THE MOLECULAR BIOLOGY OF CANCER

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Edited by

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Preface

In the ten years since "An Introduction to the Biochemistry of the Cancer Cell" was published an enormous amount of progress has been made in the cancer field. The events that were underway at that time which provided a basis for the understanding of gene function and the various roles of DNA, RNA, gene control proteins, and other important elements of cellular function have partially reached fruition. A huge literature has developed which is difficult for the graduate student, fellow, and many workers in the field to fully comprehend, and, accordingly, it seemed appropriate at this time to once again attempt to prepare a treatise that would at least cover the broad areas of this field. The goal of this volume is to acquaint the student of oncology with the state of progress in the molecular biology of cancer and to provide literature references which hopefully will give a more detailed review of special topics.

The cancer cell is characterized by its ability to escape from homeostatic controls. It can metastasize, invade, and grow independently of host controls whereas other cells must contribute to the welfare of the host. It is still uncertain whether the special features of cancer cells are simply aberrant manifestations of normal gene readouts or whether new information is brought into the cell that produces unusual functions. This volume presents the current status of information regarding these aspects of molecular biology of cancer in Part I, a number of aspects of chemical and viral carcinogenesis in Part II, and some special features of the variable phenotypes of cancer cells in Part III.

In a sense the cancer problem is very similar to an iceberg in that only a peak of information on its complexity is visible. It is clear from the literature that enormous progress is required at the molecular level in cancer in important areas such as the chemistry of DNA and messenger RNA; it is unfortunately slow because of the serious difficulties in making technological advances in these fields. On the other hand, there is gratifying progress in the field of protein synthesis, including structural and functional information on contributory molecules and, recently, in the field of gene control by nuclear proteins. Unfortunately, it has not yet been possible to specifically single out either critical elements involved in cell growth or more importantly the special features of the cancer process.

In the fields of carcinogenesis, basic and meaningful advances have occurred in our understanding of metabolism of chemical carcinogens and in the multiple types of oncogenic viruses. Progress in these fields has been impressive at the

experimental level, but extension or application of this information to the human problem has been slow and very difficult as indicated in Chapters X and XI.

As noted in "An Introduction to the Biochemistry of the Cancer Cell," cancer cells repress many phenotypic functions of their cells of orgin and derepress other phenotypic features. As pointed out in Chapter XII some of these alterations of phenotype reflect quantitative reductions of gene activity. Conversely, others reflect a production of new gene products such as species of molecules found only in embryos rather than in adult cells. Some of these events are apparently random and others may be of great importance to growth and survival of cancer cells. However, there is still no clear single phenotype that is characteristic of cancer cells.

Many of the older generation of research workers in the cancer field were greatly stimulated by Jesse Greenstein's "The Biochemistry of Cancer" and some of the earlier works that dealt primarily with carbohydrate metabolism. The enormous progress in molecular biology has reoriented cancer research by providing new methods, new concepts, and new information. Many of these important methods in cancer research are reviewed in the current series of ten volumes which deal specifically with the uses and evaluation of methods in this field (*Methods in Cancer Research*, H. Busch, ed.)

In connection with the literature covered, it should be noted that the amount of research in the cancer field as well as in allied disciplines is great. There are now multiple encyclopedias and other volumes on specific aspects of the problem. This volume is not intended to substitute for such works, but rather to balance a broad and general review with sufficient detail for comprehension of more specific literature. The authors are apologetic for the omission of many important contributory works, but the goals of this volume could simply not have been achieved by the broadest possible coverage. For more extensive and detailed reviews the readers are urged to consult either the primary literature or such distinguished series as *Advances in Cancer Research* (S. Weinhouse and G. Klein, eds.).

Although cancer is under attack in a wide variety of areas, the need is still pressing for intensive and unremitting dedication to the task for new ideas and for the development of interest in young and keen minds. The discrepancy between the urgency of the problem that confronts both patient and clinician and the slow but steady pace of progress is all too apparent to those of us who have seen loved ones slowly dying from this disease. Yet, we all recognize that patient effort, enormous stamina, and endurance as well as all of the other attributes of dedication are the only approaches to the solution of the problem.

The present state of knowledge of cancer is the result of idealism, devotion, and effort of many distinguished and dedicated scientists. Their accomplishments provide the basis of the hope that we and our successors can continue to develop new knowledge and methods to the point that cancer can be conquered.

Harris Busch

Acknowledgments

I am extremely thankful to each of the authors of the various chapters of this work for their diligence and promptness in preparing their chapters. It is clear that as each of the contributory fields to cancer research evolves the expertise of investigators in special fields is particularly critical for both comprehension and interpretation of various types of specific information. Accordingly, it seems clear that in future works of this type more rather than fewer specialized chapters will be required.

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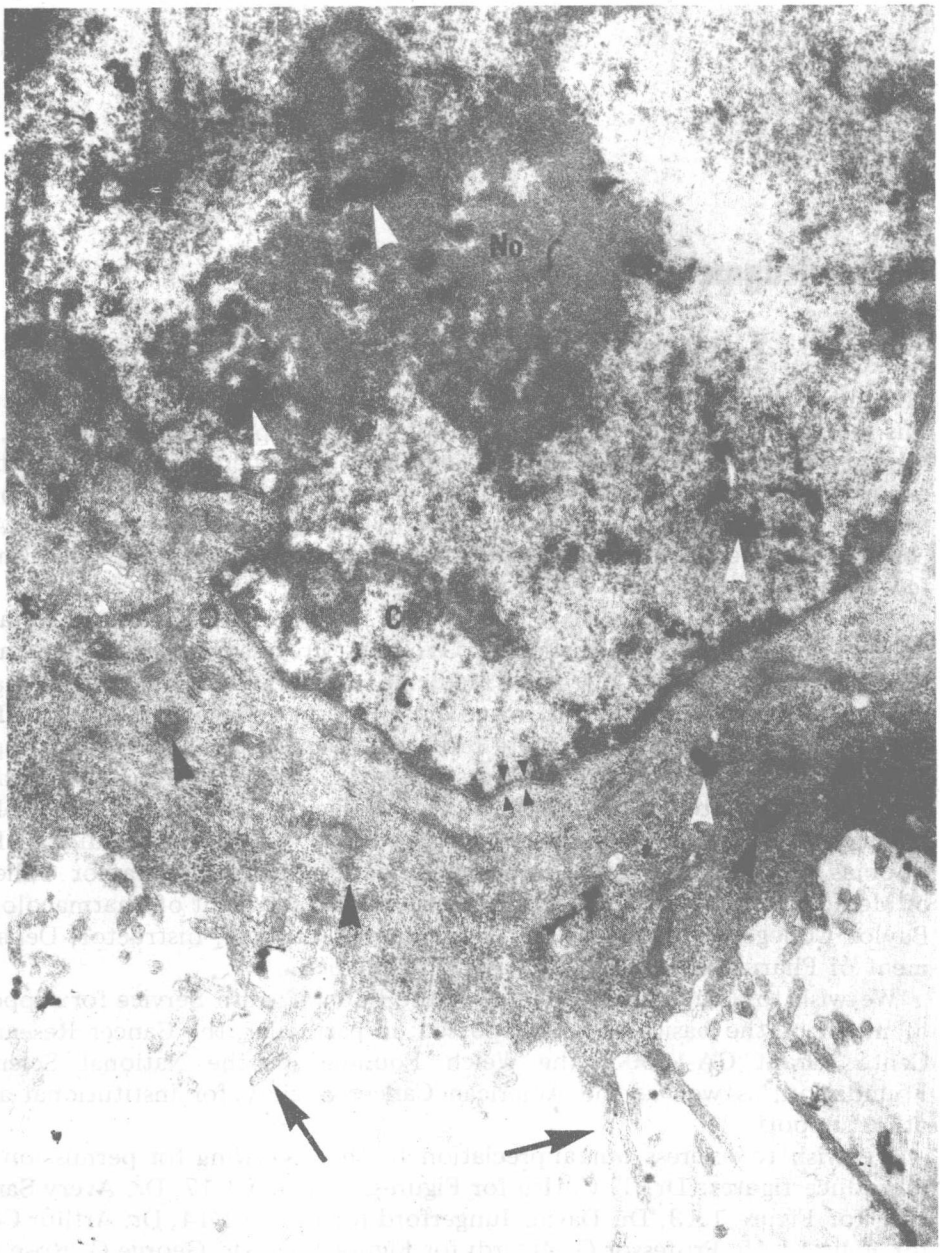

A margin of a nucleus and cytoplasm of a Novikoff hepatoma ascites cell. There are many lengthy microvilli (arrows) of the plasma membrane on the cytoplasmic surface. The two layers of the nuclear envelope are distinct (small pointer) as are the cytoplasmic mitochondria (large pointers). There are canaliculi (C) between the inner layer of the nuclear envelope and the nucleoplasm. This cell was exposed previously to labeled uridine for 60 minutes, and there are a number of grains (white pointers) in the nucleolus (No) and the nucleoplasm, as well as the cytoplasm (Courtesy of Drs. T. Unuma, K. Smetana, and Y. Daskal).

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Michael Potter

CHAPTER I

Introduction

HARRIS BUSCH

I. The Importance of Cancer as a Disease

Approximately 350,000 persons will die in the United States in 1974 from cancer or complications developing in the course of the disease. The number of new cases developed each year is estimated to be approximately twice the number. The long duration of the disease and its chronically debilitating effects produce a serious economic burden to the patients and to the community. Because cancer chiefly affects the older population, it produces a serious loss of valuable persons who have important knowledge and training. Aside from the fact that neoplastic disease is associated with death and debility, a major concern of both the laity and the medical profession is the intractable pain which may develop in the later stages of the disease. The nature of the disease and its prevalence have spurred the development of the National Cancer Act which provides for large research institutes for the study of cancer and allocation of funds to medical schools and universities for the study of fundamental aspects of the disease. Moreover, vast expenditures have been made by private agencies, pharmaceutical industries, and the government in an effort to find curative drugs, palliative drugs, and new measures for combating the disease. While advances have been made in therapy, they have not yet markedly affected the morbidity and the mortality of the disease. Accordingly, it has become increasingly clear that fundamental knowledge about the nature of the cancer cell and its distinguishing properties must be obtained before approaches can be made to therapy on truly rational grounds.

II. The Biological Nature of the Cancer Cell

The fundamental problem in cancer is the cancer cell (27) which exhibits the property of division that is not subject to the usual homeostatic control mechanisms of the host. Since the daughter cells from these divisions exhibit similar properties, the cancer problem is generally believed to be a genetic problem involving biochemical disorders or aberrations of normal molecular biology.

Neoplastic lesions, or tumors, consist of many cells which have an altered phenotype that results in differences in both histological and biological properties from other cells. For example, cancer cells have darker staining nuclei, more chromatin, and more mitoses than cells of the tissues of origin (Figs. 1.1–1.3). In addition, cancerous lesions exhibit the pathological properties of invasion of normal tissues and entry into cellular masses such as muscle cells. Metastasis is the escape of cancer cells from the original locus of the tumor and passage

via the blood or lymphatic tissues to another tissue or organ where the cells lodge and produce secondary tumor masses, which may be much larger than those of the tissue of origin and may be lethal.

The tumor masses are generally composed of many millions of cells (10^7 to 10^9 cells) and the degree of damage to the host is dependent both on the rate of cell division and the anatomic locus of the tumors. Although tumors are divided into malignant (cancerous) and nonmalignant (benign) tumors, based upon considerations of their lethality, a benign tumor may have a very "malignant location," and a malignant tumor may be so located or so slowly growing that at least initially the damage it produces is very small.

Regardless of whether they are slowly or rapidly growing, malignant tumors ultimately kill the patient. This end result may develop through local effects such as erosion or penetration of blood vessels, hemorrhage, infection, displacement, restricted oxygenation, or mass effects, e.g., colonic obstruction and loss of liver function.

A. Morphological and Ultrastructural Properties

Many efforts have been made to give a specific definition of the cancer cell. Table 1.1A and 1.1B indicate the light and electron microscopic characteristics that have been found for neoplastic cells (123). The more malignant the tumor and the more rapid the growth rate the more of these changes are found (27, 123, 162, 167). For example, Fig. 1.1 demonstrates nucleolar aberrations and dense cytoplasmic basophilia. Figures 1.2–1.4 show the irregular form of nuclei of cancer or leukemic cells. Figures 1.3 and 1.4 show densities of chromatin structures in leukemic lymphoblasts. Figures 1.5 and 1.6 show irregularities of mitochondria including defective ultrastructures and swelling. Figure 1.7 shows filamentous structures in the cytoplasm of a leukemic monoblast and a dilated perinuclear space which may be related to nuclear abnormalities. Figure 1.8 shows similar filamentous structures in the cytoplasm of a hepatoma. Figures 1.9 and 1.10 show cytoplasmic variations in a human plasmacytoma and immature leukemic lymphocytes. In Fig. 1.9 the Golgi apparatus appears to be hypertrophic but in Fig. 1.10 it is small (hypotrophic). These ultrastructural variations, particularly with respect to the cytoplasmic structures, reflect differences in the degree of differentiation and dedifferentiation of cancer cells. These variations produce the greater or lesser phenotypic expressions of the cells of origin of these tumors (17, 33, 41, 123). In some cases, such as melanomas, insulinomas, and plasmacytomas, the tumors may produce sufficient signs and symptoms to permit early diagnosis of the disease.

B. The Nucleolus

One development of the 1930's that captured the attention of oncologists and later of molecular biologists was the report first from the Mayo clinic (101–103)