CHAPTER 12
INTEGRATING THE DIAGNOSIS OF CHILDHOOD MALIGNANCIES

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Abstract: Significant progress has been made in understanding the molecular basis of pediatric malignancies. Mechanisms of pediatric acute leukemia induction include hyperdiploidy, aberrant expression of proto-oncogenes, and activation of transcription factors or kinases by aberrant fusion genes. Molecular analysis of these alterations has facilitated the recognition of distinct groups with different sensitivity to therapy, and identified potential targets for antileukemic agents. Similar analysis of pediatric soft tissue and bone tumors also resulted in the identification of specific fusion genes, and their characterization has contributed greatly to understand their biology. Molecular assays for these rearrangements have become important tools in classifying these tumors, providing important prognostic data. However, the understanding of mechanisms involved in the pathogenesis of many other pediatric malignancies, including some embryonal tumors — believed to arise due to perturbation of the normal developmental program — is still vastly incomplete.

The Department of Pathology at Texas Children's Hospital is one of the Children's Oncology Group (COG) reference centers for pediatric liver tumors. We have been particularly interested in the biology of hepatoblastoma, the most common type of pediatric liver tumor. Although a number of cytogenetic and molecular abnormalities have been described for this type of embryonal tumor, its pathogenesis is still poorly understood. In an attempt to explore the role of different signaling pathways in this disease, we analyzed the expression patterns of different histologic subtypes of hepatoblastoma using cDNA microarray analysis, qualitative reverse transcription, polymerase chain reaction (QRT-PCR), and immunohistochemistry. Wnt signaling pathway, critical both in development and in neoplasia, appears to be particularly relevant in these tumors. Mutations of the β-catenin gene are present in over 90% of hepatoblastomas, leading to activating transcription of a number of target genes. The pattern of β-catenin expression and type of mutation in groups of tumors are crucial to understand the corresponding differences in their gene expression profiles. Our findings are consistent with a relationship between poor histologic phenotype and β-catenin activation, indicating the potential utility of targeted gene expression assays to identify molecular events related to the pathogenesis and prognosis of hepatoblastomas.

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Integration of clinical, morphologic, phenotypic, cytogenetic, and molecular data has become the basis of novel prognostic prediction and therapeutic strategies in pediatric leukemia. Similarly, integration of new genetic and molecular data with clinical and other diagnostic information will be crucial for accurate classification of pediatric tumors, risk stratification, and successful development of new therapies for pediatric oncologic patients.

1. INTRODUCTION

Significant progress has been achieved during the last few decades in understanding the molecular basis of numerous pediatric malignancies. In some instances this has resulted in the development of genetic and molecular tests that are being progressively integrated in the diagnosis and clinical management of these patients.

The pediatric and adult cancer disease spectrum is different, as it is the stem cell population targeted by mutations, the type and number of necessary mutations to induce a fully malignant phenotype, and the internal homeostatic environment of the host (developing vs a fully mature). All these result in a different approach to diagnose pediatric cancer, as many of these processes lack morphologic evidence of differentiation and are difficult to classify. Most of pediatric cancer patients are enrolled in cooperative group therapy protocols (90% of children in the USA), which are tailored to specific tumor types and subgroups, often requiring assessment of biologic tumor markers [1].

2. PEDIATRIC HEMATOPOIETIC MALIGNANCIES

The best example of how the application of newly gained biological knowledge in a malignancy type has resulted in improvements in diagnosis, classification and clinical management, is pediatric hematopoietic malignancies. True treatment success has been achieved in many pediatric acute leukemias and lymphomas, much more so than for adult hematopoietic malignancies. These differences in therapeutic success are probably due to a combination of factors, including biological differences of the neoplastic processes, host-dependent features and treatment strategies, and also a better understanding of normal hematopoietic development and of the molecular pathology of these malignancies [1,2].

2.1. Pediatric acute lymphoblastic leukemia

Pediatric acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood, representing approximately 50% of all pediatric cancers. During the last decade a better understanding of normal hematopoietic development and of the molecular events involved in leukemic malignant transformation, has been achieved. As a result, significant improvements have occurred in our ability