Urologic Oncology

Editor

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Preface

A surgeon is merely an internist who does an occasional case.

—CHARLES ROBB, M.D., F.R.C.S., F.A.C.S.
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Just as the field of urologic oncology has become a specialized discipline within the field of urology, the treatment of urologic malignancies has progressed from the traditional approach of one physician to a team of specialists. The tremendous growth in both basic scientific understanding as well as the application of these findings to the clinical setting has made it impossible for one individual to be proficient in all aspects of cancer care. The development of the comprehensive care concept for the treatment of malignant disease has been even further reflected in the establishment of centers that are devoted primarily to the treatment of these patients.

Urologic malignancies are no longer approached as strictly a surgical exercise. In addition, the urologist should be familiar with nutrition, critical care, chemotherapy, radiation therapy, and many other aspects that cover the entire spectrum of medical care. Recent advances in basic science research with direct clinical applicability have made it imperative that the clinician also have an understanding of the scientific processes that may impact on the patient's prognosis.

The purpose of this volume is to provide a sourcebook in urologic oncology that covers the field not from only a clinical urologic standpoint, but also addresses the basic and clinical scientific aspects that may impact on the outcome. This volume is divided into four parts: basic science; clinical science; clinical management; and specific problems of cancer care that are important for the long-term well being of the patient. The basic science section is designed to cover most of the salient points of basic research as it relates to cancer, including immunology, virology, and biochemistry. The clinical science section is directed toward diagnosis and therapy from the point of view of the radiologist, anesthesiologist, and internist, all of whom have important input in the total care of the patient.

The third section deals with the approach to the patient by the urologist. This section emulates other texts in the classic approach of history, diagnosis, and therapy. This section, however, is written by authors who are younger and are among the future leaders of academic urology. This approach was taken to obtain a fresh viewpoint on traditional topics.

The fourth section is directed to certain technical aspects involving patient care. These technical aspects include the psychology of the cancer patient, the use of prosthetics, enterostomal therapy, and various general surgical techniques that may be of use in these patients.

This book provides a comprehensive reference for the student of urologic oncology. Although the text is designed to be complete with regard to the issues in cancer treatment, more specific information may be obtained through the references.

This volume will be of interest to all students, residents, and practitioners who are interested in the entire spectrum of urology.

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CANCER IMMUNOLOGY

Cancer immunology is a field that has recently returned to the limelight. Early in this century, optimism was generated by observing the rejection of tumor transplants in mice. This enthusiasm evaporated with the discovery of transplantation antigens and the realization that the immunity was directed against genetically foreign grafts and not against tumor antigens per se.

The modern era of cancer immunology began in 1943, with Ludwig Gross's observation (14) that inbred mice could be immunized against transplants of chemically induced sarcomas. Because of prevailing skepticism engendered by earlier unfulfilled promises, this work lay largely ignored for 10 years. At that time, E. J. Foley (12) demonstrated that a methylcholanthrene-induced tumor transplanted from one inbred mouse to another and subsequently removed induced resistance to a second transplant of the same tumor. In 1957, Prehn and Main (22) showed that inbred mice could not be protected from a tumor transplant by prior immunization with normal tissues, concluding that tumors possessed antigens that were different from normal tissue. Subsequent work by G. Klein (18) showed that even the mouse in which the tumor was originally induced could be immunized against cells from its own tumor, eliminating any doubt that transplantation antigens might be playing a role in inducing resistance.

This work has now been reproduced in several laboratories throughout the world, and the existence of tumor-specific transplantation antigens (TSTA) in chemical and viral-induced tumors has been firmly established. It also has been shown that tumors induced by a given virus will share common TSTA. Conversely, each individual tumor induced by a chemical carcinogen possesses unique tumor antigens. Even within the same animal, multiple sites of tumor induced by the same carcinogen each possess different TSTA.

Although the existence of TSTA in induced animal tumors has been clearly established, the situation in spontaneous human tumors is far less clear. To a great extent this is because of the much greater complexity in addressing the problem. Although there are virtually countless reports in the literature describing human tumor-specific antigens, none of these has stood the test of time (21).

Studies utilizing cellular immune systems were difficult to perform and suffered from lack of complete understanding of the mechanisms involved. Serological analysis suffered from the difficulty of precisely analyzing the specificity of an antigen–antibody reaction in the context of conventional antiserum (containing thousands or millions of different antibody molecules) and complex antigens (e.g., cells containing hundreds or thousands of antigenic determinants). The availability of hybridomas producing monoclonal antibodies promises a much more precise analysis of antigenic differences between a normal cell and its transformed counterpart.

HUMORAL IMMUNOLOGY

Various cell types function in concert as the immune system. The major cell type is the lymphocyte, which has receptor molecules on its surface membrane. These receptors allow recognition of antigen as well as communication and cooperation between different cell types of the immune system. This communication and cooperation among the different cell types represents a hallmark of the immune system. Interaction of antigen with its receptor activates the lymphocyte, which in turn performs its designated effector function.

Lymphocytes can be divided into two major groups: B lymphocytes and T lymphocytes. The B lymphocytes are derived from bone marrow stem cells and are the progenitors of the antibody-synthesizing cells. The T lymphocytes derive from the thymus and are responsible for cellular immunity and regulatory functions. Both B and T lymphocytes are heterogeneous groups and are composed of different cellular subsets.

Another cell type involved in the immune system is the macrophage. This cell performs at least two functions. First, it plays an early role in the immune reaction, phagocytizing, processing, and "presenting" antigen to the lymphocytes. Second, it acts as an effector cell in cellular immune reactions.

T cells, covered in more depth elsewhere in this text, are composed of various subsets. These can be distinguished both functionally and molecularly. For example, macrophages present antigen to helper T cells. These cells act to induce antibody production by cells of the B lymphocyte lineage. Helper T cells can be distinguished by their cell surface phenotype. Like all mature T cells, they express the molecule denoted Thy 1. In addition, helper cells express the Ly 1 molecule but not the molecule designated Ly 2,3 (i.e., Thy 1^+, Ly 1^+, Ly $2,3^-$). Conversely, suppressor T cells serve to modulate the extent of the immune response. They differ in their cell surface phenotype. Suppressor cells are Thy 1^+, Ly 1^-, Ly $2,3^+$. Yet a third subset is known as the cytotoxic T lymphocyte. This population, although it does not differ phenotypically regarding expression of either the Thy 1, Ly 1, or Ly 2,3 antigens from the suppressor subset, functions to kill target cells in a cellular immune response.

Lymphocytes, as noted earlier, possess antigen-specific receptors on their surface. Each lymphocyte responds to its specific antigen but not to other dissimilar antigens.

In the case of the T lymphocytes, this receptor is just now being elucidated. It is in many ways analogous to the surface immunoglobulin receptor present on B cells (*vide infra*). The T cell receptor is composed of two chains (α and β). The ends of these molecules, which protrude from the cell surface, are variable in primary amino acid sequence to allow the diversity necessary for interacting with different antigens. Research in this area is proceeding at a rapid pace, and the genes coding for each chain of the T cell receptor have recently been cloned.

As noted above, a macrophage phagocytizes and then presents antigen to helper T cells and to the B cell population that has the appropriate antigen-specific receptor. The mature B cell is *not* an antibody-secreting cell but possesses membrane-bound immunoglobulin molecules on its surface. This immunoglobulin molecule differs from circulating immunoglobulin in that the former contains an additional hydrophobic tailpiece that anchors it to the membrane. The immunoglobulin molecules produced by any single B cell are identical and will interact only with its respective antigen. On contact of B cell membrane-bound immunoglobulin with its appropriate antigen, the B cell is stimulated both to divide and to differentiate. (Here again, cellular cooperation is necessary, as this will not occur in the absence of T cells.) This produces expansion of this particular clone of cells—that is, those that are genetically coded to produce immunoglobulin specific to the stimulating antigen. In addition to dividing, these mature B cells differentiate into plasma cells. Plasma cells, unlike their B cell progenitors, synthesize the same immunoglobulin molecule but without the hydrophobic tail. This results in secretion of the synthesized immunoglobulin and lack of detectable surface-bound immunoglobulin. It is an important concept that each mature B cell has been genetically "edited" to synthesize immunoglobulin molecules of a particular amino acid sequence. This immunoglobulin molecule will combine only with its respective antigen; each of the "daughter" cells of this mature B cell are clonally derived and synthesize immunoglobulin of the same sequence and therefore specificity.

Much is known about the structure and function of immunoglobulin molecules that circulate throughout the body. Immunoglobulin molecules interact with their specific antigen and as such are functionally termed *antibodies*. They represent the central component of the humoral or serological immune system as distinguished from the cellular immune system. In this brief space, one can only touch on the highlights.

Immunoglobulins are glycoproteins (proteins with carbohydrate structures attached) composed of two heavy and two light chains. Differences in the amino acid sequence of the heavy chains defines five different immunoglobulin classes (G, A, M, D, E). Whereas the carboxy-terminal end of the immunoglobulin molecule is of constant amino acid sequence (within each class), the amino-terminal end is of variable sequence. It is this variation in primary sequence that in turn leads to the variation in conformation and charge that imparts the specificity of the reaction between antibody and antigen. The variable end of the molecule binds the antigen and is often referred to as the Fab (fragment, antigen binding) region. Opposite the Fab region is the Fc (fragment, crystallizable) region, which functions as the effector

region of the molecule. The Fc region mediates (a) activation of the complement system (in IgG and IgM classes), (b) transfer across the placental membrane (IgG), and (c) binding to cells that possess Fc receptors.

A foreign molecule (antigen) may contain many antigenic determinants or epitopes. These average about 6 amino acids or 6 sugar moieties in size. For each antigenic determinant there may be many slightly different antibody molecules that will bind, each with very subtle differences in amino acid sequence. In the interaction between the antigen and this narrow spectrum of antibodies, each combination will have a slightly different affinity. This represents the so-called polyclonal response, which is in turn compounded for each antigenic determinant on a complex antigen.

Studies of antibody structure, function, and molecular biology were complicated for many years by the polyclonal nature of the immune response. Attempts to establish a pure population of antibody-producing cells failed, as normal lymphocytes could neither survive in long-term culture nor could they be cloned. In 1975, however, Kohler and Milstein (19) described a technique that allowed the cloning and long-term culture of individual B cells, a method to allow analysis and dissection of the humoral immune response into its individual, component parts.

Monoclonal Antibodies

In the tumor immunologist's search for tumor-specific antigens, conventional serology is hampered by several problems. For example, serum from a tumor-immunized animal is available in relatively limited amounts. The antibodies present in the immunized animal's serum vary from one venipuncture to the next because of its evolving immune response. The serum also varies from one animal to the next, even if immumized with the same tumor. Finally, an animal immunized against a complex structure such as a tumor cell produces a mixture of antibodies directed against a large number of antigens. The serological analysis of reactions between multiple antibodies and multiple antigens proved exceedingly difficult to analyze precisely.

In a landmark paper, Kohler and Milstein (6) describe a method by which one can establish long-term cultures of antibody-producing B cells that can be cloned to yield a pure population of cells, each producing antibody to the same antigenic determinant. Their strategy was straightforward yet elegant. Although normal lymphocytes could not survive in culture, mouse B cell tumors (myelomas) could. Kohler and Milstein took normal B cells from the spleen of an immunized mouse and, using the techniques of somatic cell genetics, fused these cells to the immortalized mouse myeloma cells. The resulting fused cells, so-called hybridomas, combined the features of both parent cells. From the myeloma cell parent, they derived the ability to survive in culture indefinitely. From the immunized spleen B cell, they derived the ability to produce a specific antibody molecule. These hybridomas can be cloned to yield individual, pure, immortal populations of cells, each derived from a single hybridoma parent and therefore each secreting antibody to an individual antigenic determinant—a monoclonal antibody (mAb).

The development of mAb technology resolved the problems of conventional serology. One now had available unlimited amounts of pure antibodies, thus eliminating the problems related to dealing with mixtures of antibodies in conventional antiserum. mAbs may be used readily as "probes" that ask the question, Is the antigen (detected by this antibody) present or is it not? This greatly simplifies precise serological analysis of complex biologic structures such as tumor cells.

To date, most hybridomas developed against human tumor cells have been the product of mouse myeloma cells fused with mouse B lymphocytes, thereby producing mouse immunoglobulin. Mouse hybridomas may be generated routinely in the laboratory and represent the way the mouse immune system "sees" a human tumor cell. It is likely that the mouse recognizes antigenic determinants on the foreign human tumor cells that are either not recognized, or poorly recognized, by the patient. This means that antibodies may be produced to tumors that are not immunogenic in the host. Conversely, the mouse may not recognize antigens detected by the human immune system. Accordingly, there is great interest in the development of human hybridomas from the fusion of human myeloma cells and lymphocytes from patients with cancer. These would allow the dissection (into its component B cell populations) of the human serological immune response to antigens seen as foreign by the human host. In addition, administration of mAbs to patients would be less difficult with human mAbs compared to the foreign mouse proteins, which themselves will generate an immune response.

Human mAbs, however, are proving much more difficult to produce than their mouse counterparts. This is probably caused by several factors, including: (a) the relatively lower fusion potency of currently available human myeloma cell lines, (b) the inability to hyperimmunize patients, and (c) the difficulty in obtaining stimulated, antigen-primed B cells from peripheral blood. Attempts have been made to circumvent these problems. Many groups have fused human B cells with mouse myeloma cell lines. In general, these interspecies hybridomas have proved less stable and eventually cease production of immunoglobulin because of selective loss of human chromosomes. Others have attempted to transform human B cells directly with the Epstein–Barr virus. Although these viruses can indeed transform B cells, the lymphocytes cannot be cloned; they secrete low levels of antibody and do so only for a relatively short time.

Although there remain many obstacles to overcome before human mAb production becomes as routine as that from the mouse, a few groups are having some early success. In Dr. Lloyd Old's laboratory at Memorial Sloan–Kettering Cancer Center, human mAbs have been produced using B lymphocytes from patients with renal and breast cancers and melanomas. To date, no tumor-specific antibodies have been identified. Furthermore, the spectrum of antigens "seen" by these patients appears far different from that "seen" by the mouse. More than 90% of the human mAbs generated [Houghton et al. (17) and Cote et al. (10)] have been to intracellular rather than cell surface antigens. The reasons for this remain to be determined. The field of human hybridomas is moving rapidly but is currently far behind the level of mouse mAbs.