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HLA Typing And Its Influence On Organ Transplantation

Research Article

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Abstract

Organ transplantation is the process of moving an organ from one body to another or from a donor site to another location on the person's own body. It is often the only treatment for end stage organ failure, such as liver and heart failure. In such crucial procedures, Human Leukocyte Antigen (HLA) plays an insignificant role in matching donors with the organ needing a patient. It is a complex process that can be done at different levels of detail. The aim of the study is to review the HLA typing & its influence on organ transplantation. The objective of this study is to understand HLA typing, to explore the methods used in HLA typing and to determine the role of HLA typing in organ transplantation. Many organ transplant patients or guardians fail to recognize the importance of undergoing factors such as HLA typing before accepting a donor which leads to a misunderstanding of the Doctor in-charge. This may even further damage a good doctor-patient relationship. Thus, it will be advantageous bringing an awareness to such a group of people.

Keywords: HLA Typing; Organ; Transplantation; Antigen; Donor; Graft; Antibodies.

Introduction

Organ transplantation can be defined as the surgical removal of a healthy organ from one person and its transplantation into another person whose organ has failed or was injured. The various types of grafting techniques include by means of allograft, isograft, allograft and xenograft. Organ transplantation includes the transplantation of organs such as pancreas, kidney, lung, liver, small bowel, and heart and islet cell transplant [7]. Based on the Global Observatory on Donation and Transplantation by WHO-ONT collaboration, in 2015 a total of 126,670 organ transplantation was done with an increase of 5.8% compared to 2014. There are approximately 114,955 patients in the waiting list for donors as of May 2018 in the U.S.A [12].

When considering the organ transplantation (allograft), it is very important that there is an adaptive immunity between the donor and the recipient [9]. As the first thing to be triggered upon a foreign body involvement is the immunity. This is where the major histocompatibility complex (MHC) comes into action. The MHC molecules are cell surface molecules that have the capability to induce antigenic stimuli.

The term cross match is often used in organ transplantation referring to the production of antibodies in the recipient's body against the antigen of the donor body. Both innate and adaptive immune response is necessary for the self-tolerance that is the avoidance of self-destruction to its own tissue after transplantation [4].

The HLA typing test helps in identifying antigens, which act as markers on the cells of your body to be able to differentiate between self and non-self. This identification is very important for it allows the body to protect itself by recognizing and attacking

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something that does not belong to it such as bacteria or viruses [3].

However, when two individuals share the same HLA markers, the immune systems will not see each other as foreign and not attack each other. The HLA matching is usually based on either 8 or 10 HLA markers [22]. According to Lakshmi et al the largest number of thalassemia treatments were done only after HLA matching and another study stated how HLA can be used in diagnosis of tuberculosis granuloma and giant cell tumor of the long bone [16].

Definition

Human Leukocyte Antigens (HLA) are proteins which are inherited from our parents and thus it is a Major Histocompatibility Complex (MHC) of man [1]. It was Gorer and Snell who first identified the major histocompatibility complex in mice. After which the World Health Organization Nomenclature Committee introduced HLA as the human version of MHC [21]. The Human leukocyte antigens are actually proteins which are found situated on the surface of white blood cells and other tissues [5].

The HLA typing is the process of matching organ and tissue transplant recipients with its compatible donors by means of tissue typing where the "Tissue" refers to lymphocytes and "typing" denotes the human leukocyte antigens [6].

Classification

They can be classified into MHC Class I and MHC Class II. MHC Class I consists of main genes that are HLA-A, HLA-B and HLC-C whereas the minor genes are HLA-E, HLA-F and HLA-G. The MHC Class II can be subdivided mainly to HLA-DP (α-chain encoded by HLA-DPA1 locus & β-chain encoded by HLA-DPB1 locus), [18]. HLA-DQ (α-chain encoded by HLA-DQA1 locus & β-chain encoded by HLA-DQB1 locus) and HLA-DR (α-chain encoded by HLA-DRA locus & 4 β-chains)(19).They are present in each type as many constituents of specific proteins, such as the HLA-A has 59 various types of specific proteins like HLA-A1 and HLA-A2 [15].

ROLE OF HLA TYPING IN ORGAN TRANSPLANTATION
The HLA molecules have a very important task that is to express the peptides to the CD4 and CD8 T cells. This helps the T cells to recognize them as its own and prevents self-destruction [24]. However there are chances of HLA mismatches which may occur at antigenic or allelic level; the first are characterized by amino acid substitutions in both peptide binding and T-cell recognition regions, whereas in the case of allelic level they can be characterized by amino-acid substitution in the peptide binding regions alone [23].

During transplantation, the HLA molecules from donors are recognized by the recipient's immune system by direct and indirect methods of allo-recognition triggering an allo-immune response [14]. Since the adaptive immunity is the main response exerted to the transplanted tissue, the main target of the immune response is the MHC molecules expressed on the surface of donor cells. Thus, the T-cell activation leads to the production of cytokines and chemokines which in turn may recruit components of the innate immunity like NK cells or macrophages and complement [13].

Techniques

In the past, HLA typing was done by either serologic method using antiserum or mixed lymphocyte culture (MLC) [20]. However, as it did not provide a precise reading, DNA based HLA typing methods using molecular techniques was introduced [17]. The molecular techniques used were Sequence-Specific Primer Amplification (SSP), Sequencing-Based Typing (SBT), Reference Strand-Based Conformation Analysis (RSCA), a Sequence-Specific Oligonucleotide Probe Hybridization (SSOP) and Reverse Sequence Specific Oligonucleotide (rSSO)[10].

Reverse Sequence Specific Oligonucleotide (rSSO) is generally used for the HLA typing of the low to intermediate resolution range. That includes HLA typing for HLA-DQA, HLA-DQB and HLA-DP. Whereas the Sequence-Based Typing (SBT) is done for the higher resolution identification.Later, many modifications were done such as the next-generation sequencing (NGS) which portrayed the ability to sequence larger regions of genes, including introns, without additional effort or cost.

Additionally, another method using short tandem repeat (STR) genotyping was found for precise determination of the extent of HLA identity in families where HLA haplotype inheritance was ambiguous, due to extensive homozygosity or shared parental haplotypes [11].

Examination Of HLA Types

Serotyping

It is said to be a crude way of identifying HLA receptors and receptor isoforms. In this procedure, blood from animals or humans is taken and the blood cells are allowed to separate from the serum, and the serum is diluted to its optimal sensitivity and used to type cells from other individuals or animals. Serologic method was also used in screening for HLA antibodies in the recipient. These antibodies are important because they are reactive with lymphocytes of a prospective donor (cross matching).

Gene Sequencing

The sequence of the antigens determines the antibody relativities, and so having a good sequencing capability (or sequence-based typing) obviates the need for serological reactions. In this way, the various serotype reactions may be indicating the need to sequence a person's HLA to determine a new gene sequence. The diversities in allelic level makes it necessary to use broad antigen typing followed by gene sequencing because there is an increased risk of misidentifying by serotyping techniques.

Cellular Typing

Cellular typing is a mixed lymphocyte culture and it has been used to determine the HLA class II types. The cellular assay is more sensitive in detecting HLA differences than serotyping. This is because minor differences unrecognized by allo-antisera can stimulate T cells. This typing is designated as Dw types.

Haplotypes

HLA haplotype is a series of HLA "genes" (loci-alleles) by chromosome, one passed from the mother and one from the father. These haplotypes can be used to trace migrations in the human population because they are often much like a fingerprint of an event that has occurred in evolution.

Phenotyping

In this strategy, PCR primers called SSP-PCR which are specific to a variant region of DNA are used. If a product of the right size is found, the assumption is that the HLA allele has been identified. New gene sequences often result in an increasing appearance of ambiguity. Because gene typing is based on SSP-PCR, it is possible that new variants, in particular in the class I and DRB1 loci, may be missed [8].

Graft Rejection

Graft failure is the condition where the body does not accept the new component added to its surrounding and expresses this as swellings, fever or pain at site. The graft rejection can occur any time after organ transplantation or it may even develop and appear at a later stage. This is generally due to cases of the recipient's immune response which acts against the donor's immune-hematopoietic cells. The other causes of graft failure includes viral infections such as the cytomegalovirus infection, drug toxicity and septicemia.

The failed immunological response can be due to various factors such as major histocompatibility complex (MHC), NK-mediated allograft rejection.

In transplantation immunology, the major impact in graft loss comes from the effects of HLA-B and -DR antigens. The effects of HLA-DR mismatches are the most important in the first 6 months after transplantation, the HLA-B effect emerges in the first 2 years, and HLA-A mismatches have a deleterious effect on long-term graft survival [2].

Conclusion

Over the time, many have been saved by the great advancements of organ transplantation. Thus, there is more significance of having to remove the factors which leads to failure or becomes an obstruction. It will become an advantageous action by bringing awareness amongst organ transplant patients and guardians. As the majority still do not recognize the importance of undergoing factors such as HLA typing before accepting a donor.

The continuous research and development in the technologies are hoped to guide us accurately to the identification of parameters that best correlates with and predict transplant outcomes. In current years, serological methods have been replaced with DNA based typing methods.

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