Biological Markers of Neoplasia: *Basic and Applied Aspects*

Edited by

RAYMOND W. RUDDON

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Preface

It is likely that improvement in cancer treatment, at least for the immediate future, will depend upon earlier diagnosis and better use of currently available treatment modalities. This realization has intensified the search for "biological markers" of cancer. A variety of tumor associated antigens, enzymes, ectopic hormones, and products of cellular metabolism have been utilized as markers for cancer in man. With few exceptions, none of these has provided the sensitivity and specificity needed for a definitive diagnostic tool in the screening for early cancer; however, a number of them have proven to be useful in evaluating a patient's response (or lack of response) to therapy and in determining disease recurrence.

The basic research currently going on in a number of related disciplines is providing new insights into the nature of gene products produced and secreted by malignant cells, and it was thought that it would be timely to bring together scientists who are experts in these fields to focus on the products of malignant cells which could be utilized in the diagnosis and treatment of cancer in man. Accordingly, the first International Conference on Biological Markers of Neoplasia: Basic & Applied Aspects was organized and held in Leesburg, Virginia on May 22-26, 1978. This volume contains the proceedings of that conference.

The goals of the conference were: (1) to provide a state of the art review of the basic research underlying the development of new cancer markers and (2) to indicate how this research can be applied to solving clinical problems in the diagnosis and therapeutic management of malignant disease. The participants represented a variety of disciplines, including biochemistry, cell biology, immunology, virology, endocrinology, and clinical oncology, and are internationally recognized as experts in their fields of research. We encouraged the participants to include an overview of their area of research as well as their most pertinent experimental data in the manuscripts. In the great majority of cases this has been done, rendering this volume an accurate and valuable representation of what was accomplished at the conference. In addition, we have included the discussions which followed each paper, and these discussions contain a number of "pearls" which add to the value of the presentations.

The conference was sponsored by Litton Bionetics, Inc. in cooperation with the National Cancer Institute – Frederick Cancer Research Center. I wish to thank the chairmen who conducted the individual

sessions: Lloyd Law (National Cancer Institute), Raymond Gilden (Frederick Cancer Research Center), Michael Crumpton (National Institute for Medical Research, Mill Hill, England), John Marchalonis (Frederick Cancer Research Center), Saul Rosen (National Institute of Arthritis, Metabolism, and Digestive Diseases), Harris Busch (Baylor College of Medicine), Edward Reich (Rockefeller University), Richard Roblin (Frederick Cancer Research Center), and Morton Schwartz (Memorial Sloan-Kettering Cancer Center). A special note of thanks goes to Dottie Green (Biological Markers Laboratory, Frederick Cancer Research Center) whose attention to detail and perseverance contributed in large measure to making the conference a success. I am also very greatful to JoAnn Tichnell (Biological Markers Laboratory), who organized and supervised the preparation of the manuscripts for this publication and to Sally Miller (Biological Markers Laboratory), who made a significant contribution to the planning of the conference and the preparation of the proceedings.

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ROLE OF BIOLOGICAL MARKERS IN CANCER DIAGNOSIS AND TREATMENT

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Three of the most important questions facing clinicians involved in cancer diagnosis and treatment are: (1) How can cancer be diagnosed earlier in order to maximize the patient's chance for survival? (2) How can it be determined whether the patient's disease is responding to treatment? (3) How long should the patient be treated in the face of an apparent clinical remission? These questions are central to any good program in cancer management, but they are very difficult to answer. Definite advances have been made in the earlier diagnosis of malignant disease, exemplified by advances in exfoliative cytology (e.g., Papanicolaou test for cervical cancer), radiographic detection techniques, and endoscopic examination. The limits of the sensitivity of these methods at their best, however, usually still precludes the detection of cancers smaller than 10^9 cells. Thus, more sensitive tests are still needed. A number of biochemical and immunological tests for cancer have been developed in recent years. For lack of a better term, these have collectively become known as "biological markers" of cancer. Biological markers can be used in three general ways: (1) to screen the general population or specific populations at high risk for cancer development, (2) to aid in the differential diagnosis of cancer in patients who have come to the physician with signs or symptoms potentially relating to cancer, and (3) to follow the clinical course of patients with cancer. The first of these goals is by far the most difficult to accomplish because, in order for a test to be useful for screening, it must be extremely sensitive, specific for malignant disease, and cost-effective.

The need for biological markers of malignant neoplastic disease remains a high priority item because, for the immediate future, improvement in cancer therapy will continue to depend largely on earlier detection and better use of currently available treatment modalities. Both early detection and improved use of therapeutic modalities would be greatly facilitated by the identification of tumor markers that are: (1) specific for the malignant process, (2) tumor-type specific, (3) readily detectable in body fluids and tissue extracts, (4) detectable early in the course of disease before it is clinically evident,

(5) indicative of the overall tumor cell burden in the body, (6) related to the degree of success of anti-cancer therapy, (7) indicative of the presence of micrometastases, and (8) predictive of disease recurrence.

Of the markers that are currently available, human chorionic gonadotropin (hCG) as a marker for choriocarcinoma comes the closest to the ideal.[1] Elevated levels of hCG are indicative of the presence of choriocarcinoma, and a decrease in hCG correlates well with successful therapy. Recurrence of disease is also heralded by increasing hCG levels. Clearly, the ability to follow the therapeutic response of other cancers, in a manner similar to that which can be done for choriocarcinoma with hCG as a biomarker, would be a tremendous boon to cancer therapy.

The reports of Tatarinov[2] and Abelev et al.[3] relating the reappearance of alpha fetoprotein in the serum of adults with hepatocellular carcinoma and teratocarcinoma, and the demonstration by Gold and his colleagues[4,5] of the presence of carcinoembryonic antigen (CEA) in patients with colon cancer have been stimuli to the search for embryonic gene products which are expressed by cancer cells and which may be utilized as indicators of malignant disease. Unfortunately, CEA and other fetal antigens of this type are also associated with certain non-malignant disease states. A number of other oncofetal antigens, hormones, enzymes, and biochemical products of cell metabolism have been found to be associated with human malignant disease. Many of these markers lack specificity in that they may reflect tissue damage resulting from any of a number of mechanisms or may indicate states of hypermetabolism and increased cell turnover which occur in a variety of non-malignant proliferative disorders (Table 1). Nevertheless, in cases where a marker is elevated, even if it is not specific for that tumor type, it may still be very useful in following the course of a given patient's disease and response to therapy. Why the latter is a very important use for biological markers is depicted in Figure 1, which is a schematic plot of the log number of cancer cells in a patient vs. the time after initiation of treatment.[6] In a patient with a tumor burden of 10^{12} cells, a two log kill may be sufficient to put the patient in apparent clinical remission, based on shrinkage of tumor mass, improvement in performance status, etc. Further treatment may reduce the tumor mass to 10^{9} cells, at which point the tumor usually becomes clinically undetectable. Obviously a patient still harboring a billion cancer cells is not cured. In fact, there is a lot of experimental animal data which indicates that the burden of viable tumor cells has to be reduced to zero in order for cure to be obtained.[7] Thus, one of

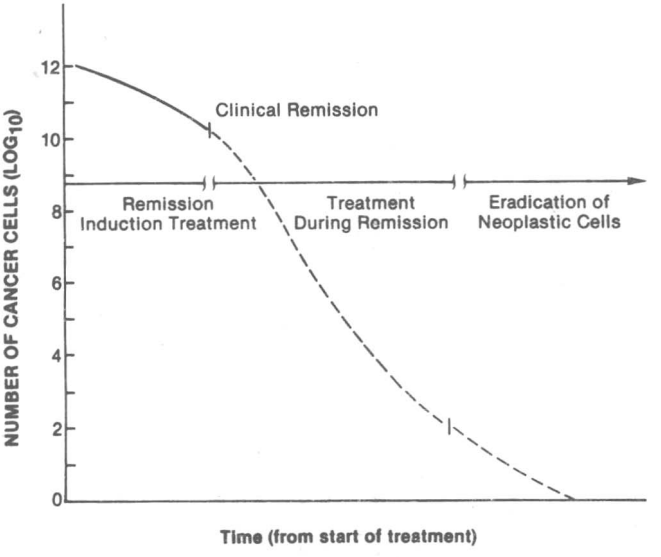

Fig. 1. Number of viable cancer cells vs. time after initiation of anticancer therapy. Adapted from Frei.[6]

the important but sometimes overlooked roles for biological markers is to indicate to medical oncologists, radiotherapists, or cancer surgeons whether or not their treatment program has completely eliminated the disease.

It is clear that future research needs to be directed at discovering biological markers which are specific for the malignant process and hopefully also for the tissue of origin of the tumor. In order for a marker to have a significant impact in cancer detection, it should be able to be detected in body fluids when a tumor is smaller than 1 cm in diameter ($\approx 10^9$ cells). This will require very specific and sensitive assays. It is possible that assays several-fold more sensitive than currently available radioimmunoassays will have to be developed. It is hoped that the subsequent papers presented in this monograph will provide some new insights to basic cancer biologists and clinicians in order to stimulate the search for better cancer markers and to facilitate the utilization of markers that are now being developed, but which have not yet found their way into the clinic.

TABLE 1

SOME BIOLOGICAL MARKERS OF HUMAN MALIGNANT DISEASE

Classification	Marker	Conditions associated with elevated levels or abnormal isoenzyme patterns	
		Malignant	Nonmalignant
Oncofetal antigens	Alpha$_1$-feto-protein	Hepatocellular carcinoma; testicular and ovarian teratocarcinoma; pancreatic, gastric, colonic, and bronchogenic carcinoma	Ataxia telangiectasia, hepatitis, cirrhosis, pregnancy
	CEA	Carcinomas of colon and rectum, pancreas, liver, breast, uterus, ovary, testis, prostate, kidney, bladder and lung; leukemia; lymphoma; neuroblastoma	Cirrhosis, pancreatitis, tuberculosis, chronic bronchitis and emphysema, inflammatory bowel disease, peptic ulcer, colorectal polyps
Ectopic hormones	ACTH	Carcinomas of lung; carcinoid tumors of bronchus, stomach, pancreas; islet cell carcinoma of pancreas; thymoma; medullary carcinoma of thyroid; pheochromocytoma; neuroblastoma and ganglioneuroblastoma; ovarian carcinoma; adenocarcinoma of colon	Nonmalignant neuroendocrine disorders causing Cushing's disease
	Calcitonin	Oat cell carcinoma of lung; breast carcinoma; medullary carcinoma of thyroid	Renal insufficiency
	hCG	Choriocarcinoma; testicular embryonal carcinoma; carcinomas of lung, breast, ovary, stomach, small intestine, pancreas, biliary tract, liver, colon/rectum; lymphoma; melanoma	Pregnancy, regional enteritis, ulcerative colitis, hepatic cirrhosis, gastric and duodenal ulcer
Enzymes	Acid phosphatase	Carcinoma of the prostate; breast carcinoma	Gaucher's disease

Enzymes	Placental alkaline phosphatase	Choriocarcinoma; carcinomas of ovary, pancreas, colon, breast, uterus, bronchus; testicular cancers; reticulum cell sarcoma; Hodgkin's disease; multiple myeloma	Pregnancy
	Non-placental alkaline phosphatase	Osteogenic sarcoma; parathyroid carcinoma; cancers metastatic to bone, e.g. from prostate, breast; multiple myeloma; infiltrative cancers of liver such as Hodgkin's disease, leukemia, reticulum cell sarcoma	Hepatitis, cirrhosis, amyloidosis, tuberculosis
	Aminopeptidases	Carcinomas of pancreas, liver, stomach, lung; carcinoma metastatic to liver	Viral hepatitis, biliary tract obstruction
	Galactosyl transferase	Carcinomas of lung, breast, esophagus, stomach, pancreas, colon, gallbladder; chronic lymphocytic leukemia	Polycythemia rubra vera, diverticulosis, celiac disease
	Gamma glutamyl transpeptidase	Carcinoma metastatic to liver	Alcoholism, malabsorption syndromes, biliary obstruction, myocardial infarction, neurological diseases, anticonvulsant drug therapy
	5'-Nucleotidase	Carcinoma metastatic to liver (note: activity may be elevated in patients with metastatic carcinoma even though bilirubin is normal)	Hepatobiliary disease
	Ribonuclease	Carcinoma of pancreas	Pancreatitis, obstructive biliary disease, renal insufficiency
	Sialyl transferase	Carcinomas of breast, colon, lung, prostate; leiomyosarcoma; leukemia; lymphoma; melanoma	Rheumatoid arthritis

(continued on next page)

TABLE 1 (continued)

SOME BIOLOGICAL MARKERS OF HUMAN MALIGNANT DISEASE

Classification	Marker	Conditions associated with elevated levels or abnormal isoenzyme patterns	
		Malignant	Nonmalignant
Metabolic products	Beta amino isobutyric acid	Burkitt's lymphoma	
	Hydroxyproline	Carcinoma metastatic to bone	Hydroxyprolinemia, inflammation
	"Minor" nucleosides (e.g. pseudouridine, N^2,N^2-dimethylguanosine, 1-methyl inosine)	Leukemia; lymphoma; carcinomas of breast, lung, colon, GI tract; melanoma; brain tumors	Hepatitis, chronic obstructive lung disease, cirrhosis, acute cholecystitis, acute pancreatitis, regional enteritis, rheumatoid arthritis, ulcerative colitis, psoriasis, gout
	Polyamines (putrescine, cadaverine, spermine, spermidine)	Carcinomas of breast, prostate, colon, bladder, testes; leukemia; lymphomas; multiple myeloma; melanoma; fibrosarcoma; liposarcoma	Pernicious anemia, hemolytic anemia, rheumatoid arthritis, polymyositis, chronic obstructive lung disease, tuberculosis, psoriasis, liver abscess
	Protein bound fucose	Carcinomas of breast, lung, stomach, colon, thyroid, liver, pancreas, salivary gland, cervix, ovary	Acute ileitis, ulcerative colitis, hyperthyroidism, tuberculosis, emphysema, uremia
Serum protein degradation products	Complement component C_3 derived polypeptide (C3DP)	Carcinomas of breast, ovary, cervix, prostate, lung, larynx, stomach, pancreas, rectum, liver; brain tumors; leukemia; lymphoma; melanoma	Chronic leukopenia, hemochromatosis, mastitis, peritonitis
	Fibrin degradation products	Carcinoma of ovary, prostate	Endometriosis, uterine myoma, myometriosis, genitourinary tract infection, renal disease

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