Significance of Surface Immunoglobulin in Murine and Human Myeloma and Chronic Lymphocytic Leukemia

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ABSTRACT

One important factor in the production of the immunologic deficiency in myeloma appears to be the alteration of the surface immunoglobulin by a macromolecular, RNA containing factor released by the tumor. In contrast, the cells of chronic lymphocytic leukemia are not influenced by factors outside the cell and their lack of immunologic reactivity is due to an intrinsic defect. These characteristics may be occasionally important in differential-diagnostic considerations.

Introduction

The discovery of specific biochemically or immunochemically identifiable surface structures of lymphocytes has led to a formidable array of new knowledge about the function of lymphocytes. Clinical scientists, of course, expected that the classification of lymphocytes into B and T cells and into the various subgroups (1) would become a mainspring of discoveries about the pathogenesis and nature of diseases of the lymphoid system, (2) would explain immunologic anomalies associated with these diseases and (3) would yield clinically important information that could be utilized for valuable clinical tests. The first expectation has probably been fulfilled to a greater extent than the hope for clinical usefulness. Nevertheless, the characterization of lymphocytes has become an essential ingredient in the classification of hereditary immunodeficiency diseases and of the lymphomas and lymphocytic leukemias. The determination that a particular lymphocytic leukemia is of T- or B cell origin or is devoid of the traditional surface markers (null cells) probably also has therapeutic and prognostic significance; however, this remains to be firmly established.3

What are the implications of characterizing peripheral lymphocytes in multiple myeloma, another neoplastic disease of the immune system? Multiple myeloma is a B cell disorder and, therefore, it might be expected that the most characteristic property of B cells, namely their surface immunoglobulin (SIg), should have important implications in our understanding of the B-cell dysfunction in this malignant immunoproliferative disease. The features of the B cell...
dysfunction and immunologic deficiency associated with multiple myeloma are reduced plasma levels and decreased synthesis of normal immunoglobulin causing diminished primary responsiveness to antigens. The cause of this disturbance is likely to be multifactorial.

A recently heavily emphasized observation is the increased activity of suppressor cells, either T cells or macrophages or both that inhibit normal antibody production. There are, however, several fundamental questions that need exploration. How are suppressor cells stimulated into augmented activity or increased proliferation? Might this be by direct contact with "activating" cells, e.g., malignant plasma cells, or by a product of these cells? How do suppressor cells exert their function? Would this be by direct contact or the production of a suppressor substance? What are the molecular events in the cell membrane following these encounters? Do suppressor cells have specificity? All these questions can be expected to be explored in the next few years, and it is likely that the abnormal activity of suppressor cells in disease may be only one of several interacting factors leading to disturbed function.

In our studies of myeloma, the hypothesis has been tested that in this disease the role of surface immunoglobulins in the recognition of antigens and in the initiation of a humoral immune response is disturbed. BALB/c mice with plasmacytoma were studied. The following observations were made by us: the relative proportion of lymphocytes with normal SIg begins to decrease within a few days after the implantation of the plasmacytoma cells (figure 1). This decrease is accompanied by an increase of lymphocytes that have plasmacytoma specific SIg, demonstrable with antiidiotype antiserum. The decrease of lymphocytes with normal SIg was shown by immunocytoadhesion and immunofluorescence. It was a matter of great interest that the plasmacytoma specific SIg in most cases was not recognizable by antisera to normal immunoglobulin, but only by antiidiotype antisera suggesting that on these cells only the idiotypic portion of the Fab fragment was accessible to the antisera.

When normal lymphocytes in a millipore chamber (pore size: 0.1 μm) were implanted into tumor bearing animals, and tumor cells in such a chamber into normal animals, the SIg of the normal cells
in both cases assumed the immunochemical properties of the myeloma globulin (figure 2). Absorption of myeloma globulin to the lymphocytes was excluded by extensive washing, by the regeneration of SIg after trypsinization and by the failure of already converted lymphocytes to change their SIg following incubation with another myeloma plasma. These experiments implicated a diffusible factor as being responsible for the conversion of the lymphocyte SIg. Attempts to isolate and characterize this factor led to the discovery that it is macromolecular and that its SIg converting activity depends on the presence of 14 to 18S RNA with poly-A sequences.

It stands to reason to assume that the function of normal B cells as antigen receptors would be interfered with by the change of the immunochemical properties of the surface immunoglobulin, since most myeloma globulins are devoid of antibody activity. The finding that the same factor that initiates SIg conversion also causes impairment of antibody production seems to link these two phenomena. In agreement with this possibility is the observation that this factor extracted from a plasmacytoma whose Ig has antibody activity to hapten, e.g., dextran, does not abolish in normal animals the reactivity to this hapten but to all other tested antigens. The applicability of these studies to man has been enhanced by the fact that lymphocytes with monoclonal SIg in the blood of patients with myeloma have been demonstrated by several investigators (figure 3). Some have interpreted this finding as indicating that these lymphocytes are members of the malignant clone and that the malignant process starts already at the lymphocyte stage. Our data, based on the extraction of a SIg converting factor from the plasma of patients with myeloma, suggest that the development of monoclonal SIg takes place on normal lymphocytes after the development of the tumor. While these findings seem important for the elucidation of the immunologic anomaly in myeloma, they are not likely to lead to a clinically useful test. However, the associated phenomenon, namely the diminution in the proportion of normal B cells has differential-diagnostic significance, since this decrease does not occur in benign monoclonal gammopathy.

At present, it cannot yet be stated whether the activation of suppressor cells and the factor released by the malignant cells are interrelated or are independent phenomena, but it is tempting to speculate that the ribonucleic acid (RNA) containing factor not only alters SIg but also activates suppressor cells.

While the dysfunction of B lymphocytes in myeloma appears to be the result of the neoplasm and, therefore, is a "postneoplastic phenomenon" in chronic lymphocytic leukemia, the associated hypogammaglobulinemia is due to an intrinsic cellular defect. As can be shown by immunofluorescence or by radioimmunoassay, the SIg density on the

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![Figure 3](image-url). Proportion of lymphocytes with normal and "idiotypic" SIg in five patients with multiple myeloma.
numerically increased leukemic lymphocytes is markedly diminished as compared with normal lymphocytes. The CLL cells usually react only with antisera to a single light chain type thus suggesting monoclonicity of the SIg. Chronic lymphocytic leukemia (CLL) cells have a diminished proliferative activity, spontaneously and in response to pokeweed mitogen. They secrete only traces of IgM themselves, do not suppress the secretory activity of normal lymphocytes and are also refractory to any "help" by normal helper cells. These immunochemically distinctive features may occasionally have diagnostic importance in the differentiation of severe lymphocytosis from CLL. The determination of SIg density by immunofluorescence or radioimmunoassay and the determination of the kappa-lambda ratio of the surface immunoglobulin, which is close to parity for normal lymphocytes and severely deviating from one in the case of monoclonicity, deserve the attention of the clinical scientist.

References