LIVER TRANSPLANTATION

AN ESSAY

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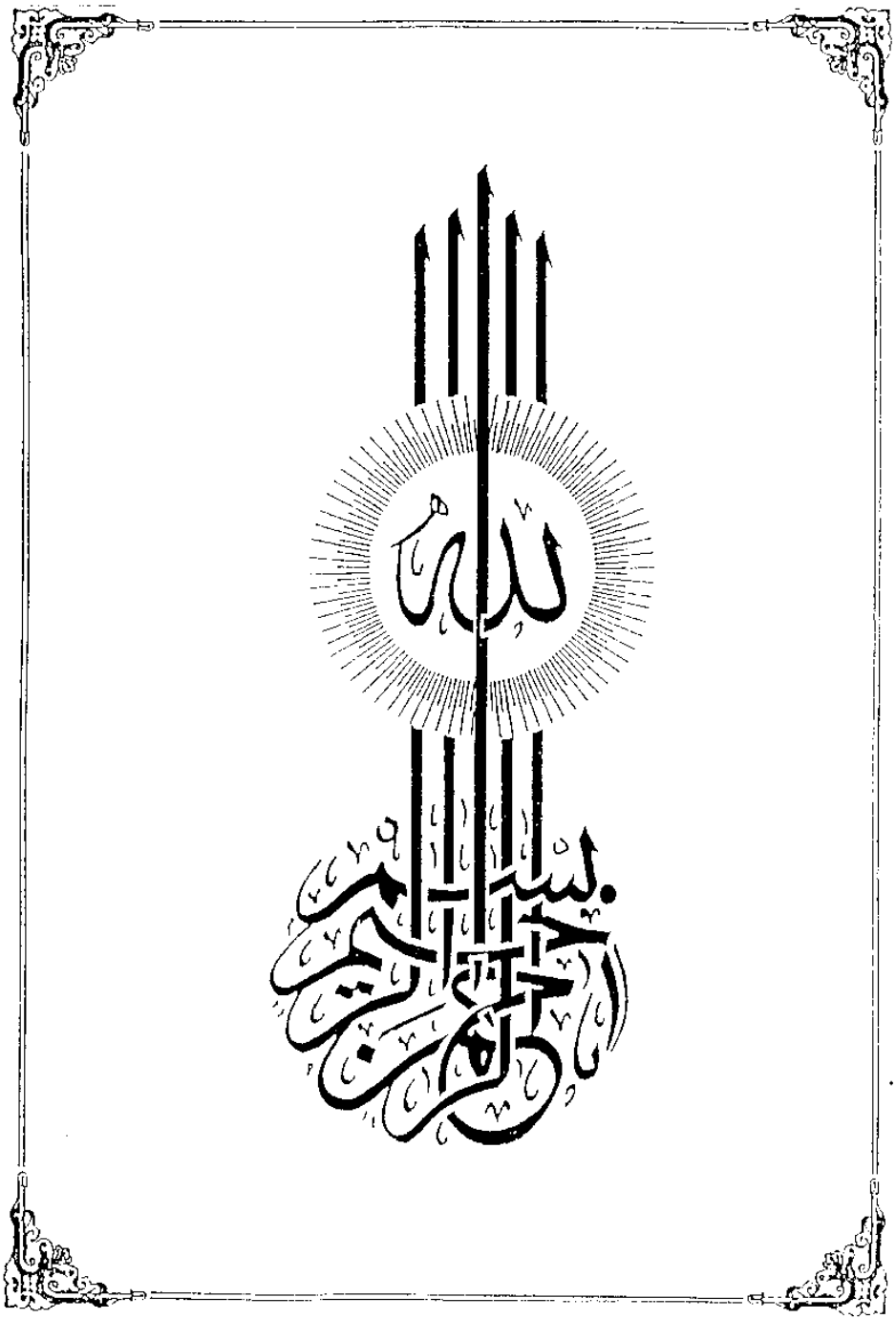

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Since the first human orthotopic liver transplant was performed in 1963 , a number of improvements in operative technique , post-operative care and immuno-suppressive agents have made this operation appropriate treatment for patients with end stage liver disease .

In 1967 Starzl performed the first successful liver transplant . Since then , more than 500 liver transplants have been performed at centers in Pittsburgh , Cambridge , Hannover, Gronigen , Minneapolis and Memphis in addition to a number of other institutions . (Starzl et al 1982) .

Although liver transplantation still places a formidable strain on the patient , the surgeon , the anaesthetist and all others concerned , the procedure is considerably less of an adventure than it was in the early days . Nevertheless it remains for the anaesthetic and intensive care services an extremely demanding and time consuming procedure .

Orthotopic liver transplantation is the procedure of choice and is preferably used in all centers .

Heterotopic liver transplantation which consists of grafting an additional liver into the recepient has been less frequently used and led to long term success in a very limited number of patients . Nevertheless , this technique has several theoretical advantages compared to orthotopic liver transplant-ation and a true comparative study of the two procedures has never been done .

Heterotopic liver transplantation was the basis of a large number of experimental studies related to surgical technique , liver trophicity , liver rejection and treatment of acute liver failure .

It is possible that in the future , heterotopic liver transplantation will appear as a useful technique in selected very ill patients with end-stage acute or chronic liver failure for whom orthotopic transplantation , a very major and risky procedure , is contraindicated by most transplant surgeons .

Several advances are responsible for improved results in this field . The introduction of cyclosporine immunosuppression , meticulous harvesting techniques with slow in situ organ flushing , the use of portasystemic venous bypass and improved techniques of biliary drainage have enhanced patient management . In addition , early recognition and treatment of rejection and other post-operative complications have contributed to improved survival . (Starzl et al 1982) .

This essay displays recent trends in the indications , technique and post-operative care of patients subjected to liver transplantation .

IMMUNOLOGY

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IMMUNOLOGICAL ASPECTS OF LIVER TRANSPLANTATION

Major histocompatibility antigens

When foreign tissues are transplanted , a state of immunity is generated which results in rejection of the graft .

The antigens which provoke this rejection are the histocompatibility (H) molecules of which two groups exist , major and minor .

All vertebrates studied so far conform to this pattern .

The major (H) molecules induce acute rejection of allo-antigeneic (genetically dissimilar) tissue , in contrast to the allo-antigeneic minor (H) molecules , which normally induce chronic graft rejection .

If the transplanted tissue is either syngeneic (genetically identical) or autologous from the same individual , graft rejection does not occur .

In man there are two classes of major histocompatibility locus antigens (HLA) which are involved in graft rejection , class I and class II . The genes for these are on chromosome 6 , in a cluster called the major histocompatibility complex (MHC) . The class I molecules are encoded by three different loci : HLA-A , B & C , and the class II by three others : HLA-DP , DQ , & DR .

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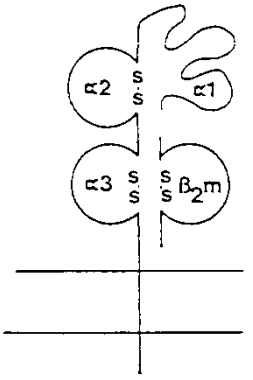
Structure of the major histocompatibility molecules

Class I

The structure of a typical class I molecule is illustrated in that figure



CLASS I

The glycoprotein is composed of two polypeptide chains . The heavy chain (α) is 45 k , and composed of three external domains : 1 , 2 , & 3 , a transmembrane segment and a cytoplasmic tail . There is one glycosylation site , the function of the attached carbohydrate R moiety being unknown , but it may confer structural integrity . The polymorphic sites of the molecule , recognition of which provoke allograft rejection , are found in the 1st and 2nd domains and appear to be generated by small changes in the amino-acid sequence of these parts of the protein . (Owen and Crompton 1980) .

The light chain β2 microglobulin (12 k) , is encoded by a gene not within the MHC , but on chromosome 15 . (Goodfellow et al 1975) .

The molecule is invariant , does not span the membrane and is non covalently attached to the α chain to form a dimer on the cell membrane .

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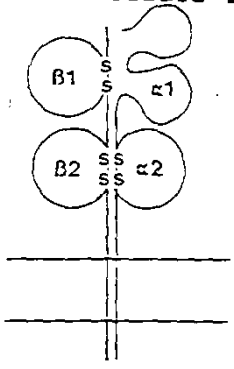
Class II

The class II molecules are also two chain structures , both of which are encoded by genes found within the MHC .

The structure of a typical molecule is shown in the figure



CLASS II

Each chain carries two external domains , spans the cell membrane , and carries a cytoplasmic tail .

The α chain (33 k _ 35 K) carries two glycosylation sites and the β chain (28 K _ 31 K) only one . The polymorphic sites are found on the β chain of DP and DR , and on both the α and β chains of DQ molecules . (Bodmer et al 1985) .

Finally although the class I and class II molecules show extensive polymorphism , they are essentially very similar . In addition , they show strong homology to immunoglobulins (Ig) . It is presumed that this similarity arises as a result of evolution of the HLA and Ig molecules from a common ancestral cell surface molecule . This family has recently been expanded to include the antigen specific receptor on T-lymphocytes and the poly Ig receptor . (Williams 1984) .

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Molecular genetics :

With the advent of appropriate techniques , our knowledge of the molecular genetics of the MHC has expanded rapidly . Genetic maps have been obtained for specific class I and class II molecules . (Jordon et al 1984) .

In eukaryotic cells , genes are composed of coding sequence of DNA (exons) separated by intervening sequences (introns) . The function of these introns is not known at present .

For both the class I and the class II molecules it has been demonstrated that each functional domain of the molecule is encoded by one exon within the gene corresponds to that of the domain in the synthesized molecule . In addition each gene includes an extra exon coding for a protein called the leader sequence . This molecule facilitates the intra-cellular transport of the synthesized protein through the endoplasmic reticulum and Golgi of the cell . It is cleaned off once the molecule is inserted into the cell membrane .

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Serology and cell defined polymorphisms

As previously mentioned , the MHC molecules show extensive polymorphism .Conventionally , the different antigens are identified by the pattern of their reactions with selected cytotoxic anti-sera . The latest number of agreed class I specificities is 23 HLA-A , 49 HLA-B and 8 HLA-C . (Bodmer et al 1984) .

As yet , the number of serologically identified class II antigens is smaller , 16 HLA-DR and 3 HLA-DQ . Some monoclonal antibodies are now available which discriminate between classII variants . (Beckman 1984) . However , their patterns of reactivity are complicated and do not correlate in a simple fasion with the specificities defined by HLA typing anti-sera .

Cellular typing methods (mixed lymphocyte cultures and primed lymphocyte typing) are also used for defining class II polymorphism . These techniques define epitopes different to those defined serologically which may be on the same or different molecules . These cell defined specificities are designed as members of the HLA-D series . (Bach et al 1983) .

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Distribution :

Class I molecules are found on virtually all nucleated cells of the body . By contrast ,class II molecules show a very different distribution . Originally thoughtto be present only on B-lymphocytes , activated T-lymphocytes and accessory cells such as monocytes and dendritic cells , it is now known that many other cell types which normally do not constitutively express class II molecules can be induced to do so . In vivo this can occur during graft rejection (de Waal et al 1983) , graft versus host disease (Lampert et al 1981) and auto-immune tissue damage (Hanafuse et al 1983) .

Induction of class II molecule is probably due to γ interferon as in vitro studies have shown that γ interferon (known to be produced by activated T-lymphocytes) has this

effect .

This phenomenon may have relevance to the fate of liver allografts as although only dendritic cells of normal liver express class II HLA molecules , biliary epithelium can be induced to do (Takacs et al 1983) .

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Function of MHC molecule in the immune responses

The normal physiological role of MHC molecules is to govern regulation of the immune response .

A central role is played by the antigen presenting cell (APC) , normally a macrophage or dendritic cell . The virus e.g. is processed by the APC and subsequently small antigenic fragments become associated with HLA molecules on the APC surface (Ag - MHC complex) . This step is essential for recognition of antigen by the receptor on responding T-lymphocytes , T-cells will only respond to antigen in association with MHC molecules . The class of MHC molecules used for antigen recognition correlates strongly but not absolutely with the phenotype of the interacting T-cell . Thus cytotoxic T-lymphlcytes which are T 8 positive respond to antigen in association with class I molecules and helper / inducer T-cells which are T 4 positive to antigen in assciation with class II molecules (Rheinherz 1983) . Binding of the Ag - MHC complex by the helper T-cell stimulates the APC to secrete a soluble factor interleukin 1 (IL1) . (Oppenheim 1984) . This molecule appearsto be a maturation factor for all T-cell responses . Interleukin 1 , plus Ag - MHC complex

binding , programmes the helper T-cell to synthesize growth and maturation factors , for itself and other populations involved in the response . Thus , the final step for a cytotoxic T-cell response to the virus is growth and maturation of the precursor cytotoxic T-cell induced by interleukin II (IL 2) and an incompoetely characterized maturation factor (Raulet et al 1982) . The mature cytotoxic T-cell is now capable of lysing virus infected cells to which it binds by the Ag - MHC complex on the target cell surface . Unlike T-cell, the B-cell receptor (Ig) binds directly to soluble Ag in the abscence of MHC molecules (Nisonoff 1982) . Regulation of the immune response is still dependent on T-cell function because the majority of mature B-cells will only secrete antibody if they first bind antigen and then receive T-cell synthesized growth and maturation factors (Vitetta et al 1984) .

Finally , the role of suppressor T-cells in such a response needs to be considered . Down regulation of both B & T-cell responses is mediated by such cells, although at present we do not fully understand how the receptor on suppressor T-cell is triggered either by binding to Ag - MHC (possibly Ag alone) , or to idiotypic determinants carried on the receptors of other responding T- and B-cells (Roser et al 1983) .It has been postulated that after activation , suppressor T-cells secrete soluble factors which mediate suppression .

As yet neither this nor the target cells have been adequately defined . In addition , regulation of responsiveness can occur as a consequence of possession immune response (IR)