Cancer and Autoimmunity

Yehuda Shoenfeld
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Dedication

We dedicate this book to our wives:

Irit and Laurel

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PREFACE

To some people, the study of cancer and autoimmunity may be something only slightly less sterile than a Johnson & Johnson gauze pad, a pursuit followed by dilettanti and pseudo-scholastic professors. To others, the word connotates the exotic, the esoteric and the desirable. To us, it embodies the hopes and ambitions of generating an anti-tumor response in the patient.

It is somewhat ironic that over forty years ago there were two disciplines that started with "TI". There was tumor immunology and there was transplantation immunology. The latter thrived and has led to some of the most critical discoveries in immunobiology. The former continues to thwart bench scientists and clinicians alike. In fact, the original hope that cancer cells would each contain a novel antigen that might be recognized by the immune system has proven, for the most part, to be naive. On the other hand, it was perhaps equally naive to assume that a process as biologically conserved as neoplasia, would lead to the production of something as simple as a unique antigen that would be common to all patients. The work, however, on tumor immunology has been productive and has led to interrelationships between the molecular processes of neoplastic development and the understanding of the phenotypic changes which occur. These changes which were once considered to be only involved in cell surface markers, now encompass the disciplines of signal transduction, apoptosis, and differentiation.

As immunologists, our goal is to develop a simple and effective means to manipulate cancer *in vivo*. This manipulation can encompass several venues. First, it might be as direct as the original hope and aspiration of identifying a phenotypic marker and the use of either active or passive immunization. Second, it might include the use of passive reagents carrying "warheads" to selectively destroy cancer cells. Third, it might include altering the basic process of cell survival, be it via nucleic acid or protein biosynthesis, or programmed cell death. The list goes on and on as the black box gets bigger and bigger. In fact, we used to teach our students that the immune system was little more than a large black box, except that upon opening the box, one only discovered multiple smaller black boxes, and so on. This volume is an attempt by a collection of workers in many disciplines, to present a theme which has not been well described before. The papers include both basic and clinical science and range from sophisticated molecular biology to little more than phenomenology (e.g., the increased association of cancer in some autoimmune diseases and increased presentation of autoimmune phenomena in malignant conditions). This, however, is state-of-the-art. Our hope is that this collection of themes will be of use not only to bench scientists, but also to clinicians who treat patients. We also expect that as we enter the millenium, that much of this work will become an anachronism. The latter of course would be a great success and would imply real progress. In fact, as we finish this volume, the editors realize more than anything else the need to update this book 5–10 years hence.

We greatly appreciate the help of our contributors. We have done our best to edit the manuscripts. The errors which remain are ours alone.

Y.S. and M.E.G.

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1. INTRODUCTION

Autoimmune diseases stand as important causes of morbidity and mortality in western society and as such, they impose a heavy burden in financial terms. The significance of autoimmune diseases can be demonstrated by the study showing that half of the patients with RA are unemployed due to medical disabilities resulting from their illness [1]. Similarly, patients with insulin dependent diabetes mellitus, an additional autoimmune disease, who today have a longer life expectancy, increasingly require supporting medical facilities such as dialysis.

The pathogenesis and the relative importance of factors leading to autoimmunity are not defined precisely. Key questions include: what is the origin of autoantibodies, thought to play a detrimental role in autoimmunity, their interrelations with the autoantigens to which they are directed and the influence of this interplay on the immune system. The enigma is further intensified by the detection of natural autoantibodies found in healthy organisms and thought to possess regulatory and protective properties. Moreover, the cellular immune response has similarly been shown to participate in the evolvement of autoimmunity through its principal effector—the T-cell. However, the initiating events rendering these cells autoreactive and therefore capable of precipitating damage to cell-structures and the precise nature of this reaction still await comprehensive elucidation.

2. THE ESSENTIALS OF THE IMMUNE RESPONSE

The principal role of the immune system is to confer protection on the organism against foreign invading pathogens, which can gain access to the body by different routes. The targeted (specific) immune response is generated by the combined interaction of the cellular and humoral responses, both coordinated by the production of active substances—the *cytokines*. Cellular immunity refers to the immune mechanisms mediated by T lymphocytes, regardless of immunoglobulin molecules, whereas humoral immunity denotes secretion of antibodies by B lymphocytes. The humoral and cellular arms of the immune system should be viewed, not as two independent mechanisms of self defense, but rather as acting in an orchestrated and synergistic manner to accomplish protection [2].

2.1. Humoral Immune Response

B-cells stem from bone marrow precursors and later localize in the circulation as well as in follicles of peripheral lymphoid tissues. They are responsible for the production of antibodies, once they have differentiated into plasma cells [3]. B-lymphocytes are also involved in antigen presentation to T-cells, secretion of immunoregulating cytokines and establishment of 'memory' towards antigenic determinants [4].

Direct activation of B-cells by distinct antigens is facilitated by binding to antigen receptors located within the membrane of the B-lymphocytes and under the influence of cytokines. This complex interac-

tion activates B-cells after which they proliferate and produce the appropriate antibody.

The final function of the B-cell (i.e., memory cell, plasma cell or cytokine secreting cell) is determined by the profile of the cytokines present, and the mechanisms of activation (through B-cell receptors for the Fc region of IgG, or for complement components) [4]. The end product following antigenic stimulation is a population of B-cells producing and secreting one specific antibody against the introduced antigen.

Immunoglobulins are glycoproteins forming 9 classes of isotypes: IgG, divided to 4 subclasses (IgG1-4), IgM, IgA comprising 2 subclasses (IgA1-2), IgD and IgE (Tables 1) [5]. The basic structure of immunoglobulins (similar in all five isotypes) consists of two identical heavy chains (MW 50,000–75,000) combined with two identical light chains (MW 25,000). Antigen specificity is determined by variable areas containing the antigen binding site, whereas the constant region (as can be inferred from its name), is common to all immunoglobulins of a certain class. The hypervariable region is located in the variable region, representing the closest relationship to the epitope (its corresponding site on the antigen). The idiotypes, located in the variable region are the antigenic determinants (defining antigen binding) of the immunoglobulins themselves.

The diversity of antibody response is formulated due to encoding of the heavy and light chains by multiple genetic elements. As such, light chains are generated following pairing of VK and JK genes, whereas heavy chains exhibit greater diversity since they are created following the assembly of three germline genes (VH, DH, JH).

2.2. Cellular Immune Response

A T-cell cycle is initiated in hematopoietic stem cells, differentiating in the thymus and subsequently wandering to the lymphoid tissue in the periphery [2, 6]. T-cells are heterogeneous by virtue of their different functions (lysis of foreign cells, modulation of the interaction between B and T cells, regulation of monocyte functions). The peripheral T-cells are discerned by their expression of antigenic markers. As such, T-cells carrying CD4 molecules (T-helpers) interact with antigen associated with MHC class II on the surface of the antigen presenting cell, and T-cells expressing CD8 molecules (cytotoxic T-cells) engage in suppression of the immune response. The T-cell receptor is a molecule present on the surface of the T-cell, responsible for recognition of the complex antigen-MHC II molecule [7]. The variety of T-cell receptors is immense, thus accounting for its ability to recognize diverse antigens.

The immune response is mounted following presentation of the antigen to the lymphocytes by antigen presenting cells, examples of which are: macrophages, Langerhans cells and dendritic cells. The process of presentation requires the participation of MHC class II molecules on the surface of the antigen presenting cell. The antigen, prior to its presentation to the T-cell is processed and degraded and later associated with the MHC class II molecule to form a complex reacting with the T-cell receptor. It should be outlined that the APCs are capable of secreting cytokines that act to facilitate the interaction described above.

2.3. Coordination of the Immune Response

Several intrinsic factors belonging to the immune system itself are responsible for the modulation and regulation of the immune response.

Cytokines are small proteins (MW 8000-30,000) produced and secreted by a diverse population of cells (i.e., macrophages, monocytes, T and B cells, as well as nonlymphoid cells) [8]. Cytokines elicit different actions (Table 2) including proinflammatory (TNF, IL-1, IL-2) and anti-inflammatory (TGF, IL-4, IL-6, IL-10) functions and stimulation of lymphocyte proliferation (IL-2, IL-7).

The regulation of cytokines is under the supervision of genetic factors (capable of generating corresponding inhibitors) and by the liberation of soluble forms of cytokine receptors.

The complement system consists of circulating glycoprotein constituents that can be triggered and activated in two major patterns to initiate a cascadic chain of events, the consequence of which leads to diverse influences on the progression and perpetuation of the immune response [9]. This cascade can, therefore, be activated by the *classical* pathway (immune complexes comprising IgM and IgG) or by the *alternative* pathway—independent of antibodies (by bacterial LPS).

The idiotypic system—will later be reviewed in detail.

Table 1. Characteristics of human immunoglobulin subclasses

Characteristic	IgG	IgM	IgA	IgD	IgE
Molecular form	Monomer	Pentamer, hexamer	Monemer, dimer	Monomer	Monomer
Molecular weight	160,000	900,000	170,000	180,000	190,000
Subclasses	1, 2, 3, 4	None	1, 2	None	None
Serum half life(days)	23	5.1	5.8	2.8	2.3
Valence	2	10, 12	2, 4	2	2
Serum concentration (mg/dl)	1000–1500	100–150	250–300	0.3–30	0.0015–0.2
Sedimentation constant	7S	19S	7S (9, 11, 13)	7S	8S
Percentage of serum immunoglobulins	75–85	5–10	7–15	0.3	0.0003
Placental transfer	+	–	–	–	–

Table 2. Representative cytokins and their corresponding biological activities

Cytokine	Activities
IL-α, IL-β	Lymphocyte acivation; bone resorption, induction of fibroblasts synovial cells and endothelial cells; prostaglandin liberation.
IL-2	T and B growth factor; increased secretion of several cytokines; activation of cytotoxic cells.
IL-3	Proliferation of marrow stem cells; growth factor for: macrophages, eosinophils, mast cells.
IL-4	Activation of B-cells and macrophages; stimulated proliferation of T-cells and mast cells; Induce secretion of IgE by B-cells.
IL-6	Induce antibody production and acute phase protein production by the hepatocytes.
IL-10	Inhibit production of several cytokines
IFN-α	Decrease cell replication; Increases MHC class I replication; disrupts viral replication.
IFN-γ	Activate NK cells, cytotoxic T cells, endothelial cells and macrophages; anti-tumoral effects; Increase expression of MHC class I and II.
TNF-α	Acute phase reactant; anti-tumoral; activate macrophages; increase expression of MHC class I; bone resorption.
TGF-β	Inhibit IL-1; enhance tissue repair; suppress lymphocyte proliferation.

Suppressor T-cells. As can be recalled, suppressor T-cells constitute a distinct subset of T-cells in charge of down-regulating the expression of either T cells and immunoglobulin secreting cells [10].

3. EVOLUTION OF THE AUTOIMMUNITY CONCEPT

Paul Ehrlich was the first to coin the term *autoimmunity* [11] with regard to the harmful aspects of immunity, namely—the emergence of autoantibodies directed against the organism's own antigens. However, the expression used ('horror autotoxicus') has served to denote a mechanism avoiding autoimmunization, exemplified in goat models (producing alloantibodies but not autoantibodies).

The revolutionary ideas expressed by *Ehrlich* were subsequently abandoned for a century although anecdotal works confirming his notions were sporadically reported. The turning point, leading to the general acceptance of the autoimmunity concept was the experiments by Witebski & Rose (reviewed in Reference [12]) showing that rabbits immunized with rabbit thyroglobulin developed thyroiditis following production of anti-thyroglobulin autoantibodies. These observations were supported by the models of autoimmune hemolytic anemia and thrombocytopenia in which anti-red blood cell antibodies were detected and had been shown to be associated with bouts of hemolysis and thrombocytopenia [13].

The discovery of the NZB mouse (a strain which develops spontaneous autoimmune disease) provided a new tool for the study of autoimmmunity, con-