Editorial

New gene signatures for pediatric brain tumors: a step forward in the understanding of molecular basis of CNS PNET

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Knowledge about the molecular etiology of human cancer underwent a significant shift when researchers identified that gain and loss of function of oncogenes and tumor suppressor genes respectively are early events in cancer development. This molecular approach involved the development of increasingly sophisticated genome-wide methods looking for genetic alterations that have led to the concept of *gene signatures* for each tumor type. In last years, the data from these studies has been especially relevant to better understand the molecular characteristics of brain tumors in which the complexity of its anatomic, pathologic and clinical classifications is itself problematic (1). This complexity reaches its higher levels in the pediatric brain tumors that are distinct from their adult counterparts, mainly because they are thought to arise from aberrations in normal CNS development.

These tumors are the most common solid cancer of childhood, being the leading cause of death in children, aside from trauma (2). Among them, we highlight medulloblastoma and CNS primitive neuro-ectodermal brain tumors (CNS PNETs), which represent the most common and aggressive neoplasms in this population (3). Although tremendous progress has been achieved in the recent years in the characterization of molecular alterations and treatment of medulloblastoma, the molecular etiology of CNS PNETs is poorly studied and remains unknown (4). These aspects underscore the importance of understanding its molecular basis to better understand its complex etiology and to develop therapeutic strategies that specifically target the cause of this disease. So, it is necessary to establish what we know about CNS PNETs, describing the recent advances in the understanding of its molecular signatures and, finally, what we think that it could be the future directions in the CNS PNETs research.

In general, we can consider CNS PNETs as complex embryonal brain tumors of WHO grade IV lesions that show a specific anatomical location, characterized by a cellular heterogeneity with variable neuronal, ependymal or glial differentiation, showing the worse clinical outcome and a significant resistance to tumor-specific treatments (5). They comprise 3-7% of brain tumors in children and young adults, and are associated with a dismal prognosis (6). As we said, unlike medulloblastoma, where it has been identified tumor subgroups with distinct clinical, biological and genetic profiles (3,7), in CNS PNETs it is necessary to establish different molecular subgroups that correlate with clinical features of the patients. In this regard, in a recent paper, Picard and colleagues (5) delineate the cellular and molecular pathogenesis of CNS PNETs laying the groundwork for improving the diagnosis, prognosis and design of new tumor-specific treatments. Analyzing the highest number of samples employed up to now, they identify three distinct molecular subgroups characterized by differences in the expression of cell lineage markers *LIN28* and *OLIG2* that are associated with treatment failures and distinct demographic and clinical phenotypes, which notably improves the results obtained in previous studies. Group 1 is most significant enriched for genes associated with embryonic or neural stem cells and are distinctly aggressive tumors that arise in young children, preferably in females. In this group, by contrast with group 2, the authors describe an upregulation of the non-canonical WNT and SHH signaling pathway, suggesting that they could be targets for potential subgroup specific therapies. On the other hand, group 2 tumors present an upregulation of oligoneural differentiation genes that arise in older children in specific anatomical locations, whereas

group 3 tumors show reduced expression at all ages of *LIN28* and *OLIG2*, upregulation of *IGF2*, are associated with a high incidence of metastases and, as in group 2, arise more frequently in males. In this group Picard *et al.*, describe an upregulation of PTEN and TGFβ signaling, making these pathways attractive targets for new treatments.

In conclusion, we think that the study of Picard and colleagues describe new markers that represent molecular identifiers for childhood CNS PNETs that improve our understanding of the clinical and biological spectra of the disease focusing on its diagnosis, classification and treatment. Although the authors describe specific genetic changes that disturb the normal function of signal transduction pathways that regulate different cellular processes, we have to keep in mind that the signaling network in cancer results from a number of molecular alterations that genetics alone cannot explain, i.e. epigenetic marks. Since it is well established that a specific epigenetic profile exists for every tumor type, the study of the specific epigenetic alterations associated with the molecular subgroups described in this work will significantly improve our knowledge about the etiology of this complex disease. In this way, it could be interesting to study the epigenetic status of genes known as master regulators of totipotency and inducer of totipotency, such as *LIN28* (8), a gene described in the paper of Picard *et al.*, that has a crucial role in the establishment of new three distinct molecular CNS PNET subgroups.

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Footnote

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