

PREFACE

The war against cancer has seen enormous successes, but also painful frustration. While major conceptual breakthroughs have been made in our understanding of how cell proliferation is regulated, the translation of this information into effective treatment discoveries has lagged terribly behind. Modern molecular oncology has begun to inch closer to treatment-related questions because the pathways under study are now known to regulate events such as cell death, the precise goal of cancer treatment. Because tumor suppressor biology has not yet translated into a therapy-oriented discipline, the purpose of *Tumor Suppressor Genes in Human Cancer* is to present a view of the current field which simultaneously highlights the clinically relevant directions which have already emerged while stimulating the discovery of new ones.

Through the detailed presentation of tumor suppressor genes with a molecular biological and genetic perspective, two paradigms emerge: 1) a finite number of discrete pathways exist into which tumor suppressors and dominant oncogenes reside and 2) cancer biology rests heavily on both regulators of cell proliferation and cell death. In the current climate of informatics, genomics, and molecularly driven drug discovery, cancer research holds greater promise than ever. *Tumor Suppressor Genes in Human Cancer* first sets the stage by presenting the background of systems for the study of tumor suppressor genes as well as the fields of apoptotic cell death and cancer drug discovery. The second section of *Tumor Suppressor Genes in Human Cancer* proceeds to present detailed analyses of major tumor suppressors and, most important, the pathways into which they fit. The intended audience is the student of cancer biology, from those engaged in graduate or medical education to clinicians or drug development professionals seeking to understand the context of cancer cell biology and its promise for therapeutic gains in the coming years.

The concept that individual genes underlie the biology of malignant transformation harkens back to the early 1900s with the discovery by Peyton Rous of avian sarcomas that were caused by infectious viruses. Many decades later, the identification of the *Src* oncogene placed into focus the notion of the dominant oncogene, a factor whose inappropriate activation confers cellular changes associated with malignant transformation. Alfred Knudsen predicted the existence of a second class of oncogenes whose contribution to cancer is recessively inherited. His hypothesis was based upon clinical observations of cancer risk in familial cancer inheritance patterns and the notion that disease predisposition may represent a multi-hit phenomenon with loss-of-function mutations contributing to the malignant phenotype. Thus the concept of tumor suppressor gene was born and has been abundantly validated by observations that span bench to bedside.

The most striking validation of the tumor suppressor concept comes from the discovery of inactivating mutations or deletions of candidate genes in cancer

prone families. Originally discovered for retinoblastoma, the list has been dramatically extended to include p53, p16/Ink4a/ARF, the NF family, DNA mismatch repair genes, Wilms, von Hippel Lindau, Fanconi Anemia, and other genes. In these cases heterozygous germline disruption of a single allele is associated with cancer predisposition in affected family members. Loss of heterozygosity is frequently observed at the genetic locus within tumors that develop in affected individuals. Mechanisms for tumor suppressor inactivation are diverse and are still being discovered today. For example, in addition to traditional loss of function mutations or deletions, the more recently appreciated inactivating mechanisms include transcriptional silencing (e.g., p16/Ink4a), targeted protein degradation (e.g., p53), and functional disruption of tumor suppressing gene activities (e.g., bcl-2 or Mdm2). These diverse mechanisms of tumor suppressor inactivation highlight one of the most striking breakthroughs in cancer biology, the discovery of discrete pathways in which dominantly acting and tumor suppressing genes converge.

The functional convergence of dominant oncogenes and tumor suppressor genes in cellular growth or survival pathways represents such a powerful clue in the puzzle of carcinogenesis that the ability to fit into a known growth regulatory pathway has become a virtual requirement for a gene's acceptance as a true cancer modifier. Moreover much of the data defining these interactions stemmed from the convergence of clinically derived questions with more basic laboratory science. For example, the retinoblastoma tumor suppressor was found to be targeted by multiple dominant oncogenes discovered through the analysis of animal DNA tumor viruses. The existence of additional interactions between tumor suppressors and dominant oncogenes has cemented the notion that key cellular pathways produce the phenotypes associated with cancer, and the homeostatic regulators of these pathways are potent and common targets of carcinogenic disruption.

The pathways that tumor suppressor genes modulate in cancer have been found to cluster around regulation of the cell cycle, cell death, growth factor signaling, DNA damage responses, and other stress responses. Nearly all tumor suppressors are thought to act through modulation of one (or several) of these pathways. Cell cycle regulation has been the traditional pathway thought to be targeted in the etiology of cancer. More recent observations have added a dramatic new dimension to this view in suggesting that cell survival pathways exist as distinct, genetically selected entities and may profoundly influence behaviors we associate with malignancy. Either dysregulated growth or inefficient death (or both) are strongly associated with tumorigenesis. The current revolution in molecular oncology has been fueled largely by the ability to place individual cancer genes within such functional pathways of known importance. Perhaps more important, these functional classifications have in some cases led to investigations that relate more than ever before to cancer treatment.

The study of cancer cell death carries with it the hope of intervening in the very same process for therapeutic benefit. Rarely has a field of fundamental basic

science become so mainstream in biologic inquiry while simultaneously focusing on questions of direct therapeutic importance. The interface between research on cell death and clinical ramifications of that work is well illustrated by the actions of tumor suppressor genes, many of which are now recognized to regulate cell survival.

Tumor Suppressor Genes in Human Cancer is not an attempt to fully synthesize cancer biology and treatment, since the field has not arrived at a stage where such a synthesis is yet possible. However the convergence of new technologies suggests that the coming years will begin to see treatment discoveries more directly interface with basic research. Genomics and systematic gene expression technologies will provide thorough catalogs of information whose discovery currently occupies substantial research effort. Linkage of these catalogs to clinical data including treatment responses (pharmacogenomics) promises to dramatically alter drug discovery and treatment design. The pillar of this revolution is the basic biology of disease, and tumor suppressor genes lie at the core of that pillar.

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