# Progress in Clinical and Biological Research Volume 16

# HLA AND MALIGNANCY

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# HLA AND MALIGNANCY

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# HLA AND MALIGNANCY

## PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH

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# Preface

Significant associations have been found between the HLA antigens or haplotypes and certain diseases or deficiencies. These associations have offered new areas for immunologic epidemiologic and clinical investigations.

At the recent June 1976 First International Symposium on HLA and Disease, organized by Professors J. Dausset and A. Svejgaard, the predisposition to disease and clinical implications were reviewed in relation to histocompatibility antigens. section was concerned with HLA and malignant diseases.

A Symposium on HLA and Malignancy was organized and held at the Roswell Park Memorial Institute, Research Studies Center, New York State Department of Health in Buffalo, New York, August 19 and 20, 1976.

Topics and cochairmen for the symposium were:

Genetics of HLA antigens
Elias Cohen, RPMI
Kamal Mittal, FDA, HEW

Hematologic neoplasias and leukemia associated antigens
John E. Fitzpatrick, RPMI
Dharam P. Singal, McMaster University

HLA and selected solid tumor and other neoplasias
Bernard Carpenter, Peter Bent Brigham
Kyoichu Kano, SUNYAB

Transplantation antigens and malignancy
Felix Milgrom, SUNYAB
David Pressman, RPMI

The goals of the symposium were a) a critical appraisal of the relationshio of HLA antigens or haplotypes with malignancy; b) an evaluation of the potential for biomedical application of the knowledge of HLA or other antigenic phenotypes or genotypes to diagnosis, prognosis, or treatment of malignant disease.

A total of 25 papers were presented and included in this text. They deal with such topics as the HLA complex and B cell immunogenetics; the ordering of genes for HLA antigens and complement components; experimental models with possible


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implications for the role of HLA in malignancy; possible mechanisms for association of HLA antigens and disease. Hematologic neoplasias and leukemia-associated antigens were discussed, as well as an evaluation of HLA antigenicity, T and B cell markers, and MLC reactivity in acute lymphocytic leukemia and non-Hodgkin's lymphoma. Alloantisera to human leukemic blast cells and the detection of leukemia-associated antigens (LAA), as well as antibodies to LAA in normal plasmapheresis were described. The effect of non-HLA antibodies in reagent sera on HLA frequency data in leukemia was emphasized.

The reports dealt with selected solid tumor and other neoplasias, including nasopharyngeal cancer, breast cancer, malignant melanoma, and with HLA antigens of peripheral lymphocytes in reference to the presence of these antigens on splenic tissue or lymph nodes.

The principal guest speaker was Professor Jean Dausset, whose paper, included in this text, is entitled "HLA and Association With Malignancy – A Critical View."

Transplantation antigens and malignancy were analyzed in reports on the selective combination of beta-2-microglobulin with HLA large component in cultured cell lines, and the structure of HLA antigens. Related potential disease-state models presented included regression retinal blastoma and sarcoidosis.

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# Contents

# Genetic and Immunologic Considerations of the HLA System of Human Lymphocytes and Tissues

D. Bernard Amos and Armead H. Johnson

The internationally recognized components of the HLA region are genetic loci designated HLA-A, B, C, and D. Of these, HLA-A and B code for glycoproteins of MW approximately 45,000 daltons to which are bound, noncovalently, $\beta_2$-microglobulin molecules of MW 11,000 daltons. The HLA-C locus product is also a glycoprotein associated with a $\beta_2$-microglobulin molecule. However, the HLA-C glycoprotein is less well-characterized than the A or B locus products which have been analysed for amino acid composition and partially sequenced. The nature of the HLA-D gene product is unknown.

Alleles of the A, B, and C loci are distinguished through the reactions of carefully selected alloantisera, usually obtained from parous women. From studies within families the codominant inheritance of alleles of the A, B, C, and D loci as a unit, called a haplotype, has been established; and from studies in families which include a recombinant, the map order of the loci of the HLA system has been established. It has been shown that the assortment of alleles on the haplotype is nonrandom. From population studies, gene frequencies have been determined. From a knowledge of the frequency of alleles of the A and B loci the frequency with which a given A allele should pair with a given B allele can be calculated. Most combinations of alleles fit the expectation, but a few occur together more frequently than would be expected by chance. This phenomenon is called linkage-disequilibrium (delta). High delta ($\Delta$) values have been reported between some A and B alleles; high $\Delta$ are common between B and D; and very high $\Delta$ are found between B and C.

Alleles of HLA-D can at present be identified with certainty only through a special form of mixed lymphocyte culture (MLC) reaction called a typing cell response. This procedure uses lymphocytes from individuals who are homozy-


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gous at the HLA-D locus (homozygous typing cells or HTC) as stimulating cells in the MLC reaction. Responder lymphocytes from individuals who share the same HLA-D allele with the typing cell remain in a resting state and fail to incorporate radioactive thymidine. Cells from individuals who do not share the same HLA-D allele are stimulated to divide (1). Another procedure for identifying HLA-D alleles currently being developed is the primed lymphocyte test (PLT) (2). Cells from one family member are used to stimulate (or prime) cells from another family member who differs at one HLA haplotype from the stimulator, the other haplotype being common to both. Examples are parent-child and haploidentical sib pairs. Unrelated donors who share the immunizing HLA-D allele of the stimulator give accelerated responses to the primed cells. Donors who do not share the HLA-D of the stimulating family member stimulate a primary response which peaks later. Stocks of primed cells of different specificities may be maintained in frozen storage.

A serologic approach to HLA-D typing identifies a genetic locus which is either HLA-D itself or a locus very closely linked to it, and thus in extremely high linkage-disequilibrium with it. The gene product of this locus is expressed on B type (surface immunoglobulin-carrying) lymphocytes, and the reaction is detected by indirect immunofluorescence (3) or by complement-mediated cytotoxicity (4). The B-cell antigen differs from the A, B, and C locus antigens in being of lower MW (approximately 30,000 daltons), and in not having a $\beta_2$-microglobulin molecule bound to it.

Biological properties of the HLA complex are manifested in several ways. First demonstrated was the effect of HLA compatibility on the rejection of skin or kidney grafts. HLA-identical sibling pairs are rarely stimulating in MLR. Skin grafts between such pairs survive for a mean of 23 days, and recipients of HLA-identical kidney grafts require relatively small amounts of immunosuppressive drugs to retain their transplant (5). Kidney survival rates approach those of monozygotic twins. Donor recipient pairs differing by one haplotype give moderate stimulation in MLR, have shorter skin graft survival times (14 days), and require more immunosuppression to retain a renal graft. Donor recipient pairs differing by two haplotypes give stronger stimulation in MLR, and grafts are more vigorously reacted against, giving shorter skin graft survival (12 days) and requiring, on the average, even more immunosuppression to retain renal function. Transplanted lymphocytes from bone marrow or transfused blood given to an immunologic cripple react against the recipient (graft-versus-host or gvh reaction) most severely if there is an HLA difference between donor and recipient, although gvh can occur between HLA-identical sibs, especially in leukemic subjects (6).

Of growing interest is the association of HLA with disease. This is best documented in rheumatoid diseases such as ankylosing spondylitis, where the association with HLA-B27 is extraordinarily high (7). Weaker but still striking associations have been reported for several other B and D alleles, while a slight

but reproducible increase in the freqneucy of A2 is found in acute lymphocytic leukemia (8), and the 3-7 and 3-14 haplotype is frequently found in hemochromatosis, suggesting a frequent association with an A locus allele (9). Many HLA-associated diseases tend to be most frequent in individuals with a particular HLA specificity at the population level. Other diseases, such as ragweed hay fever, may segregate with one of the haplotypes in a family, and do not appear to be associated with any particular allele in a population (10). In the mouse, developmental abnormalities may be caused by alleles of loci linked to H-2 (cleft palate, brachyury), and there are important interactions between some viruses and H-2 and with chemical haptens. At least two powerful series of immune response genes (in the IA and IC region) are also closely linked to H-2, as are genes controlling complement components. Susceptibility to Gross, Friend, Rauscher, Maloney, Rous, Bittner, and Tennant virus-related neoplasms are all H-2-associated. Evidence for similar associations with HLA in man are being sought for or are accumulating. Interestingly, choice of mate appears to be associated with some H-2-related characteristic, possibly scent (11). While some individuals have been seen to sport badges questioning "Are you my HLA type?" there is as yet no systematic study of this point!

These, then, are some of the salient facts about the major histocompatibility complex. We would now like to discuss some of the less well-known attributes of the system with special reference to reactions demonstrated by the antiglobulin cytotoxicity test (ACT), by lymphocyte-dependent-antibody-mediated reactions (LDA).

The antiglobulin cytotoxocity test uses rabbit or goat anti-whole human globulin to develop additional reactions in the conventional microcytotoxicity test (12). The test involves the addition of alloantibody to lymphocytes in microcytotoxicity plates and incubation for 60 min. The cells are then washed by adding buffer to fill the wells with mixing. The plates are centrifuged, the supernatant is removed by flicking. This wash, pack, flick cycle is repeated three or four times (13). Interestingly, this wash manipulation by itself greatly increases the sensitivity of the test. Many reactions that are negative without washing or with only one wash become strongly positive, while controls and responses to some sera remain negative. Antiglobulin diluted to a predetermined level of maximum lytic effect is added, and followed after 1 min by complement. This further increases the sensitivity of the test.

Not all antiglobulin sera are effective, and the effectiveness is not related to the precipitin titer of the serum. Further, in unpublished experiments performed by the authors in collaboration with Dr. Jenny Goudemand of Lille, France, it was shown that precipitation of the antiglobulin with purified IgG or with whole serum did not diminish the potentiating effect of the antiglobulin serum. The potentiating effect does, however, appear to be due to antibody, since it has specificity and is complement-dependent, and the reaction is, in most

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