Editorial

Integrative genomics reveals molecular and clinical heterogeneity in central nervous system primitive neuroectodermal tumors in children

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Through advances in genome science, we are becoming increasingly aware that tumors that appear identical under the pathologist's microscope can be very different in their genetic composition and clinical behavior. Pediatric embryonal brain tumors share a characteristic histological feature—densely packed sheets of cells with hyperchromatic nuclei and scant cytoplasm. Despite their common appearance, however, embryonic brain tumors are a diverse set of tumors, including medulloblastomas and atypical teratoid rhabdoid tumors, which arise in the hindbrain structures in the posterior cranial fossa, and central nervous system primitive neuroectodermal tumors (CNS PNETs), which arise in the cerebral hemispheres. Picard and colleagues recently published results of an international study of 142 CNS PNETs collected from 20 hospitals in nine countries (1). The global scope of the collaboration made it possible to accrue a large number of these uncommon tumors, which account for only 3-5% of pediatric brain tumors. The investigators made the striking discovery that CNS PNETs do not make up a single disease, but rather distinct tumor subgroups.

The heterogeneity of CNS PNETs became apparent when the research team examined the gene expression profiles of these tumors and observed three distinct groups. Group 1 tumors showed increased expression of genes associated with self-renewal of embryonal and neural stem cells, like *LIN28* and *CRABP1*. In group 2 tumors, by contrast, genes involved in the differentiation of neural stem cells into oligodendrocytes, like *OLIG2*, were expressed at high levels. Group 3 tumors showed decreased expression of neural differentiation genes and increased expression of epithelial and mesenchymal differentiation genes, like *COLA2* and *COL5A*, which encode collagen subunits. Of great practical significance was the discovery that antibody markers could detect expression of *LIN28* and *OLIG2* reliably in tissue sections, making it possible to classify tumors by conventional immunostaining using these two markers alone.

When the tumors were divided into these three groups based on gene expression profiling or immunostaining for LIN28 and OLIG2, the patients showed significantly different ages and treatment responses. Group 1 tumors ($LIN28^+/OLIG2^-$, primitive neural type) occurred in infants and responded poorly to treatment. Group 2 tumors ($LIN28^-/OLIG2^+$, oligoneural type) and group 3 tumors ($LIN28^-/OLIG2^-$, mesenchymal type) occurred in older children and took a less aggressive clinical course. It is tempting to attribute the short survival times in young children to the widely accepted practice of sparing infants from the neurotoxic effects of therapeutic radiation. Nevertheless, the fact that the correlation between molecular subgroup and survival remained valid when analyzed separately in children older and younger than four years indicates that inherent differences in molecular biology are the critical determinants of tumor behavior.

Surprisingly, dissemination of tumor cells to the leptomeningeal spaces of the brain and spine or metastasis to extraneural sites was more common in patients in group 3, who live much longer than patients in groups 1 and 2. This result seems paradoxical because metastatic dissemination is a powerful predictor of short survival times for medulloblastoma patients.

The newly discovered molecular diversity of CNS PNETs raises hopes that treatment efficacy can be improved by targeting group-specific signaling molecules, and the Picard *et al*. study offered some insights into molecular targets. The gene expression profiles of the aggressive group 1 tumors, for example, revealed activation of the Hedgehog signaling pathway. This finding suggests that treatment with Smoothened inhibitor GDC-0449, which is now in clinical trials, might be an effective strategy (2). The increased expression of genes involved in phosphatidylinositol 3-kinase (PI3K) signaling in the highly metastatic Group 3 tumors suggests a target for the many promising drugs that inhibit this oncogenic pathway. Enthusiasm for this approach is heightened by the fact that PI3K signaling mediates many aspects of metastasis, including the epithelial–mesenchymal transition (3). The prospect of more effective chemotherapy is welcome news because CNS PNETs often afflict children at an age (<3 years) when the nervous system is not sufficiently mature to tolerate radiation therapy.

The pediatric oncology community will be eager to learn whether genome-wide sequencing of CNS PNETs will show whether somatically acquired genetic mutations are specific to the three tumor groups, as was shown recently in medulloblastoma (4-6). This study makes it clear that we must revise our thinking not only about the molecular pathogenesis of pediatric brain tumors but also about our therapeutic strategy as we move forward in the post-genomic era of biology.

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Footnote

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