Lymphoid Malignancy and Development, Differentiation, and Function of the Lymphoreticular System

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Summary

There are 2 pathways of normal lymphoid differentiation. The thymus is responsible for initiation and control of cellular differentiation directed toward the small lymphocyte and cellular immunity. The avian bursa of Fabricius, and perhaps Peyer's patches of man, initiates and controls another lymphoid differentiation pathway directed toward the plasma cell and immunoglobulin production. Thymus-dependent and bursa-dependent lymphocytic malignancies have been defined in the mouse and chicken, respectively, and are featured by abnormal lymphoid differentiation beginning in one or the other central lymphoid organ. It is proposed that clinical lymphoid malignancies may also be usefully classified as either thymus system or immunoglobulin-producing system malignancies. In this view Hodgkin's disease appears to be a thymus system disease, and more focused study of its central organ seems indicated.

Introduction

In a discussion of the immunologic defects in patients with Hodgkin's disease and other lymphoreticular malignancies, it seems appropriate to attempt to relate them to some of the current thinking on the normal development, differentiation, and function of the lymphoreticular system.

Clinical and experimental observations have long suggested a dissociation of the immune system, a split phrased most conventionally as cellular versus humoral immunity. Immunologic deficiencies were classified in this way, sex-linked recessive agammaglobulinemia constituting a virtually complete failure of the humoral type with relatively intact cellular immunity; deficiencies were classified in this way, sex-linked recessive agammaglobulinemia constituting a virtually complete failure of the humoral type with relatively intact cellular immunity; and Hodgkin's disease, in many patients, coming close to a clinical loss of cellular immunity with relatively intact immunoglobulin production (2, 27).

Warner and Szenberg (65, 67, 68), on the basis of immunologic study of chickens treated with testosterone during incubation, proposed dissociation of the lymphoid system and of immunologic function based on thymic versus bursal influence. Least consistent with the conventional functional division of immunity was the classification of delayed hypersensitivity with antibody responses as bursa-dependent, and its separation from homograft immunity classified as thymus-dependent, and certain graft versus host capabilities viewed as not clearly dependent on either thymus or bursa. Although the concept of dissociation has been amply confirmed (5, 13-16, 33-35), it now seems clear that the functional division in the chicken is more consistent with clinical evidence and with the immunologic defects produced in rodents by neonatal thymectomy (26, 37, 46). It has also been possible to identify the components of the two systems morphologically.

Thymus-Dependent System

Thus, we have recently proposed that the lymphoid system of both mammals and birds has two major components or cell systems (13-16, 56). In this view, the thymus-dependent system is composed of the thymus as the central or source organ, and of lymphoid cells in the periphery largely classified as small lymphocytes. Observations on the development of the lymphoid systems in many species have long suggested that this cell system begins its differentiation in the thymus (10, 31), a thesis most convincingly supported by the studies of Auerbach (6, 8) in which the early lymphoid differentiation of epithelial thymus explants was shown to depend on an as yet undefined mesenchymal inductive influence. Evidence of both a direct and indirect nature indicates that thymic lymphoid cells may populate the peripheral lymphoid tissues by a seeding process (7, 50, 53, 62), and that a humoral thymus factor is apparently necessary for at least functional completion of thymus system differentiation (42, 54).

The functional role of the thymus system of cells has been approached from 2 main directions. One has involved the definition of immunologic defects in animals with gross deficiency of the thymus system following thymectomy early in life or thymus removal coupled with various means of peripheral small lymphocyte depletion, e.g. X-irradiation or anti-lymphocyte serum administration (25, 26, 37, 38, 46, 47, 49). The 2nd approach has involved assessment of immunologic function in patients (23, 27) and experimental animals (13-16) with an intact thymus system but an extreme deficiency of the immunoglobulin-producing system. Such studies have indicated that the thymus system of cells is the effector of graft versus host reactivity and delayed hypersensitivity, plays a major role in homograft rejection, and probably provides the recognition-specificity component of antibody responses. Immunologic memory may also be a function of this cell system.
Immunoglobulin Production System

The bursa of Fabricius of chickens appears to be the central or source organ for the immunoglobulin-production system, represented in peripheral lymphoid tissue by the lymphoid cells of the germinal centers, hemocytoblasts, and plasma cells. Chickens irradiated and bursectomized in the newly hatched period are entirely lacking this system of cells, are agammaglobulinemic, and are incapable of specific antibody production. This experimental model is a striking parallel to the Brütonglobulinemia type of agammaglobulinemia (11, 15, 16).

Ackerman and Knouff's developmental studies of the bursa suggest that gut epithelial cells differentiate into bursal lymphoid cells (1), and our own work suggests a continuum of differentiation of these cells to mature plasma cells (Refs. 16, 17 and Clawson, Cooper, and Good, unpublished observations). A bursal humoral factor is apparently required for functional maturation of this cell system (24, 36, 64).

This system of cells has not yet been experimentally manipulated in mammals, and a mammalian equivalent of the bursa has not been demonstrated. However, the immunoglobulin-producing system seems to be relatively intact in neonatally thymectomized rodents (4, 19, 32) and in patients with certain extreme congenital lymphopenias associated with failure of thymus development (3, 52). Thus, it appears that in mammals as well as in birds, germinal center cells and plasma cells represent a separate pathway of differentiation beginning in a site other than the thymus.

Reticuloendothelial System

The reticuloendothelial system, necessary for the clearing and processing of foreign substances (20-22), shows no definable morphologic or functional deficiency following manipulation of either the thymus or immunoglobulin-production system (16). This is not to say that this system is normal under these circumstances, since there is some evidence of enhanced reactivity and hypercellularity when the thymus-dependent development is deficient (46, 60). This evidence does indicate that the reticuloendothelial system is separate from the lymphoid cell systems.

Thymus System Malignancies

As Aisenberg (2) has pointed out, there is no experimental model of Hodgkin's disease. It is apparent, however, that the lymphocyte depletion, defective delayed hypersensitivity, abnormal homograft rejection pattern, poor response to phytohemagglutinin stimulation, and mild abnormality in antibody-producing capacity manifested in many patients with Hodgkin's disease all point to a defect of the thymus system.

There are several parallels between Hodgkin's disease and mouse lymphocytic malignancies. The lymphocytic malignancies of mice, whether spontaneous or induced by X-ray, chemical agents, or viruses, appear to involve primarily the thymus-dependent system (Peterson et al.*). In each of these models, thymectomy during the pre lymphoma period reduces the incidence of subsequent lymphoma (28, 39, 41, 43-45). These malignancies often begin in the thymus or appear to arise in the thymus-dependent small lymphocyte population in peripheral tissues. During the incubation period of the leukemia induced by Gross' passage A virus, C3H mice show immunologic defects similar to those defined in neonatally thymectomized mice, although these defects appear less exaggerated in the prelymphoma mice (18, 59).

The role of the thymus in the development of lymphocytic malignancies appears to relate closely to current concepts of its role in the normal differentiation and development of the thymus system of cells and cellular immunity. Kaplan (40) first focused attention to the relationship between the presence of abundant undifferentiated cells in the thymus and the susceptibility to lymphomagenesis. It appears from these and other investigations (9, 51) that thymus cells in a critical early phase of differentiation are necessary for susceptibility to some lymphomagenic viruses. It has been proposed on the basis of these observations that lymphomagenic viruses alter thymic cells in such a way that differentiation might be slowed or that these cells are deviated from their normal differentiation pathway, thus gaining inheritable independence from normal environmental growth controls (9).

There is clinical support for the thesis that lymphocytic malignancies primarily involve only 1 of the lymphoid tissue components as we have defined them: at least 3 boys with sex-linked recessive agammaglobulinemia have developed a malignancy, apparently of the thymus system, in 1 instance presenting initially as a huge thymoma (55, 61). This patient group has an infinitesimal amount of γ-globulin, usually below 10 mg/100 ml, and in our present view represents the clinical counterpart of bursectomized-irradiated chickens. They appear to be entirely lacking in germinal centers and plasma cells, and we believe that they represent virtually complete failure of development of the immunoglobulin-production system as we have defined it experimentally (23, 27, 58). It is provocative that these lymphocytic malignancies not only develop in these patients but they develop in what appears to be increased frequency.

One of the investigations of the past, now about 10 years old, that warrants reevaluation, is that of Thomson (66) on the thymic origin of Hodgkin's disease, a thesis presented before the immunologic defects in Hodgkin's disease had been well defined and before the new view of thymic function. One of Thomson's major points was a comparison of the normal embryonic development of Hassall's corpuscles with some of the histopathologic features of Hodgkin's disease. He believed that epithelial cells converted to large mononuclear cells with a vesicular nucleus and prominent nucleolus, progressing to the "owl's-eye" appearance of the "mirror-image" type of double nucleated giant cell, then to giant cells with many nuclei, and finally to fully formed Hassall's corpuscles. He stated that with an admixture of these cells, lymphocytes, and polymorphonuclear leukocytes encased in a fibrous stroma, the histologic picture of Hodgkin's disease is produced. It is of considerable interest that of 5 Hodgkin's patients thymectomized on the basis of Thomson's concept, 1 subsequently developed myeloid leukemia (56). This is highly reminiscent of the experience with myeloid leukemia in mice previously inoculated with Gross' passage A virus (29).

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Bursal System Malignancies

It may be useful at this point to contrast the avian leukemia model, visceral lymphomatosis, with the "thymus system malignancies" of mice and men. This virus-induced lymphoma malignancy of chickens appears to represent a primary involvement of the immunoglobulin-producing system. Young chickens are most susceptible to the oncogenic influence of the RPL12 virus (12), and bursectomy early in life prevents progress of the disease which normally kills the birds (57, 60). Serial histologic study of chickens infected at birth with RPL12 virus reveals malignant transformation of bursal follicles well before evidence of malignancy in other tissues. At this early stage 1 malignant bursal follicle may be surrounded by over 500 morphologically normal bursal follicles. Later malignant cells may be seen in germinal center distribution in the spleen and other organs. In contrast to normal bursa-derived germinal center cells, the malignant cells fail to show organization of cytoplasmic ribosomes and formation of endoplasmic reticulum. These malignant cells also contain no γ-globulin. These observations (Cooper et al., unpublished observations) indicate that visceral lymphomatosis begins in the bursa of Fabricius and is featured by abnormal differentiation of bursal lymphoid cells. Interesting also in this light is the fact that the thymus is almost never involved (28).

The lymph nodes of patients with giant follicular lymphoblastoma exhibit remarkable morphologic similarities to the spleens of chickens with visceral lymphomatosis. Some patients with this malignancy become agammaglobulinemic (58). Hemocytoblast accumulation but no plasma cells are seen in such patients.

Discussion

On the basis of these views we have postulated that it may be useful to attempt classification of experimental and human lymphocytic malignancies by site of initial involvement, either the thymus-dependent system or the immunoglobulin production system (14, and Peterson et al.4).

Among the elements we must encompass in any over-all hypothesis are a degree of specificity of the virus oncogenic effect on a given cell line and what appears to be the controlling influence of the thymus or bursa on development of the lymphoma in its early stages. Oncogenic virus particles find genetically specific receptor sites on certain cells, and penetrate occurs. Some selectivity on the basis of cell type could also occur at this level. This event need not immediately arrest cell differentiation, migration, and multiplication. When, however, sufficient numbers of oncogenic virus particles attack sufficient numbers of a cell type in a critical early phase of differentiation—a phase characteristic of central or source lymphoid tissues such as the thymus and bursa representing the sites of the initial lymphoid differentiation—cellular biosynthetic mechanisms are predominately occupied with virus production or otherwise altered, eventually producing, in effect, a differentiation arrest. Even though protein synthesis may continue, in the case of at least some of the "immunoglobulin production system malignancies," specific synthesis of γ-globulin and its functional correlate, circulating antibody, is deficient. It would appear that in the "thymus system malignancies" the production of "cellular antibody" may also be deficient.

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