would benefit from adjuvant therapy. Histological grading as per the World Health Organization criteria has been insufficient in accurately predicting patient outcome, and complete resection of the tumor has only variably been associated with improved patient survival; moreover, metastatic seeding into cerebrospinal fluid spaces remains problematic. Efforts to identify prognostic molecular markers generated early enthusiasm, but the degree to which they could accurately predict outcome was limited. Specifically, epidermal growth factor receptor family proteins (ERBB1, 2, and 4) appear to be promising markers of poor prognosis and potential indicators for response to targeted therapy, yet clinical trials of inhibitors of the ERBB pathway have not been effective in improving survival (Gilbertson et al., 2002; Jakacki et al., 2008; Zacharoulis and Moreno, 2009). To date, the most consistent molecular marker for poor prognosis is a gain of chromosome 1 (Carter et al., 2002), but the salient genes affected by this chromosomal copy number alteration have not been identified.

A series of recent breakthrough studies have begun to uncover the biology of ependymomas. Using genomic technologies to identify molecular and biological subtypes previously hidden within the tumor class, insights into the tumor's cell of origin have been made particularly for supratentorial ependymomas. Supratentorial ependymomas comprise one third of all ependymomas and are three times more common in children than adults. Using gene expression profiles, Taylor et al. (2005) proposed radial glia as the cell of origin for supratentorial and spinal cord ependymomas. They were able to purify cancer stem cells based on the $CD133^+/RC2^+/BLPB^+$ immunophenotype and showed upregulation of EphB-Ephrin and Notch signaling pathways in these supratentorial tumors. Building on the importance of Ephrin signaling, Johnson et al. (2010) generated the first mouse model for supratentorial ependymomas. Mice transplanted with mouse neural stem cells with loss of Ink4a/Arf activity and overexpression of Eph2b developed brain tumors.

Work from Taylor, Pfister, and colleagues presented in this issue specifically focus on posterior fossa ependymoma (Witt et al., 2011). They profiled the transcriptome of 177 primary posterior fossa ependymomas from two separate cohorts and used unsupervised clustering methods for class discovery. Their analysis identified two distinct subtypes of posterior fossa ependymoma, termed subtypes A and B, which highly correlated with age, location of tumor, biological signaling pathways, genomic instability, and prognosis (Figure 1). The subtypes identified by these methods were highly concordant with and reproducible in an independent patient cohort.

Subtype A tumors occurred in younger patients, were more likely to be found extending laterally into the cerebellopontine angle, and had a gender bias as 70% male (Figures 1A and 1B). Tumors in this subtype had relatively less genomic instability; the most frequent DNA copy number variants included gain of chromosome 1 or loss of chromosome 22. Tumors of subtype B, on the other hand, occurred in older patients and were more likely to be found in the spinal cord or the midline of the cerebellum. This subtype had a much higher degree of genomic instability, with extensive chromosomal aberrations (Figure 1C). An analysis of clinical outcomes for each disease found subtype A tumors to have worse prognosis, with 56% of patients eventually having recurrent disease and 35% of patients dying of their disease within five years (Figure 1C). Patients with Subtype B tumors had a 25% and 5% rate of recurrence and death within five years, respectively.

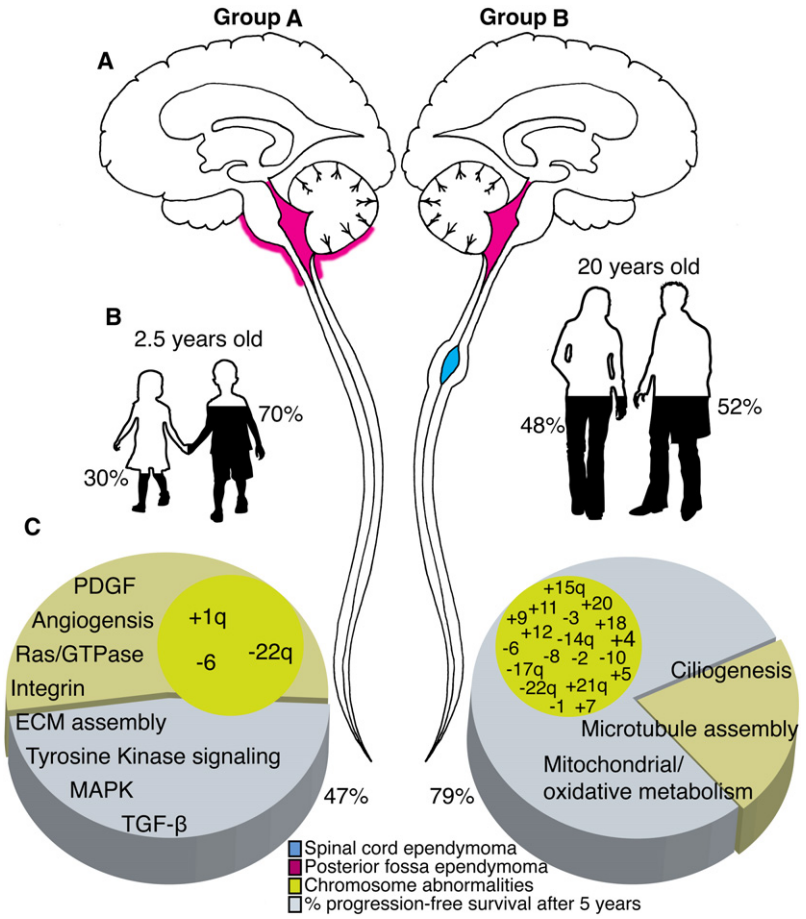

Figure 1. Two Distinct Subtypes of Posterior Fossa Ependymoma
(A) Schematic of human CNS indicates location of tumor in either group. Group A is more likely to form tumors in the ventricle, which can grow through the Foramina of Luschka into the extra-axial space surrounding the brain stem and cerebellum (pink). Group B tumors form either within the ventricle (pink) or in the central canal of the spinal cord (blue), causing distention.
(B) Patient median age and gender bias of each subtype.
(C) Pie chart indicates the percent of patients that survive without cancer progression for at least five years. The lists of overexpressed signaling pathways in each group and common chromosome abnormalities are superimposed on the pie charts.

Pathway enrichment analysis further identified signaling pathways enriched in each disease subtype (Figure 1C). Subtype A had enrichment of genes associated with signaling pathways for angiogenesis, PDGF, MAPK, EGFR, TGF-β, integrins, extracellular matrix (ECM) assembly, RAS/GTPase, and tyrosine kinase receptor signaling. Subtype B tumors were found to overexpress genes associated with ciliogenesis, microtubule assembly, and mitochondria/oxidation metabolism. These findings were validated using immunohistochemical analysis. As Subtype A had overexpression of ECM assembly, two markers of ECM signaling, Tenascin-C and Laminin alpha-2, were selected, while ciliogenesis signaling and microtubule assembly markers indicative of Subtype B were assayed, specifically Kinesin Family Member-27, and Neural Epidermal Growth Factor Like-2. The authors show that commercially available antibodies against these proteins were robust and suggested their potential use in clinical pathology labs to help risk-stratify ependymoma patients.

In summary, what emerges from this study is the clear delineation of two subtypes of posterior fossa ependymoma—one with a predilection for younger children and associated with high mortality and morbidity and the other arising in both children and adults with better prognosis—that can be efficiently identified using standard and widely available immunohistochemical techniques. Looking forward, once further validated in prospective clinical studies, the molecular markers presented here could be used to identify the ependymoma patients most "at risk" for recurrence and in need of maximal adjuvant therapy. This study also provides a foundation from which driver genes and signaling pathways controlling the growth of various ependymoma subtypes can be identified, ushering in newer, targeted, and more effective treatment strategies.

REFERENCES

Carter, M., Nicholson, J., Ross, F., Crolla, J., Allibone, R., Balaji, V., Perry, R., Walker, D., Gilbertson, R., and Ellison, D.W. (2002). Br. J. Cancer *86*, 929–939.

Dubuc, A.M., Northcott, P.A., Mack, S., Witt, H., Pfister, S., and Taylor, M.D. (2010). Curr. Neurol. Neurosci. Rep. *10*, 215–223.

Gilbertson, R.J., Bentley, L., Hernan, R., Junttila, T.T., Frank, A.J., Haapasalo, H., Connelly, M., Wetmore, C., Curran, T., Elenius, K., and Ellison, D.W. (2002). Clin. Cancer Res. *8*, 3054–3064.

Jakacki, R.I., Hamilton, M., Gilbertson, R.J., Blaney, S.M., Tersak, J., Krailo, M.D., Ingle, A.M., Voss, S.D., Dancey, J.E., and Adamson, P.C. (2008). J. Clin. Oncol. *26*, 4921–4927.

Johnson, R.A., Wright, K.D., Poppleton, H., Mohankumar, K.M., Finkelstein, D., Pounds, S.B., Rand, V., Leary, S.E.S., White, E., Eden, C., et al. (2010). Nature *466*, 632–636.

Pevny, L., and Rao, M.S. (2003). Trends Neurosci. *26*, 351–359.

Taylor, M.D., Poppleton, H., Fuller, C., Su, X., Liu, Y., Jensen, P., Magdaleno, S., Dalton, J., Calabrese, C., Board, J., et al. (2005). Cancer Cell *8*, 323–335.

Witt, H., Mack, S.C., Ryzhova, M., Bender, S., Sill, M., Isserlin, R., Benner, A., Hielscher, T., Milde, T., Remke, M., et al. (2011). Cancer Cell *20*, this issue, 143–157.

Zacharoulis, S., and Moreno, L. (2009). J. Child Neurol. *24*, 1431–1438.