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The Childhood Solid Tumor Network: A new resource for the developmental biology and oncology research communities

Elizabeth Stewart [a], Sara Federico [a], Asa Karlstrom [b], Anang Shelat [c], Andras Sablauer [d], Alberto Pappo [a], Michael A. Dyer [b,e,*]

[a] Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[b] Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[c] Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[d] Department of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[e] Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA

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ABSTRACT

Significant advances have been made over the past 25 years in our understanding of the most common adult solid tumors such as breast, colon, lung and prostate cancer. Much less is known about childhood solid tumors because they are rare and because they originate in developing organs during fetal development, childhood and adolescence. It can be very difficult to study the cellular origins of pediatric solid tumors in developing organs characterized by rapid proliferative expansion, growth factor signaling, developmental angiogenesis, programmed cell death, tissue reorganization and cell migration. Not only has the etiology of pediatric cancer remained elusive because of their developmental origins, but it also makes it more difficult to treat. Molecular targeted therapeutics that alter developmental pathway signaling may have devastating effects on normal organ development. Therefore, basic research focused on the mechanisms of development provides an essential foundation for pediatric solid tumor translational research. In this article, we describe new resources available for the developmental biology and oncology research communities. In a companion paper, we present the detailed characterization of an orthotopic xenograft of a pediatric solid tumor derived from sympathoadrenal lineage during development.

1. Introduction

Pediatric solid tumors have diverse molecular and cellular features that reflect their unique cellular origins. With the recent completion of sequence analysis of more than 1000 pediatric solid tumor genomes, we now have a broad understanding of the genomic landscape of childhood cancers that are derived from mesodermal, ectodermal, and endodermal lineages (Downing et al., 2012; Chen et al., in preparation). These data provide the foundation to launch new research efforts to address a central question in cancer biology: Why are cells of some lineages more susceptible to malignant transformation at certain developmental stages than are cells of other lineages? Due to their molecular, cellular, developmental, and genetic diversity, pediatric solid tumors provide an ideal platform on which to address this question.

We have recently introduced a new unifying concept that we call cellular pliancy, with broad implications for cancer susceptibility and the developmental origins of pediatric solid tumors (Chen et al., in preparation). To complement this new cellular pliancy framework for answering fundamental questions about cancer susceptibility and development, we have also established a unique set of laboratory models with which to study childhood solid tumors. To eliminate the barriers to developmental biologists who are interested in studying the developmental origins and cell biology of pediatric solid tumors, we have built a comprehensive Childhood Solid Tumor Network (CSTN) that includes genomic and other molecular data, cell lines, patient-derived orthotopic xenografts, and genetically engineered mouse models of childhood solid tumors. All data, samples, and animal models are shared freely through an online request form without obligation to collaborate. In this report, we describe the major pediatric solid tumor types and the resources available through the CSTN. In a

* Corresponding author at: Department of Developmental Neurobiology, MS 323, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, USA. Fax: +1 901 595 3143.
E-mail address: michael.dyer@stjude.org (M.A. Dyer).

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companion paper, we present the detailed characterization of a neuroblastoma orthotopic xenograft to provide an example of the type of data and resources that are available through the CSTN.

2. Ectodermally derived tumors

2.1. Retinoblastoma

Retinoblastoma is a rare cancer of the developing retina that is usually diagnosed before 3 years of age. Retinoblastoma can be hereditary or sporadic, and approximately 40% of patients have a germline genetic defect in the retinoblastoma susceptibility gene, *RB1*, that can lead to multiple tumor foci in each eye. The *RB1* gene is a tumor suppressor that regulates the cell cycle, differentiation, and epigenetic processes (Dyer and Bremner, 2005; Macpherson and Dyer, 2007; Dyer, in press). The cell of origin for retinoblastoma has not yet been determined but is likely to be a retinal progenitor cell that fails to cease proliferating during fetal development (Dyer and Bremner, 2005; Macpherson and Dyer, 2007; McEvoy et al., 2011). Importantly, individual tumor cells express multiple retinal differentiation programs that are not normally expressed at the same time in individual cells during retinal development (McEvoy et al., 2011). This expression pattern is partially due to epigenetic deregulation of retinal development; epigenetic perturbations also contribute to tumor progression (Zhang et al., 2012). Retinoblastomas have relatively stable genomes and some tumors have only *RB1* gene mutations (Zhang et al., 2012; McEvoy et al., in press). Overall, retinoblastomas are relatively homogenous tumors with features of retinal neurons and progenitor cells (McEvoy et al., 2011; Johnson et al., 2007). Genomic, epigenomic, drug sensitivity, and gene expression data are available for human and mouse retinoblastomas. Also, human orthotopic xenografts, genetically engineered mouse models, and cell lines are freely available through the CSTN.

2.2. Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in children and can arise from any neural crest element of the sympathetic nervous system (Cheung and Dyer, 2013). It most frequently originates in one of the adrenal glands but can also develop in sympathetic ganglia in the neck, chest, abdomen, or pelvis (Cheung and Dyer, 2013). Most patients with neuroblastoma are young (median age at diagnosis, 18 months) and approximately 40–50% have disseminated disease at first presentation.

Amplification of the *MYCN* oncogene is one of the most frequent genetic lesions in neuroblastoma and is associated with poor outcome (Brodeur, 2003). Germline mutations in the transcription factor *PHOX2B*, which normally coordinates proliferation and differentiation of the sympathoadrenal lineage during development, can predispose children to neuroblastoma (Mosse et al., 2004; Trochet et al., 2005; Raabe et al., 2008). Similarly, germline mutations in the *ALK* gene can lead to perturbations in signal transduction pathways in the same lineage and predispose children to neuroblastoma (Chen et al., 2008; George et al., 2008; Mosse et al., 2008). Neuroblastoma cells have molecular, cellular, neuroanatomical, and neurochemical features of differentiated neurons and accumulate catecholamines in dense core vesicles (Cheung and Dyer, 2013). Indeed, catecholamine levels in urine are measured to test for neuroblastoma. The recent discovery of recurrent somatic mutations in the *ARID1A/1B* genes (Sausen et al., 2013), which encode chromatin remodeling proteins, and in the *ATRX* gene, which encodes an ATP-dependent helicase (Cheung et al., 2012), points to a role for epigenetics in neuroblastoma initiation and progression. Neuroblastoma outcome is associated with the patient's age at diagnosis. Young children whose tumors have favorable biology have excellent survival rates in excess of 90%; however, children older than 18 months at diagnosis have only a 50% survival rate, which drops to 5% in patients aged 10 years or older at diagnosis (Mosse et al., 2014; London et al., 2005). ATRX mutations are associated with the older age group, but it is unclear whether they directly contribute to the poor outcome in this patient population (Cheung et al., 2012; London et al., 2005).

Overall, neuroblastoma is a complex disease with multiple risk factors that may reflect important differences in the developmental origins of these tumors (Cheung and Dyer, 2013). Genomic, epigenomic, drug sensitivity, and gene expression data are available for human neuroblastomas through the CSTN. Additionally, gene expression and genomic data are available for genetically engineered mouse models of neuroblastoma. Also, human orthotopic xenografts, genetically engineered mouse models, and cell lines are available from the CSTN upon request.

2.3. Pediatric melanoma

Melanoma in children and adolescents accounts for less than 2% of all cases of melanoma (Wong et al., 2013). Although germline mutations associated with xeroderma pigmentosum, Werner syndrome, or retinoblastoma can predispose children and adolescents to melanoma, most melanoma cases are sporadic (Abramson et al., 1979; Pappo, 2003). As in adults, exposure to sunlight at an early age increases the risk of melanoma (Strouse et al., 2005; Whiteman et al., 1997). Recent genomic analysis showed that most pediatric conventional melanomas are very similar to adult melanomas, with oncogenic *BRAF* mutations, *TERT* promoter mutations, and UV-induced DNA damage (Lu et al., in press). Through the CSTN, genomic data and patient-derived xenografts of pediatric melanoma are available.

3. Mesodermally derived tumors

3.1. Osteosarcoma

Osteosarcoma is the most common type of bone cancer in children and teens, arising most often in long bones such as the femur, tibia, and humerus. However, it can also occur in flat bones, such as the pelvis and the skull, that support and protect vital organs. Although most cases are sporadic, the risk of osteosarcoma is increased in those with various genetic diseases, including hereditary retinoblastoma, Li Fraumeni syndrome, and germline mutations of *RecQL4* (McIntyre et al., 1994; Hicks et al., 2007; Kleinerman et al., 2005). Approximately 15–20% of patients have metastatic disease at the time of diagnosis, with the lungs being the most common site (Meyers et al., 1993).

Osteosarcomas occur most often in children and young adults, and the peak age of diagnosis coincides with the onset of puberty. Osteosarcoma is thought to arise from osteoblasts, with the rapid expansion of this cell population during periods of growth contributing to tumor initiation. It is also possible that changes in hormone, cytokine, or chemokine levels associated with puberty contribute to osteosarcoma initiation in adolescents and young adults. Interestingly, children who have germline mutations in the *RB1* gene and develop retinoblastoma as infants are predisposed to develop osteosarcoma in adolescence.

Virtually all osteosarcomas have initiating mutations in the *TP53* tumor suppressor gene, which is important for DNA repair, stress response, and cell cycle progression (Chen et al., 2014). Of all childhood cancers, osteosarcomas have the highest rate of chromosomal breaks leading to structural variations and copy number variations; they are thought to have unstable genomes and exhibit

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