Human Cytogenetic Cancer Markers

人类细胞遗传学癌症标记物

Edited by
Sandra R. Wolman, MD
Stewart Sell, MD

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Edited by

Sandra R. Wolman, MD

Uniformed Services University of the Health Sciences, Bethesda, MD

and

Stewart Sell, MD

Albany Medical College, Albany, NY

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Preface

The series on Cancer Markers published by Humana Press illustrates the expanding base of knowledge of the different types of markers and their applications to the study of cancer. In an earlier volume in this series, the development of different eras of investigation of cancer markers was described. The first era was the time of earliest recognition that tumor cell products, such as myeloma proteins, hormones, and isozymes, could be used to detect and monitor tumor growth. After some delay, the second era, beginning in the early 1960s, was notable for the discovery of developmental antigens, alphafetoprotein (AFP) and carcinoembryonic antigen (CEA), that were re-expressed in many tumors, and that were detectable by conventional antisera. The first two books in the series, published in 1980 and 1982, covered the rapid accumulation of information on these topics and included early studies on prostate-specific antigen (PSA) and other organ-specific antigens. The second book included contributions by several authors that introduced the subject of monoclonal antibodies, a new and precise approach to the identification of cancer markers. The third era, then, was characterized by the expanding uses of monoclonal antibodies to detect carbohydrates, mucins, and cytoplasmic proteins, as well as cell surface markers in different forms of cancer. These topics and many other applications of cancer markers were presented in the next three books in the series.

The current perception of the fundamental role of genetic changes in basic and clinical aspects of the study of cancer has led to the conclusion that the fourth era of cancer marker study will concentrate on nuclear events. Alterations detectable as quantitative or qualitative differences in DNA and its packaging into chromosomes may

be useful in cancer diagnosis and prognosis, and also reflect the heritable, progressive, and mutable nature of the disease. Thus, *Human Cytogenetic Cancer Markers* focuses on the chromosomal era, which began with the discovery of the Philadelphia chromosome by Nowell and Hungerford in 1960, and its chapters represent the coming of age of cytogenetic markers of human cancer.

We have assembled an outstanding group of contributing authors, whose work spans from basic research to clinical diagnostic applications, and from current theory to newly developing technology. The first part of the book is devoted to a section on Perspectives. Its chapters on DNA cytometry, molecular cytogenetics, and molecular genetics provide an introductory framework for the, organ- and site-specific chapters that follow. The need for integration of these disciplines with conventional cytogenetics is apparent throughout, although, as in many emerging fields, the available data do not always appear directly correlated, and may even appear inherently inconsistent. The site-specific chapters present striking differences in the degrees of data collected, integration of information from different technologies, and clinical utilities with respect to individual tumor types.

With the exception of the leukemias and lymphomas, there have been few attempts as yet to correlate the chromosomal aberrations in cancers with expression of other types of cancer markers, and with careful histological discriminations. We hope this volume will stimulate further work in these areas.

Sandra R. Wolman
Stewart Sell

Contributors

GEORGIA BARDI • *Department of Clinical Genetics, University Hospital, Lund, Sweden; Department of Genetics, Papanikolaou Research Institute, Saint Savas Hospital, Athens, Greece*

DAPHNE W. BELL • *Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA*

JULIA A. BRIDGE • *Departments of Pathology, Pediatrics, and Orthopedics, University of Nebraska Medical Center, Omaha, NE*

ARTHUR R. BROTHMAN • *Departments of Pediatrics and Human Genetics, University Medical Center, Salt Lake City, UT*

LINDA A. CANNIZZARO • *Department of Pathology, Albert Einstein College of Medicine, Bronx, NY*

CEES J. CORNELISSE • *Department of Pathology, University of Leiden, The Netherlands*

NORMAN L. EBERHARDT • *Departments of Medicine and Biochemistry/Molecular Biology, Mayo Clinic, Rochester, MN*

JONATHAN A. FLETCHER • *Department of Pathology, Brigham and Women's Hospital, Boston, MA*

STEFAN K. G. GREBE • *Department of Medicine, Mayo Clinic, Rochester, MN*

CONSTANCE A. GRIFFIN • *Departments of Pathology and Oncology, Johns Hopkins University, Baltimore, MD*

SVERRE HEIM • *Department of Clinical Genetics, University Hospital, Lund, Sweden; Department of Genetics, The Norwegian Radium Hospital and Institute for Cancer Research, Oslo, Norway*

LORI HOFFNER • *Department of Pathology, Magee Womens Hospital, Pittsburgh, PA*

ANTON H. N. HOPMAN • *Department of Molecular Cell Biology and Genetics, University of Limburg, Maastricht, The Netherlands*

ROBERT B. JENKINS • *Departments of Laboratory Medicine and Pathology and Biochemistry/Molecular Biology, Mayo Clinic, Rochester, MN*

SAKARI KNUUTILA • *Department of Medical Genetics, University of Helsinki, Finland*

MIN LEE • *Department of Pathology, Henry Ford Hospital, Detroit, MI*

FELIX MITELMAN • *Department of Clinical Genetics, University Hospital, Lund, Sweden*

S. DAVID NATHANSON • *Department of Surgery, Henry Ford Hospital, Detroit, MI*

TIMOTHY J. O'LEARY • *Department of Cellular Pathology, Armed Forces Institute of Pathology, Washington, DC*

NIKOS PANDIS • *Department of Clinical Genetics, University Hospital, Lund, Sweden; Department of Genetics, Papanikolaou Research Institute, Saint Savas Hospital, Athens, Greece*

FRANS C. S. RAMAEKERS • *Department of Molecular Cell Biology and Genetics, University of Limburg, Maastricht, The Netherlands*

ADRIENNE C. SCHECK • *Department of Neurology Research, Barrow Neurological Institute, Phoenix, AZ*

STEWART SELL • *Department of Pathology, Albany Medical College, Albany, NY*

T. VINCENT SHANKEY • *Departments of Urology and Pathology, Loyola University Medical Center, Maywood, IL*

JOAN RANKIN SHAPIRO • *Department of Neurology Research, Barrow Neurological Institute, Phoenix, AZ*

MARILYN L. SLOVAK • *Department of Pathology, City of Hope National Medical Center, Duarte, CA*

ERNST J. M. SPEEL • *Department of Molecular Cell Biology and Genetics, University of Limburg, Maastricht, The Netherlands*

URVASHI SURTI • *Department of Pathology, Magee Womens Hospital, Pittsburgh, PA*
JOSEPH R. TESTA • *Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA*
CHRISTINA E. M. VOORTER • *Department of Molecular Cell Biology and Genetics, University of Limburg, Maastricht, The Netherlands*
BRIANA J. WILLIAMS • *Department of Urology, Louisiana State University, Shreveport, LA*
ERIC WOLMAN • *Department of Operations Research and Engineering, George Mason University, Fairfax, VA*
SANDRA R. WOLMAN • *Department of Pathology, Uniformed Services University of the Health Sciences, Bethesda, MD*
MARIA J. WORSHAM • *Department of Pathology, Henry Ford Hospital, Detroit, MI*

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An Introduction to Cancer Markers and Cytogenetics

Sandra R. Wolman, Stewart Sell, and Eric Wolman

Introduction

The goal of this series of books on cancer markers is to summarize and illustrate the state of the art in the use of markers for diagnosis, prognosis, and monitoring the effect of therapy on malignant tumors *(1–5)*. The purpose of this volume in the series is to present the current status of chromosomal markers of cancer, not only for their potential and realized clinical utility in diagnosis, prognosis, and disease monitoring, but also for their contributions to understanding mechanisms of tumor development and progression. These mechanisms have been identified largely by localization of relevant oncogenes and tumor suppressor genes, and by recognition of new gene constructs (and their protein products and cellular functions) that result from translocation in the course of carcinogenesis.

At present, the practical clinical diagnosis and prognosis of cancer depend on the recognition of gross and microscopic features of the individual lesion. Grossly, the size and degree of tissue infiltration combined with the presence or absence of metastasis is used to predict the clinical outcome. Microscopically malignant features reflect the "less-differentiated" state of cancer cells and tissues as compared to well-differentiated normal tissues and cells. However, there are

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many examples in which the diagnosis and prognosis of cancer are determined, at least in part, by serologic, molecular, or chromosomal changes in the tumor. The first two types of markers, serologic and molecular, have been the subjects of previous books in this series on cancer markers; and relationships between chromosomal and molecular genetic events are a recurring theme in this volume.

The first serologic marker, Bence-Jones protein, was identified in patients with multiple myeloma (mollities ossium) in 1846, but the applications of serologic marker analysis had little impact on clinical patient management until after the discoveries of α-fetoprotein (AFP) by Garri Abelev in 1963, and carcinoembryonic antigen (CEA) by Gold and Freeman in 1965. With the notable exception of prostate-specific antigens (PSA), most serologic markers have been disappointing as diagnostic and prognostic tools. On the other hand, many have important roles in determining the response to therapy. If the serum level of a marker (e.g., CEA, AFP, PSA, ectopic hormone, Bence-Jones protein, or cancer carbohydrate and mucin markers detected by monoclonal antibodies) is elevated in a given patient, then a falling serum level indicates a positive response to therapy. However, if the serum level fails to fall to normal and then rises, residual tumor or metastasis is likely. Occasionally, elevations of these serologic markers are also found in benign conditions, and the levels may overlap those found with malignant lesions. Nevertheless, high and sustained levels of AFP in individuals at high risk for hepatocellular carcinoma are essentially diagnostic for the presence of tumor. Similarly, very high and sustained levels of different serologic markers strongly indicate other malignant diseases. Thus, serologic and other markers are of considerable value when interpreted within the context of other clinical and pathologic findings.

Over the past decade, molecular markers have promised far more precise and specific definition of tumors and their behavior, but that promise has not yet been realized. The definitive diagnosis of cancer still depends mainly on histologic criteria. In microscopic examination of thin slices of tissues, early pathologists noted the resemblance between cancerous tissue and embryonic tissues. They used terms such as "poorly differentiated," "undifferentiated," and "well-differentiated" to describe the appearance of a tumor in embryonic terms. More recently, it has been recognized that cancerous

tissues often contain detectable mutations and altered expression of genes that control cell-cycle activation or progression. This raised the possibility that measurement of these mutations or changes might be used to make the diagnosis or determine the prognosis of individual cancers. Unfortunately, although general relationships have been identified, many molecular biologic changes do not correlate closely enough with specific behavior patterns of a malignant tumor to provide "stand-alone" clinical guidelines for individual patient care. They complement, rather than replace, the standard parameters used to describe a tumor. Therefore, the diagnoses of most forms of cancer for the foreseeable future will remain linked with the classic histologic features of the tumors, although markers will modify and increase discrimination of the diagnosis. Similarly, markers will contribute to prognosis, although the location, size, histologic type and grade, and presence or absence of metastatic lesions will remain important components of that determination. Such factors as ploidy, mitotic frequency, immunohistochemical markers for proliferating cells (Ki67, PCNA), angiogenesis, and vascular invasion all correlate with prognosis; their predictive power modifies, but is not independent of, that based on histologic criteria. The same is true for serum markers (e.g., CEA, CA-15-3, CA-249), mucin cancer antigens, and tissue polypeptide antigen; and it is equally true for expression of oncogenes (e.g., *bcl*-2, p53, c-*erb*B-2, c-*myc*, and nm23), and for markers of invasion or metastasis (e.g., cathepsin D, laminin receptors, plasminogen activator, angiogenesis factors, and expression of cell adhesion molecules). Expression of all these markers correlates with degree of malignancy, and their determination adds in varying degrees to prediction of tumor behavior when histologic type and grade are known; but we do not yet have foolproof "magic markers."

This volume addresses the status of chromosomal markers. Some chromosomal markers are causally related to individual tumors and have achieved primary diagnostic "stand-alone" status, such as the t(9;22)* of chronic myelogenous leukemia and the

*Cytogenetic terminology is based on ISCN nomenclature. [ISCN 1985 International System for Human Cytogenetic Nomenclature (1985) March of Dimes Birth Defects Foundation and Cytogenetics and Cell Genetics S. Karger, Basel, Switzerland. (Guidelines for Cancer Cytogenetics ed. Mitelman F. Supplement 1991 and 1995)]

t(15;17) of acute promyelocytic leukemia. Others, such as the t(X;18) of synovial sarcoma, are highly discriminatory in differential diagnosis. For many forms of human cancer, however, unique and tumor-specific chromosomal patterns have not yet been discerned, largely because of the extent and complexity of chromosomal change in many solid tumors. When the critical biologic events in each tumor can be chromosomally localized, molecularly identified, and appropriately correlated with clinical findings, it is likely that markers will play a much greater role in medical management. **Because we believe that cancers are genetic diseases, genetic markers should eventually provide the most accurate means to signify their diagnosis and prognosis.** Detection may be based on classical cytogenetic means, but in solid tumors molecular cytogenetic techniques that do not depend on metaphase analysis will probably be of greater utility for finding such markers as loss of heterozygosity (LOH) of certain genes, gene amplifications, or fusion constructs such as the *BCR/ABL* translocation.

The first association between genetic and chromosomal aberrations and malignancy was made by Boveri *(6)*, who originated the theory of a somatic mutational basis for cancer. Muller *(7)* then showed that chromosome damage was one of the immediate biological results of exposure to ionizing radiation. Shortly thereafter, animal studies indicated that a later consequence of radiation exposure was tumor formation *(8)*. In the 1940s and 1950s, several investigators reported chromosome aberrations in experimental tumor models such as mouse ascites tumors. Later the atomic bomb explosions resulted, among other grim sequelae, in ample evidence of dose-related induction of tumors in humans by radiation *(9)*. Effects similar to those of radiation on chromosomes (breakage, rearrangements) could be induced by a variety of chemicals that were also implicated in tumor induction. These observations eventually led to the conviction that agents capable of inducing chromosome damage were potentially tumorigenic and, therefore, that chromosome aberrations could have an etiologic role in tumor formation.

The new age of chromosomal changes in human cancer began in 1960 with the discovery of the Philadelphia chromosome by Nowell and Hungerford *(10)*, shortly after simple modifications of technique permitted accurate recognition that the normal diploid