IMMUNOLOGICAL ASPECTS OF CANCER

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PREFACE

Many books have been written about cancer immunology. However, the subject is still in its infancy regarding full understanding of the complex mechanisms and interactions involved and their relevance to the clinical situation. Exciting developments are being seen in the fields of research, involving, for example, monoclonal antibodies and biological response modifiers. We, therefore, feel fully justified in introducing this new text, which is intended for clinical oncologists wishing to know more about the status of immunology in cancer and as a source of reference for workers, in all branches of oncology research, seeking up-to-date reviews. Contributors have, therefore, given both explanatory and more detailed accounts of developments in their particular fields of expertise.

IMMUNOLOGICAL ASPECTS OF CANCER

CONTENTS

1. BASIC IMMUNOLOGY

A. MILFORD WARD

INTRODUCTION

The immune response represents the normal physiological process by which the body maintains homeostasis in the response to infection or to introduction of foreign material. The immune system that generates this response is complex in that it exerts its action by means of circulating cellular and humoral components capable of acting at sites far distant from their site of formation and by its interaction with a variety of biological effector systems.

CELLS OF THE IMMUNE SYSTEM

The major cell types of the immune system are the macrophages and the lymphocytes. Macrophages, as nonantigen-specific cells, are responsible for concentrating and presenting antigen to the lymphocyte in the generation of antigen-specific responses. They are also responsible for the production and secretion of biologically active components that modify or modulate lymphocyte responsiveness and initiate increased production of nonspecific factors such as the acute phase reactant proteins. Lymphocytes are the antigen-specific cells of the system acting via antigen-specific receptors on their cell surface. Lymphocytes responsible, in the main, for the cellular responses of delayed-type hypersensitivity are of thymic origin and termed *T-cells,* whilst those that mature into antibody-forming cells are bone-marrow derived and termed *B-cells.* These two major classes of lymphocyte differ in their surface membrane and functional characteristics.

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Functional subpopulations of lymphocytes

Lymphocytes, in common with macrophages, polymorphs, and erythrocytes, originate from the primordial haematopoetic cell. Lymphocyte precursors originate from the primitive haematopoetic foci in the fetal liver and bone marrow to populate the thymus and secondary lymphoid organs, where they proliferate and undergo the initial stages of maturation. During this stage of maturation, surface membrane characteristics are acquired that allow the identification of the various functional subpopulations of lymphocytes.

As cellular components of the thymus and peripheral lymphoid organs, the lymphocytes are not a static population but pursue a continual recirculating course from the lymphoid organs through the lymphatics to the vascular system and back via interstitial tissues or directly through the postcapillary venules to the lymphoid organs. This continual migration is an essential feature of the antigen-searching and -entrapment function system and explains why immune reactions assume a generalised character despite localised antigenic stimulation.

Different subpopulations of lymphocytes can be defined by their capacity to undergo transformation in response to mitogenic stimulation and by their surface membrane characteristics (table 1–1). The advent of monoclonal antibodies to cell surface antigens specific to the subpopulations and to different functional subsets has allowed this division to be further refined. Three major commercial sources of these antisera are now readily available; the interrelationship of the sera is shown on table 1–2.

T-lymphocytes

The lymphocyte precursor that populates the thymus acquires specific alloantigens and matures into a thymocyte. This maturation process continues in the medulla of the thymus to give rise to the T-lymphocyte, which is then ready to join the recirculating pool and populate the peripheral lymphoid system. The thymic environment does not seem to be essential for this maturation process, as uncommitted lymphocytes can be stimulated to T-cell maturation by exposure to thymic hormone in vitro.

The next stage of differentiation of the T-lymphocyte is dependent on antigen contact. Antigen contact or stimulation gives rise to the development of functionally and phenotypically distinct subsets: those that assist or cooperate in antibody production by B-lymphocytes—the T-helper or inducer cells—and those that modulate or control T-inducer cell function—the T-suppressor cells. A third subset of T-cells, the cytotoxic

Table 1–1. Surface membrane characteristics of T-cells and B-cells

	T-cells	B-cells
Sheep erythrocyte rosette forming cells	+	–
Mouse erythrocyte rosette forming cells	–	+
EAC rosette forming cells	–	+
Surface immunoglobulin	–	+
PHA transformation	+	–

Table 1–2. Monoclonal antibodies from commerical sources used for the definition of functional subsets of lymphocytes

Pan T-cell	OKT3, OKT1, T101, Leu-1, Leu-4
T-helper/inducer cell	OKT4, T4, Leu-3
T-suppressor/cytotoxic cell	OKT8, OKT5, T8, Leu-2
E-rosette receptor	OKT11, Leu-5
Thymocyte	OKT6, Leu-6
NK/K-cell	Leu-7
Monocyte/macrophage	OKT1a1, OKM-1, LeuM1-3, HLA-DR
B-cell	OKT1a1, HLA-DR, Leu-10

T-cells, which can lyse target cells by direct contact, are also recognised. The cytolytic action of cytotoxic T-lymphocytes is the basis of the in vitro mixed lymphocyte culture (MLC) reaction, is antigen-specific in its initial phase, and does not require the presence of antibody or complement.

Helper-suppressor ratios

The relative proportion of T-helper inducer cells to T-suppressor cytotoxic cells in the peripheral circulation is fairly constant. With the advent of monoclonal antibodies for the definition of the T-cell subsets, this has become referred to as the T4:T8 ratio. In the normal state the T4:T8 ratio is in the order of 2.0:2.5. In infection the T4 numbers are reduced and the ratio reversed. T4-reactive cells are very low or absent in chronic or persistent viral infection and in acquired immunodeficiency syndromes. The T4:T8 ratio is also reversed in graft versus host disease and in transplant rejection, but this is a reflection of the absolute increase in T-suppressor cells rather than of a reduction in T-helper cells.

Natural killer cells

Antibody-dependent cell-mediated cytotoxicity (ADCC) is the function of further subsets of lymphocytes, killer cells (K-cells), and natural killer cells (NK-cells). The precise lineage of these cells, whether they are T-cell or B-cell related, is not clear, and the distinction between the two is not absolute. These cells act by virtue of Fc receptors on their surface membrane binding to antibody-coated target cells. NK-cells would appear to be of particular importance in nonspecific defense against viral infection and are believed to have an immune surveillance role in preventing the development of some tumours.

B-lymphocytes

The primordial B-lymphocyte undergoes its formative stages of differentiation within the bone marrow, from whence it emerges to populate the thymic independent areas of peripheral lymphoid tissue. These areas include the follicles and medulla of lymph nodes, follicles of the gut-associated lymphoid tissue, and the periphery of the white pulp of the spleen. The mature B-cell is an essentially sedentary cell of restricted longevity. It bears antigen receptors on its surface membrane in the form of IgD and monomeric IgM. On exposure to antigen it undergoes transformation in a blast-type cell and proceeds to undergo a number

of maturation divisions to give rise to the final antibody-producing cell, the plasma cell.

For the majority of antigens this B-cell activation requires both antigen stimulation and the cooperation of the T-inducer cell. Antigens that are capable of activation of B-cells without this cellular interaction are termed *thymus-independent antigens.* The evoked immune response results in the formation of IgM antibody but allows no switch to IgG antibody production and no generation of immunologic memory. The cooperation of the T-inducer cell with B-cell maturation allows the amplification of the IgM antibody response and also the cellular switch to synthesis of IgG, IgA, and IgE class antibody. Some activated B-cells do not mature to form plasma cells but revert to the morphological form of small lymphocytes. These B-memory cells differ from unstimulated B-cells in that they are no longer sedentary but join the recirculating pool and have a much increased longevity. These B-cells are responsible for the rapid increase in antibody synthesis of the secondary immune response.

EFFECT OF IMMUNOSUPPRESSIVE AGENTS ON THE IMMUNE SYSTEM

Immunosuppression by anticancer drugs or agents may be profound. The extent and selectivity of the suppression depends on various factors:

1. Pharmacological characteristics of the drug.
2. Cellular characteristics of the immune response.
3. Temporal relationship between antigenic stimulation and drug administration.

The immunosuppressive effect on the anticancer drugs is the result of selective effects on specific cells and factors altering the regulation of this complex cellular interactive defense system. Any alteration in the balance between effector and regulating cells in the immune system will result in changes in the immune responsiveness of the individual [1].

The immunosuppressive action of cytoxic drugs and corticosteroids is more effective in primary than in secondary responses. These drugs do not, however, affect equally all components of the immune system.

This differential effect is well illustrated by the impairment or suppression of the primary immune response after renal allotransplantation by azathioprine and corticosteroids, but these same drugs will not prevent the second set rejection in a presensitized recipient.

The immune response can be divided into an induction phase, during which antigen-responsive cells undergo transformation and replication, and an effector phase, during which the cells produce and secrete their active components. Most immunosuppressive drugs are effective during this induction phase. The drugs are most effective when administered before or immediately after antigenic challenge. There may also be a differential effect on T- and B-lymphocytes, cyclophosphamide having a greater cytotoxic effect on B-lymphocytes and a greater suppression of humoral than cellular responses (table 1–3). Paradoxical effects on immune responsiveness may be noted, and in this the temporal relationship of drug administration to antigenic stimulation is of critical importance. Irradiation or mercaptopurine administration immediately prior to antigen challenge may produce enhanced, rather than depressed, antibody and delayed-type responsiveness. Cyclophos-

phamide may produce a similar paradoxical increase in cellular responses when administered prior to antigenic stimulation by virtue of its differential cytotoxicity for T-suppressor cells.

Table 1–3. Comparative effect on corticosteroids, cyclophosphamide, azathioprine, and methotrexate on immune responses

	Corticosteroids	Cyclophosphamide	Azathioprine	Methotrexate
Primary antibody response	↓↓	↓↓	↓↓	↓↓
Secondary antibody response	↓↓	↓	(↑↓)	(↑↓)
Graft rejection	↓↓	0	↓↓	0
Second set rejection	0	0	0	0
Delayed type hypersensitivity	0	↓↑	↓	(↓↑)
Mitogenic responses	0	↓↓	0	0
NK-cell function	↓	0	↓↓	0
B-cell numbers	↓↓	↓	0	0

Corticosteroids

Administration for several days is usually associated with a reduction in circulating levels of immunoglobulins. The beneficial effects do not, however, result so much from the reduction in specific antibody titres as from the interference with reticuloendothelial cell function and phagocytosis of antibody-coated cells.

The effect on cellular immunity requires considerably longer administration but can lead to devastating and overwhelming infections, often from microorganisms not normally considered pathogenic. The effects range from inhibition of T-cell migration, reduction in lymphokine secretion, reduction in lymphocyte-monocyte interaction, and reduced target cell lysis.

Corticosteroids inhibit monocyte chemotaxis and interleukin 1 production. Fc and C3 receptors are reduced and bactericidal function suppressed. Both antigenic and mitogenic transformations and proliferation of T-cells are suppressed. In contrast, proliferation and established B-cell responses are relatively resistant to corticosteroid administration. The depression in serum immunoglobulin levels reflects a combination effect of increased catabolism and reduced synthesis and affects IgG and IgA in preference to IgM. IgE levels tend to increase.

The generation of T-suppressor cells appears to be exquisitely sensitive to corticosteroid administration, but, once generated, suppressor cell function appears unimpaired and may even be augmented. The augmentation is brought about by a combination effect of interleukin 2 absorption by the activated suppressor cell and the corticosteroid-induced inhibition of interleukin 1–stimulated interleukin 2 production by macrophages.

Corticosteroids therefore have wide-ranging effects on the immune and inflammatory systems at all levels of therapeutic administration. The precise mechanism of this immunomodulating effect is ill-understood. Whilst the role of intracytoplasmic corticosteroid