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SOCIETY FOR HEART FAILURE AND TRANSPLANTATION'S

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EDITOR'S NOTE

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Dear Readers,

Greetings from the Editor's desk.

This issue carries the first part of a series of 4 articles on Heart Transplant Immunology by Dr Chintan Sheth.

Dr. Sheth's insightful article delves into the intricate realm of transplant immunology, particularly in the context of heart transplantation. Through a comprehensive overview, Dr. Sheth highlights the critical role of understanding the immune response to allografts, emphasizing the significance of MHC or HLA matching in minimizing rejection risks. By dissecting the mechanisms of hyperacute, acute, and chronic rejection, the article underscores the complexities and clinical implications involved in post-transplant outcomes. He has adeptly navigated through the nuances of innate and adaptive immune responses, elucidating the pathways of allorecognition and their contributions to allograft rejection.

This article is a valuable resource for clinicians, offering a deeper understanding of immunological principles essential for pre-operative assessment and postoperative management in heart transplant recipients. Dr. Sheth's comprehensive analysis serves as a guiding beacon, paving the way for optimizing immunosuppressive therapies and ultimately enhancing patient care and outcomes in heart transplantation.

Dr Manoj Durairaj
Editor "The Revival"

SUB EDITOR

Dr Talha Meeran

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Dear Colleagues,

Understanding the complex chasms of transplant immunology is vital to the success of any transplant program. This current issue of REVIVAL is the first amongst a series four such review articles by Dr Chintan Seth focusing on transplant immunology. The current issue focuses on the very basis of immunology i.e the HLA / MHC molecules and the various mechanisms of acute and chronic rejection. The discussion on the cellular basis for rejection explaining the complex interactions between MHC molecules, T-cells and the antigen presenting cells is a good refresher for all levels of readers alike. The clinical pearl section highlights the importance of these basic molecular and cellular pathways and puts them into clinical perspective helping the readers apply this knowledge in their clinical practice.

Sincerely,
Dr Talha Meeran
Sub Editor "The Revival"

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Special thanks to Dr Chintan Sheth for authoring this month's article.

Designed by Maithili Kulkarni

PRESIDENTIAL MESSAGE

Dr Julius Punnen

Sr. Consultant Cardiothoracic Surgeon, Narayana Health, Bangalore

Dear Members and Colleagues,

Heart transplantation provides a lifeline to individuals grappling with end-stage irreversible heart disease, offering not only extended survival but also an enhanced quality of life. However, the success of heart transplantation relies on our ability to finely tune immunosuppressive therapies and navigate the delicate balance between rejection and the adverse effects of immunosuppressants. This underscores the critical need for a nuanced understanding of transplant immunology. Dr. Chintan Sheth, an expert Cardiac and Heart & Lung Transplant Anesthesiologist And Cardiac Critical Specialist, has written a comprehensive review on transplant immunology, starting from the basics, to mechanism of rejection and clinical implications, and immunologic testing pre- and post-heart transplant. We have divided this review into four parts, which we will be publishing in this and the subsequent issues of the Revival.

In the first part of this review, Dr. Sheth outlines the basic concepts of transplant immunology, starting from allorecognition, which is the recognition of antigens on the graft as non-self by the recipient T-cells. The antigens that are most relevant in transplant are major histocompatibility complex (MHC) molecules, but others include minor histocompatibility antigens, ABO blood group antigens, and monocytes/endothelial cell antigens. There are two classes of MHC, and these are encoded by the human leukocyte antigen (HLA) gene complex. The structure of the two classes of MHC molecules varies and they are found on different cells, which is described in details in this review. The MHC molecules play a key role in self-recognition, self-tolerance, graft rejection, or tolerance.

The article further delves into the immunology of transplant rejection, categorizing rejection types into hyperacute, acute, and chronic. The mechanisms of rejection, both nonspecific innate responses and donor-specific adaptive responses, are explored. The innate immune response, characterized by early proinflammatory signals, is a result of several injuries and exposures in the immediate post-transplant period, such as, ischemia-reperfusion injury and infections, lead to cytokine release and activation of the complement system and Nature killer cells directed cell killing. Importantly, factors like longer ischemia time, marginal donors, recipients on MCS pre-transplant, blood transfusions, primary graft dysfunction, can also lead to graft rejection via the innate immune response.

The adaptive immune response occurs later, and is antigen-specific and relies presentation of alloantigens by antigen presenting cells and alloantigen recognition by host T-cells. The direct pathway, indirect pathway, and combined direct and indirect pathways are elucidated in this article, offering insights into the intricate processes that culminate in allograft rejection.

In conclusion, this review underscores the imperative of advancing our understanding of transplant immunology to refine post-transplant management. As heart transplantation continues to be a life-saving option for many, the pursuit of knowledge in immunology remains pivotal for achieving optimal outcomes and extending the median survival of heart transplant recipients.

With warm regards,

Dr Julius Punnen

President, Society for Heart Failure and Transplantation

TRANSPLANT IMMUNOLOGY-
CLINICAL IMPLICATIONS (PART - I)

ABOUT THE AUTHOR

Dr. Chintan Sheth

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Working as a Consultant Cardiac and Heart & Lung Transplant Anesthesiologist And Cardiac Critical Specialist at Marengo CIMS Hospital for 12 years.

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Heart transplant is the treatment of choice for end stage irreversible heart failure patients providing 1-year survival for 90% and median survival for 13 – 15 years with excellent quality of life. Though our understanding improved significantly about care of the heart transplant patients, post-transplant management and fine tune of immunosuppressants is still a challenge. Understanding the basics of immunology is utmost important to manage a fine balance between risk of rejection versus risk of side effects of immunosuppressants like infection, renal insufficiency and malignancy.

Extensive immunological work up pre-heart transplant for listing purpose and post heart transplant for fine tune of immunosuppressants doses and effective management of rejection is crucial. Although our knowledge of induction and maintenance of immunosuppressants have increased significantly in last 5-10 years, still rejection is one of the major cause for early mortality post heart transplant. Acute rejection episodes' account for 10% mortality within the first three years after transplantation with majority occurs in first 1 year.[1] In the first-year incidence of Acute cellular rejection is 20-40 %, Antibody mediated rejection (AMR) is 10 – 20 % and Mixed (ACR with AMR) is 25%.[2,3,4]

This review will summarize the key basic concepts of transplant immunology and modern immunological assays, their clinical implications in pre-operative and postoperative management of heart transplant patients.

Basics of transplant immunology

When a foreign organ, such as a heart or lung, is transplanted into a non-identical individual of the same species, the organ is called an **allograft.** The immune response from the recipient to the allograft is termed an **alloimmune response.**

Alloimmune response is initiated by T-cell recognition of alloantigens is called **allorecognition.** Allorecognition is the first step of a series of complex events that leads to T-cell activation, antibody production, and allograft rejection.

Transplant alloantigens are major histocompatibility complex (MHC) molecules (most commonly responsible for rejection), minor histocompatibility antigens, ABO blood group antigens, and monocytes/endothelial cell antigens[5,6].

Major histocompatibility complex (MHC) / Human Leukocyte Antigen (HLA)

The major histocompatibility complex (MHC) is a gene region coding for cell surface proteins important for the immune system. Graft rejection was found to be associated with the development of antibodies against this cell surface proteins/ peptides (MHC). The human MHC is called the HLA (Human Leukocyte Antigen) system because these antigens were first identified and characterized using alloantibodies against leukocytes. HLA genes are located on the short arm of chromosome 6 at $6p^{21.3}$ position (Figure 1). As we all know every human cells contains 23 pairs of chromosomes (total 46 chromosomes) except matured red blood cells. **(that's reason transfusion of red blood cells doesn't require HLA cross matching)**, any transplanted solid organ like heart/lung carries its inherited and unique HLA and that's why proper matching of HLA is paramount to avoid graft rejection. MHC are important not only for graft rejection but also for self-recognition and self-tolerance and even for graft resistance or tolerance.

The key MHC genes are: class I genes (HLA-A, -B, and –C genes) and the class II genes (HLA-DP, -DQ, and -DR).

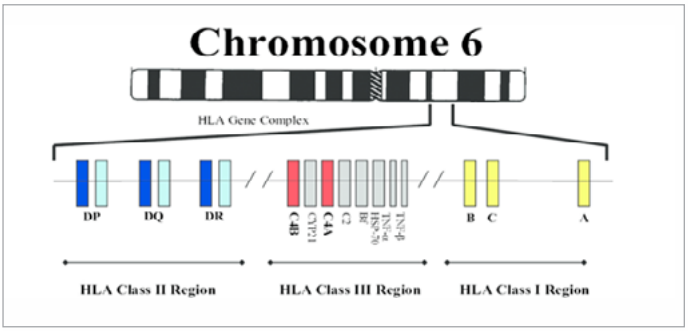

Figure 1: MHC/HLA gene complex on Chromosome 6

Figure 1 courtesy: Westover, Jonna & Sweeten, Thayne & Benson, Michael & Bray-Ward, Patricia & Torres, Anthony. (2011). Immune Dysfunction in Autism Spectrum Disorder. 10.5772/22318.

MHC-I is expressed on all nucleated cells (except RBCs) and present intracellular non-self-antigens to Killer (Cytolytic) CD8 T-cells for further activation of immune response against the presented antigen.

MHC-II is expressed only on antigen presenting cells (APC): dendritic cells, macrophages, and B cells. MHC-II is responsible from presentation of extracellular antigens to CD4 T helper cells for further activation of immune response against the antigen.

HLA is a gene complex whose alleles encode polymorphic cell surface glycoproteins which are involved in antigen recognition and presentation. HLA molecules are surface glycoproteins having a peptide-binding ability with their peptide-binding grooves. (figure 2). Depending on the genetic disparity between the donor and the recipient, graft and host HLA molecules present different peptides.

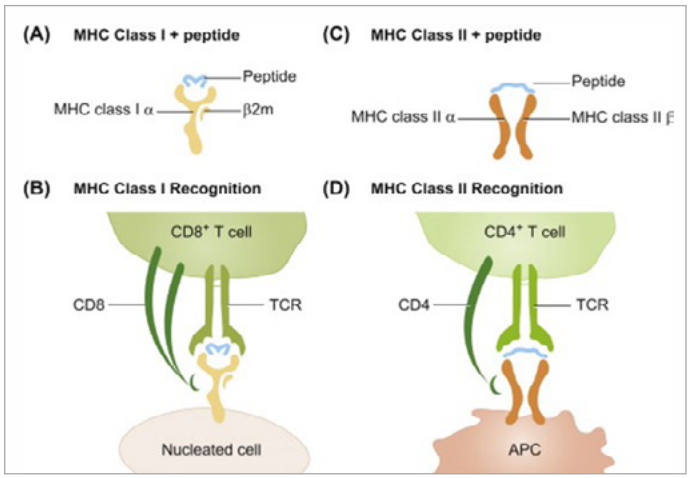

Figure 2: MHC class I and II with their binding with peptide (antigen) and presenting to T cells. TCR- T Cell Receptor, APC – antigen presenting cell

Figure 2 courtesy: Chapter 6 - The Major Histocompatibility Complex, Editor(s): Tak W. Mak, Mary E. Saunders, Bradley D. Jett, Primer to the Immune Response (Second Edition), Academic Cell, 2014, Pages 143-159

CLINICAL PEARL

The MHC class I and II molecules are the most immunogenic antigens that are recognized during rejection of allogenic transplants. The strongest antigen is HLA-DR, followed by HLA-B and then HLA-A. These 3 loci are therefore the most important for matching of donor and recipient and antibodies against these 3 HLAs can cause significant rejection and that donor should not be accepted. Antibodies against HLA-DP is not clinically significant.

Immunology of Transplant Rejection

Several types of rejection of vascularized organs can be defined according to their underlying mechanisms. The major types being hyperacute, acute, and chronic rejection. In allogeneic context and in the absence of

preformed anti-donor antibodies, cells and tissues are mainly rejected by acute cellular rejection mechanisms.

Hyperacute rejection appears in the first minutes following transplantation and occurs only in vascularized grafts. This very fast rejection is characterized by vessels thrombosis leading to graft necrosis. **Hyperacute rejection is caused by the presence of anti-donor antibodies existing in the recipient before transplantation.** These antibodies induce both complement activation and stimulation of endothelial cells to secrete Von Willebrand procoagulant factor, resulting in platelet adhesion and aggregation. The result of these series of reactions is the generation of intravascular thrombosis leading to lesion formation and ultimately to graft loss[7].

CLINICAL PEARL

- Today, this type of rejection is avoided in most cases by checking for ABO compatibility and by excluding the presence of anti-donor human leukocyte antigen (HLA) antibodies by cross-match techniques (CDC and FCXM) between donor graft cells and recipient sera. This type of rejection is also observed in models of xenotransplantation of vascularized organs between phylogenetically distant species when no immunosuppressive treatment is given to the recipients.
- **Acute rejection** is caused by an immune response directed against the graft and occurs between 1 week and several months after transplantation. Acute rejection is thought to result from two immunological mechanisms that may act alone or in combination: (1) a T-cell-dependent process that corresponds to acute cellular rejection, and (2) a B-cell-dependent process that generates the acute humoral rejection. With current immunosuppressive treatment, acute rejection occurs in less than 15% of the transplants in non-sensitized patients
- **Chronic rejection,** on the other hand, is now the leading cause of graft rejection. Chronic rejection can be mediated by either humoral or cellular mechanisms linked to memory/plasma cells and antibodies. The presence of tertiary lymphoid organs in the graft is a characteristic of this form of rejection.

Mechanism of rejection

Two major immunological mechanisms occur during allograft rejection:

1. Nonspecific innate response that predominates in the early phase of the immune response
2. donor-specific adaptive response that results from alloantigen recognition by host T cells.

1. The Innate Response – Inflammatory response

Although the adaptive response plays a central role in the mechanisms of allograft rejection, **early proinflammatory signals** (arising before the initiation of the T-cell response) are also considered as important factors of graft rejection[7].

Innate immune responses are the consequence of several events associated with clinical transplantation, such as ischemia-reperfusion injury and infections, and lead to the release and upregulation of various cytokines (ILs, macrophages, neutrophils, eosinophils), chemokines and ultimately activate the complement system and Nature killer cells directed cell killing. They also help boost and maintain the adaptive immune T-cell response.

CLINICAL PEARL

- Longer ischemia time, Marginal donors, recipients on MCS pre transplant, blood transfusions, Primary graft dysfunction all are associated with inflammation and can trigger the graft rejection by innate response.

2. Initiation of the Adaptive Response and Allograft Rejection

The adaptive immune response appears later than the innate response, its main characteristic being antigen specific. The initiation of the adaptive response is made possible by the presentation of alloantigens by APCs, mainly DCs and their allorecognition by recipient T cells. Three main pathways of allorecognition are described in the literature.

1. Direct Pathway
2. Indirect Pathway and
3. Combined direct and indirect pathway

Direct Pathway

Recipient's T cell recognizes donor's MHC (antigen) either directly by MHC present of donor tissue's cell or MHC carried by donor's APCs (antigen presenting cells). (Figure: 3) The transplanted organ carries a variable number of passenger APCs in the form of interstitial dendritic cells. The relative number of T cells that proliferate on contact with allogeneic or donor cells is extraordinarily high as

compared with the number of clones that target antigen presented by self-APC (indirect pathway).

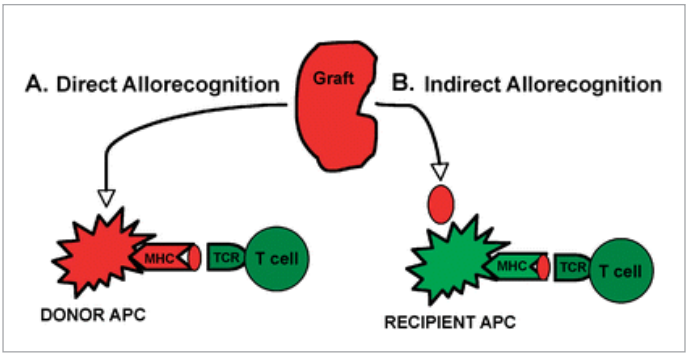

Figure 3: Direct and Indirect pathway of allorecognition

Figure 3 courtesy: Educational review, Mechanism of cellular rejection in transplantation by Elizabeth Ingulli, Pediatr Nephrol, 2010 : 25: 61-74

Indirect Pathway

In this pathway, recipient's circulatory APCs finds the donor's MHC complex/ peptides and these APC bind with these donor's MHC and then they process these MHC and then present to recipient's T cells. (Figure: 3). Three mechanisms of antigen delivery can be postulated to occur via this allorecognition pathway. **First,** antigens from the graft can be shed into the circulation and engulfed by recipient DC (dendritic cells – APCs) that reside within secondary lymphoid tissue. **Second,** donor cells can migrate to secondary lymphoid tissue where they are engulfed by recipient DC. **Third,** recipient APC can migrate into the graft, pick up antigens, and then migrate to secondary lymphoid tissue and ultimately stimulate T cells.

To Be continued...

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