ORGAN TRANSPLANTATION FROM IMMUNOLOGICAL POINT OF VIEW

THESIS

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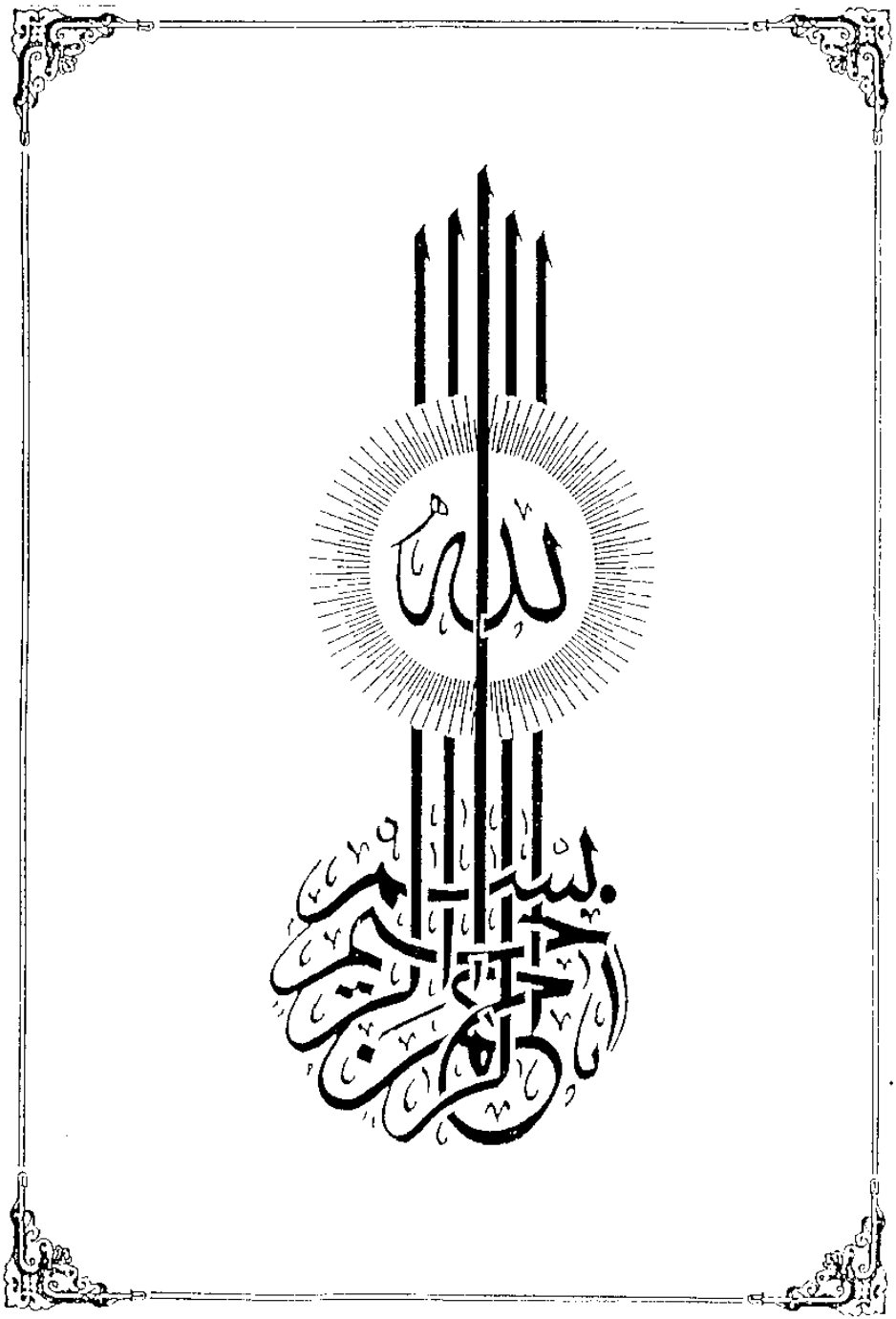

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INTRODUCTION

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The successful transfer of tissue and organs from one individual to another has been one of the great achievements of modern medicine and surgery (Cerilli, 1988).

The enormous progress made in transplantation in the 1960s was followed by a period of stability with relatively slight improvement in the 1970s. However, new information both in basic transplant immunology and in clinical transplantation has been published in the late 1970s and in the 1980s. This information has been transferred into new methods of management for transplant patients, new organs being successfully transplanted with a rising success rate (Moore, 1988).

Finally continuous rapid expansion of information in basic immunology and clinical transplantation, improves graft survival and opens the door for wider clinical application of transplantation (Moore, 1988).

Aim of this review is to collect the new progress in clinical transplantation.

REVIEW OF LITERATURE

Major Histocompatibility Complex (MHC)

The Single genetic complex in mammalian species that codes for the major cell-surface antigens capable of eliciting a rejection response is referred to as the major histo-compatibility complex (MHC). In humans, these proteins are called human leukocyte antigen (HLA) and are encoded on the short arm of chromosome 6 (Rose and Black, 1988).

* HLA Nomenclature :-

The HLA system consists of seven series of antigens (HLA -A, -B, CW, -DR, -DQ, -DP and DW) (Albert et al., 1984). Except for the DW series, which is more diffusely represented by a "region" each antigen series has a mapped or proposed "subregion" on the short arm of the 6th chromosome with loci for its component chains. These loci as well as those for the complement components (C2, C4 and Bf) reside on an area on the 6th chromosome known as the MHC (Ascher and Simmons, 1988).

Each antigen is designated by the prefix HLA followed by the locus, and then by an Arabic number for the antigen specificity, for example, HLA-A28, HLA-B7 and HLA-DR3 (Braun, 1988). If an antigen has to be distinguished from other nomenclature systems, as in case of Cw specificities to avoid confusion with

complement components, a"w" for "workshop" is inserted between the letter of the locus and the antigen number, for example HLA-Cw1 and HLA-DRw8 (Albert et al., 1984).

* Class I and Class II MHC antigens :-

The HLA locus has been dissected through immunogenetic analysis. The presence of HLA antigens on a cell surface can be detected in either of two ways. The serologic method using antigen-specific antisera, which leads to either agglutination or complement - dependent lysis of cells carrying the antigen. Antigens that poorly trigger allogenic lymphocyte proliferation and were therefore first defined by serologic techniques are called Class I antigens. A second method measures the reactivity of host lymphocytes to lymphocytes from potential donors. Antigens that can trigger the proliferation of allogenic lymphocytes are called Class II antigens (Van Rood et al., 1975).

Class I antigens include HLA-A, - B and - Cw. It consists of a heavy chain of 44,000 daltons noncovalently bound to B2 -microglobulin of 11,700 daltons (Roitt, 1988a). They are widely distributed on all nucleated cells of the body. They have certain characters which are : a)They activate and act as targets of cytotoxic T-lymphocytes. b)They provide a restriction element for minor histo- compatibility antigens such as H-Y, most viral antigens and haptens. c)They can function by themselves as alloantigen or in a restricted fashion with Class II antigens.

d)They stimulate effectively an antibody response. e)They function reliably in cell mediated lympholysis but they contribute little to mixed lymphocyte culture or graft -versus- host reaction. f)They are strong analogous to the H2D and H2K gene products of the mouse (Bach and Sachs, 1987).

Class II antigens in contrast includes HLA -DR, -DQ, -DP and -Dw. They consist of a 34,000 dalton alpha chain noncovalently bound to a 29,000 dalton B chain (Roitt, 1988a). They are distributed on a restricted number of cell types in the body such as B lymphocytes and antigen presenting cells. They have the following characters :- a)They activate T-helper lymphocytes. b) They provide restriction elements for alloantigens and certain viruses such as measles. c)They can function by themselves as alloantigens. d)They can evoke an antibody response. e)They are the primary stimulators in the mixed lymphocyte culture and graft -versus- host reaction, but they contribute little to cell-mediated lympholysis. f)They are analogous to the immune response gene products of the I region in the mouse particularly DQ with I-A and DR with I-E (Bach and Sachs, 1987).

* Distribution and expression of HLA antigens :-

Class I and Class II antigens have different tissue distribution and expression Class I antigens are found on essentially all nucleated cells, on reticulocytes, in very low density on mature erythrocytes and probably on trophoblasts and

sperms (Boettcher, 1977). Early studies demonstrated that they are present with decreasing density on spleen, lung, liver, intestine, kidney, heart, aorta, fat and brain (Berah et al., 1970). Class I antigens could also be detected in soluble form in serum, saliva, seminal fluid, urine and breast milk (Vincent et al., 1976).

In contrast, Class II antigens have a relatively restricted expression on B lymphocytes, monocytes, some macrophages,epidermal Langerhan's cells, dendritic cells, activated T-lymphocytes in both normal and diseased state (Yu et al., 1980), epithelium of gastrointestinal tract and urinary bladder, bronchial glands, thymic reticuloendothelial cells, epithelium of mammary gland, parotid acinar cells, astrocytes, alveolar macrophages, kupffer's cells, endometrium (Natali et al., 1981), bone marrow precursors cells (Radka et al., 1986) certain neoplasms (Pollack et al., 1984) and capillary and glomerular endothelium (Fuggle et al., 1983), but they are absent from platelets, unstimulated T cells and other somatic cells (Linch et al., 1984).

Various substances can alter HLA antigens. Chloramphenicol decreases the expression at least of Class I antigens on cell surface membranes (Ben-David et al., 1973). Glucocorticoids do not influence the expression of Class I antigens or B2 microglobulin, but do decreases the expression of Class II antigens (Madsen et al., 1981). Cyclosporine inhibits the induction of both Class I and Class II antigens (Halloran et

al., 1985). Prostaglandins of E series in physiological doses inhibit the expression of Class II antigens on mature macrophages in mice, an effect probably mediated by cyclic AMP (Snyder et al., 1982).

There appears to be, at least in certain tumours, a reciprocal expression between Class I and Class II histocompatibility antigens and presumed tumour antigens. A reciprocal relationship was described between Class I antigens and sarcoma cells (Seigler et al., 1971) and the presence of lymphoma (Bertrams et al., 1971).

The factors that increase the expression of HLA antigens can have a different effect on Class I versus Class II antigens, and even among the Class II antigens a different effect can occur among DR, DQ and DP. For example, all three classes of interferon enhance expression of Class I antigens on lymphocytes but only gamma interferon increases the synthesis and expression of DR antigens and B2 microglobulin (Braun, 1988). Different effects have also been described in neoplasms in which Class II antigen expression has been neatly classified as constitutive as in certain melanomas, gamma interferon inducible as in : carcinoma of the breast, colon, pancreas, bladder, kidney and brain, and gamma interferon non-inducible as in : teratocarcinoma, choriocarcinoma, neuroblastoma and a few other melanoma cell lines (Houghton et al., 1984). Although gamma interferon fails to induce Class II antigens on the latter three neoplasms Class I antigens are induced (Houghton et al., 1984).

When T lymphocytes are activated in mixed lymphocyte culture, the majority of cells express DR but not DQ and DP (Chen et al., 1984). Vascular endothelial cells, when tested in MLC, do not express Class II antigens at the outset but show it by 30 minutes and express it on about one third of the cells at 24 hours (Pober and Gimbrone, 1982).

Of particular importance is the distribution and changeable expression of histocompatibility antigens within the kidney. Class I antigens are present on cells in the glomeruli, endothelium of larger vessels and capillaries, interstitial dendritic cells, proximal and distal tubules. Class II antigens are more abundantly expressed on dendritic cells in the interstitium and appear on glomerular endothelium and some mesangial cells, but they are absent from the epithelial cells in Bowman's capsule and are either un-detectable or barely detectable on the endothelium of large vessels (Halloran et al., 1985). Perhaps, their most useful character is the fact that they do not appear normally on either the proximal or distal tubular epithelial cells, but when an immunologic stimulus occurs, such as rejection or local graft -versus- host reaction, these cells exhibit Class II antigens that are demonstrated in renal biopsies and that may appear on lymphocytes in the urinary sediment (Benson et al., 1985 and Halloran et al., 1985). Moreover, the expression of HLA-DR has been noted on peripheral T lymphocytes in allograft recipients who suffered rejection episodes or had cytomegalovirus (Van Es et al., 1984).

In addition to their altered expression on differentiated cells, Class II HLA antigens (DR, DQ, DP) vary on developing cells and can therefore be considered as differentiation antigens (Braun, 1988). The pattern of expression of Class II antigens on normal and malignant cells suggests that during differentiation the first to be expressed may be DP, then DR and finally DQ (Guy and Van Heyningen, 1983).

* Serologically and cellularly defined antigens :-

The HLA-A, - B, Cw, - DR, - DQ and some - DP antigens are serologically defined by sera derived from parous females, allograft recipients and transfused persons as well as by some monoclonal antibodies. In the A series antigens, a new specificity Aw69 a split of A28, is the first example of an officially recognized specificity identified primarily by a monoclonal antibody (Ascher and Simmons, 1988).

The DP specificities, now numbering six, were initially identified by secondary mixed lymphocyte culture (MLC) using primed lymphocyte testing (PLTs), but a monoclonal antibody has been produced that corresponds to some primed lymphocyte testing - determined specificities (Shaw et al., 1980).

The Dw antigens are cellularly defined by homozygous typing cells (HTCs). Since 1980 the number of HLA-Dw determinants has risen officially from 12 to 19 (Braun, 1988).

The HLA-Dw specificities are not exclusively associated with any one of the three D subregions (DR, DQ, DP), although they most closely resemble HLA-DR. In some cases, Dw antigens correspond very closely to the DR - specificities determined by alloantibody (e.g. Dw1 with DR1) and in other cases they do not (e.g. Dw18 and Dw19 with DR13) (Schreuder and Degos, 1984).

The Dw - DR - DQ equivalencies become more complex because different Dw specificities, such as Dw2 and Dw12, can express the same DR and DQ antigens, DR2 and DQw1 respectively. Finally, some Dw specificities, such as Dw4 and Dw6, have their sub-specificities ("splits") defined by monoclonal antibodies that have no apparent relationship to DR, DQ or DP (Braun, 1988).

Because DR, DQ and DP molecules are all stimulatory to varying degree in the primary mixed lymphocyte culture, in order for two persons to be Dw compatible they will probably have to be identical with one another not only for the HLA-DR but also for - DQ, - DP and possibly other molecules as well (Matsui et al., 1984).

* Public and Private specificities :-

Private specificities are all of the individual antigens except Bw4 and Bw6 and DRw52 and DRw53 (Ascher and Simmons, 1988).

Public antigens were constructed initially on the basis of cross reacting groups (CREGS) (Colombani et al., 1974).

Immunoprecipitation studies later showed that a public antigen called x was common to the heavy chain of the B7 - cross reacting group comprised of HLA -B7, -22, -27, -40, -42 (Schwartz et al., 1979). Similarly the B5 - cross reacting group consisting of HLA-B5, -15, -18, -35 was found to have a common determinant called "Y" (Schwartz et al., 1980).

The public determinants can function as target antigens in cell mediated cytotoxicity. The clinical revelance of such cross reacting groups or public specificities has been shown in studies of renal allografts in which matching for the better defined HLA-A and HLA-B CREGS continued to yield a significant correlation with allorgraft success and simplify prospective donor recipient matching (Festenstein et al., 1986).

Another type of public specificity consists of Bw4 and Bw6 which relate exclusively to groups of B series antigens. In fact, the B series antigens and, most importantly, different subspecificities ("splits") of these antigens can be partitioned by the Bw4/Bw6 distinction. For example, the B38 split of B16 is associated with Bw4, whereas the B39 split of B16 is associated with Bw6 (Albert et al., 1984).

Similarly, DRw52 and DRw53, formerly called MT2 and MT3 respectively, are associated with certain groups of DR antigens: