MOLECULAR BIOLOGY OF CHILDHOOD SOLID TUMORS

Promises Maintained and Promises Postponed

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1. INTRODUCTION

More than twenty years ago, the approach to tumor biology changed dramatically after the identification of genes that were shown to be specifically affected in human cancers, the cellular proto-oncogenes. By understanding their functions and by subsequently recognizing that, basically, cancer (either sporadic or inherited) is a genetic disease deriving from an accumulation of mutations able to promote clonal selection of tumor cell populations with increasingly aggressive phenotypes, new methods of study developed.\textsuperscript{1,2} Nowadays, the extensive application of the techniques of molecular biology to cancer research has led to the characterization of genes whose structural and/or functional alterations are thought to be responsible for producing and modulating the different phases of tumor development and progression.\textsuperscript{3} The great majority of these alterations take place in somatic cells and are therefore found in tumor cells alone. On the other hand, about 1% of all human tumors arise in individuals affected with inherited cancer syndromes who carry a germline mutation that is thus found in every cell of their body.\textsuperscript{4}

Understanding the critical role played by gene function disruptions in human tumors has allowed findings obtained from molecular genetics to be integrated into a wide range of clinical settings with potentially promising diagnostic and therapeutic
approaches, e.g., establishment of diagnosis, staging, assessment of risk class, monitoring of response to treatment; genetic counseling and/or testing in predisposed families; identification of specific targets for therapy and design of new anticancer drugs, and restoration of disrupted gene function.

As far as the aforementioned issues are concerned, even brief details would be beyond the limits of this introductory chapter. Nonetheless, it is undeniable that the integration of molecular genetics into clinical management has yielded promising results, particularly in pediatric oncology. The identification of several tumor histotypes based on molecular characteristics and no longer simply on their morphology has permitted, for example, a more reliable and reproducible diagnosis. It is hoped that this will enable a better evaluation of therapeutic results to be made in the future; something which appears even more likely considering that the different molecular features, for a given histotype, seem to distinguish distinct subsets of patients with different clinical outcomes. Likewise, molecular investigation, consenting in some cases a more sensitive and specific identification of rare tumor cells, has enabled more accurate staging of disease at diagnosis as well as a more precise detection of minimal residual disease during treatment. Furthermore, the assessment of risk class also including molecular markers, seems to have improved our ability to discriminate subsets of patients with different outcomes. Finally, a few genes responsible for tumor predisposition have been identified enabling genetic testing to be included in the clinical management of those individuals with well-defined inherited cancer syndromes. In many aspects, the promises of molecular biology have been maintained.

Regrettfully, despite the remarkable progress briefly summarized above, no such parallel has been obtained in patient cure rates. Ongoing studies exploiting the possibility of gene alterations, which are also responsible for the genetic instability in tumor cells, as the key to tumor cell sensitivity will require time before being clinically validated. In spite of the in-depth understanding we have gained of the gene alterations underlying tumor development and progression, Ian Tannock’s statement that “For the next few years, cancer management outside the context of a clinical trial will continue to be based almost entirely on surgery, radiation therapy, and systemic treatment with chemotherapy or hormones.” seems destined to turn out true.

2. SESSION ON “MOLECULAR BIOLOGY OF CHILDHOOD SOLID TUMORS”

This is the first time that the Symposium on Molecular Biology of Hematopoiesis dedicates, along with the traditional sessions on matters regarding hematopoiesis, a few sessions focused on both molecular genetics and clinical management of childhood solid tumors. In particular, the session on “Molecular Biology of Childhood Solid Tumors” organized and chaired by us, includes five presentations aimed at giving a brief up-to-date introduction to the molecular features of childhood solid tumors and to the present-day possibilities of integrating these data into clinical management. Since it is the first of such sessions, it would have been interesting to provide an update on each type of childhood solid tumor. However, since this is beyond the scope of the Symposium, and since other sessions focus on soft tissue sarcomas and retinoblastoma, the session presented here will be limited to the consideration of three histotypes only, namely: Wilms tumor, the Ewing family of tumors, and neuroblastoma.