Impact of Tissue Typing Matching on Early Graft Function

Thesis

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بِسْمِ اللَّهِ الرَّحْمنِ الرَّحِيمِ

"قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ"

صدق الله العظيم

سورة البقره الآيه 32

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Introduction

Kidney transplantation has become a standard therapy for end-stage renal disease. The acute immunological rejection and long time survival of kidney allografts are correlated with the human leukocyte antigen (HLA) match status between donor and recipient HLA-A, -B and -DR **(Frohn et al., 2001).**

Adult studies have shown a high renal graft survival if the donor and recipient match for each antigen of the human lymphocyte antigen (HLA)- A, B and DR loci (six-antigen match) (**McEnery and Stablein 1992).** In contrast, the production of posttransplantation antibodies directed against donor HLA-A, -B, -Cw, -DR, and -DQ mismatches are all strongly predictive of transplant failure **(Worthington et al., 2003)**.

Selecting grafts that are immunologically compatible with the recipient is still recommended despite the fact that new and improved immunosuppressive regimes have been developed **(Frohn et al., 2001).**

Matching has to be performed with respect to the **HLA** molecules when donor/recipient pairs are selected in the clinical transplantation setting. This matching significantly improves the outcome of transplantation, although other factors such as gender, race, time of ischemia and cytomegalovirus (CMV) status also contribute to graft survival **(Smits et al., 1997).**

Better HLA matching ensures fewer episodes of rejection and better long term graft survival in comparison to the poorly matched grafts. The graft survival for living non-related donors recipients was appreciably higher than that of cadaveric recipients (**Panigrahi et al., 2002).**

Aim of the work

To study the impact of human leukocyte antigen (HLA) match status between donor and recipient HLA-A, -B and –DR on the renal graft survival in the first six months post-transplant.

Chapter I:

Major histocompatibility complex

Introduction:

The major histocompatibility complex (MHC) is an extended cluster of genes that are remarkable for the number and importance of the immunological functions they encode. **(Gruen and Weissman, 1997)**

Rejection of organ and tissue allografts occurs because the mammalian genome contains several polymorphic loci that encode widely expressed tissue antigens. Persons who do not express a given allele at any of these loci recognize the protein encoded by that allele as foreign and mount a vigorous immune response that results in graft rejection. The most important genes are clustered within the major histocompatibility complex (MHC), which in humans is known as the HLA (Human Leukocyte Antigen) complex**. (Sayegh and Turka, 1998)**

These antigens are termed "major" because of their overwhelming importance in determining compatibility between a donor and a recipient in the transplantation of solid organs and bone marrow. **(Kernan and Dupont 1996)**

Historically, interest in the MHC emanated from tissue transplantation experiments, hence the reference to histocompatibility **(Gruen and Weissman, 1997)**, and then for their more general role in the immune response to pathogens and synthetic antigens. **(Singer et al., 1997)**

Nomenclature:

The genes of the MHC exhibit a remarkable genetic variability. The MHC is polygenic in that there are several genes for each class of molecule. The MHC is also polymorphic. Thus a larger number of alleles exist in the population for each of the genes. Set of MHC genes tend to be inherited as a block or haplotype. as there are relatively infrequent cross over events at mis focus. **(Bodmer et al., 1994)**

MHC genes are described by a letter (or letters) for each locus. HLA-A, HLA-B, HLA-C, HLA-DR. allelic genes have been denoted by the addition of a number or a letter and a number (HLA-A2 and HLA-A3 are alleles, as are HLA-B8 and HLA-B27). Precise designation of human genes is by a nomenclature including four-digit number following the locus (e.g. HLA-A *0101 and HLA-DRB*0101). **(Bodmer et al., 1994)**

For the MHC class II genes, the designation in the human is HLA-D. **(Duran et al., 1989)**

MHC Location :

The MHC is a well characterized region of the human genome, containing a high diversity of genes and an apparent clustering of genes involved in the immune response. **(Rhodes and Trousdale, 1999)**

The genes encoding the HLA antigens are located on the short arm of chromosome 6 **(Suthanthiran and Storm, 1994)**. The HLA complex on chromosome 6 contains over 200 genes, more than 40 of which encode leukocyte antigens. **(Klein and Sato, 2000)**

The MHC is divided into three contiguous regions that approximate the location of genes with shared characteristics. Most centromeric on chromosome 6 is the class II region, which contains the 17 known HLA class II genes and pseudogenes. Contiguous to that is the class III region, which encodes several of the components of the complement system. Telomeric to the class III region is the class I region, which encodes more than 18 HLA class I-related genes and pseudogenes. Recently a number of genes putatively involved in inflammation have been identified in the central MHC, at the telomeric end of the class III region. As presented below, this group of genes may have roles in various aspects of stress, inflammation, or infection. **(Gruen and Weissman, 1997)**

They, by several criteria, occupy a unique position within the human genome, most notably an unusually high gene density of more than 180 genes per 4 Mb. **(Shiina et al., 1999)**

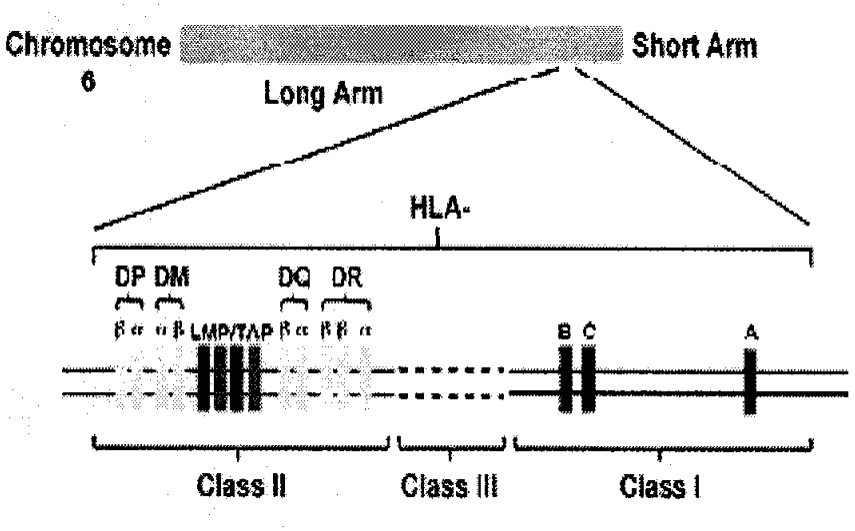


Fig (1): MHC location at chromosome 6

MHC classes:

The HLA segment is divided into three regions (from centromere to telomere): class II, class III, and class I**. (Shiina et al., 1999)**

All jawed vertebrates have two classes of structurally and functionally distinct MHC molecules that present peptides to T cell receptors. **(Kasahara et al., 2002)**

The class I and II loci comprise the core of the MHC and, with their involvement in peptide presentation, provide functional and evolutionary identity to the chromosomal segment they occupy.

Class I HLA antigen:

The Class I region is the most telomeric part of the HLA complex and contains three classical Class I gene loci, HLA-A, B, and C, as well as four non-classical Class I genes, HLA-E, F, G and H. **(Yan et al., 2003)**

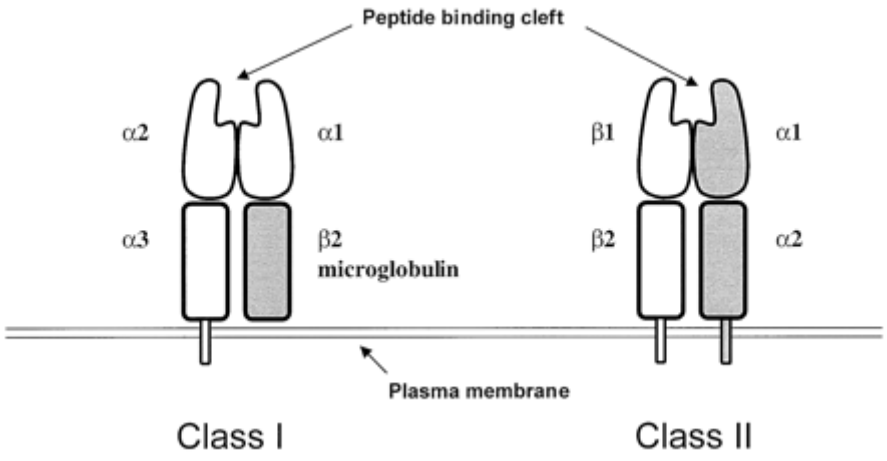
There are some 20 class I genes in the HLA region; three of these, HLA-A, B, and C, the so-called classic, or class Ia genes, are the main actors in the immunologic theater**. (Klein and Sato, 2000)**

In addition to the classical class I, or class Ia, genes described above, there are also nonclassical, or class Ib, genes whose products are structurally similar to class Ia but are generally nonpolymorphic, may or may not be MHC-linked, and can bind to molecules besides peptides. **(Ohta et al., 2000)**

Structure:

The HLA-A, B, and C antigens (class I) consist of a polymorphic chain linked to a beta-2 microglobulin encoded by chromosome 15. The class I molecules are displayed by all nucleated cells and platelets. **(Suthanthiran and Storm, 1994)**

The class I histocompatibility antigen from human cell membranes has two structural motifs: the membrane-proximal end of the glycoprotein contains two domains with immunoglobulin-folds that are paired in a novel manner, and the region distal from the membrane is a platform of eight antiparallel beta-strands topped by alpha-helices. A large groove between the alpha-helices provides a binding site for processed foreign antigens. **(Bjorkman et al., 1987)**



Fig(2): Structure of the Class I and II heterodimers. (Williams, 2001)

Mechanism of action

Class I molecules are expressed uniquitously and associate with peptides generated in the cytosol by the multicatalytic proteasome. **(Ohta et al., 2000)**

Cytotoxic CD8+ T cells survey the target cell surface for presence of unique complexes between a peptide and a MHC class I molecule and cause lysis of the target cell**. (Malarkannan et al., 1996)**

CD8, T cells with alpha/beta antigen receptors that interact with the HLA class I glycoproteins on nearly all cells. These HLA molecules bind to peptides derived from intracellular antigens, such as viral proteins, and display them on the cell surface. Binding of the alpha/beta antigen receptor to complexes of HLA class I molecules and peptide fragments of an invading virus induces the T lymphocyte to kill the infected cell. **(Raulet, 1999)**

Natural killer (NK) cells can defend an organism against a variety of threats, probably using several different strategies to discriminate between normal and aberrant cells. According to the 'missing self' hypothesis, one function of NK cells is to recognize and eliminate cells that fail to express self MHC class I molecules. **(Ljunggren and Karre, 1990)**

The presence of HLA glycoproteins actually protects the cell from attack by NK cells. The way in which HLA molecules defend cells from assault by NK cells has recently become clear. Natural killer cells express receptors that bind to HLA class I molecules on other cells. Most of these receptors inhibit cytotoxic function rather than activate it, as in the case of the antigen receptor of the T cell. **(Raulet, 1999)**

V gamma-2 and V delta-2 T cells predominate in the circulation and significantly expand in vivo during a variety of infectious diseases. Antigens identified for the V gamma-2 T cells are nonpeptide phosphate, amine, and amino-bisphosphonate compounds. In contrast, V gamma-1-encoded T-cell receptors (TCRs) account for the vast majority of gamma and delta T cells in