Immunological Mechanisms of Allograft Rejection: Cellular and Molecular Insights

Ayesha Tariq[1], Rais Ahmed[1,*], Firasat Hussain[1], Ieman Tariq[1], Raheela Sarwar[2], Aisha Tahir[3], Aamna Amanat[4], Hamna Farooq[5], Abdul Moeez Qureshi[1] and Hafsa Munir[1]

[1]Department of Microbiology, Cholistan University of Veterinary and Animal Sciences, Bahawalpur
[2]Centre of Biotechnology and Microbiology, University of Peshawar, Peshawar
[3]Department of Biosciences, COMSATS University, Islamabad
[4]Department of Management Sciences, Bahria University, Lahore
[5]Department of Zoology, Superior University, Lahore
*Corresponding author: dr.raisahmad2068@gmail.com

Abstract

Allograft rejection poses a significant obstacle in the field of transplantation, arising from intricate immune mechanisms. Hyperacute rejection occurs almost immediately due to the presence of pre-existing antibodies that activate the complement system, causing inflammation and irreversible damage to the graft. Acute rejection is largely mediated by T-cell reactions against incompatible major histocompatibility complex (MHC) molecules, which leads to tissue inflammatory damage. Chronic rejection develops gradually, featuring changes such as vascular remodelling, fibrosis, and eventual failure of the graft. Various immune cells, including T lymphocytes, macrophages, dendritic cells, and natural killer cells, play crucial roles in this response. The recruitment and activation of immune cells are enhanced by chemokines and adhesion molecules. Additionally, the complement system and co-stimulatory signals amplify inflammation, worsening tissue injury. Recent insights into these mechanisms have led to the creation of targeted immunosuppressive therapies like monoclonal antibodies and co-stimulatory inhibitors, designed to prevent and manage allograft rejection more effectively. Emerging biomarkers, such as donor-derived cell-free DNA and specific gene expression profiles, present potential for early rejection detection and the customization of immunosuppressive treatments. Combining knowledge from molecular research with clinical approaches holds promise for improving graft longevity and overall transplantation outcomes.

Keywords: Allograft, MHC, DNA, Lymphocytes, NK cells.

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Introduction

Allograft rejection is the immunological response when recipient T cells identify alloantigens. This alloreactive response can be categorized into three sequential phases. The initial step involves the detection of alloantigens by T cells in the host. The second step encompasses the activation and growth of these alloreactive T cells. Finally, the third step, known as the effector phase, entails the process by which the transplanted tissue is destroyed (Le Moine et al., 2002). Throughout history, mythology has featured stories about beings formed from a mix of different creatures, often involving the transfer of body parts and skin. In the 1950s, faced with limited medical solutions for chronic diseases like nephritis, a collaborative effort among scientists, surgeons, and altruistic patients led to the pioneering of organ transplantation, starting with the first successful kidney transplant in humans in 1954 (Nordham & Ninokawa, 2022). Familiarity with the mechanisms behind allograft rejection can facilitate the development of enhanced management approaches that lower the risk of rejection and boost the success rates of transplants. Insight into the immune response enables healthcare professionals to customize immunosuppressive treatments for each patient, decreasing graft failure chances. Since patients can have varied reactions to immunosuppressive medications, a comprehensive understanding of allograft rejection allows for more individualized treatment strategies that reflect the unique immunological characteristics of each patient.

1. Types of Allograft Rejection

i. Hyperacute Rejection

HAR happens within minutes to hours following a transplant and is triggered by preexisting antibodies in the recipient's blood that target the donor's tissue. When these antibodies recognize the donor tissue, they activate the complement system, leading to an influx of neutrophils and triggering coagulation processes. The resulting inflammation and restricted blood flow cause irreversible damage to the graft. Fortunately, current screening methods for anti-donor antibodies effectively prevent most cases of HAR (Kloc & Ghobrial, 2014).

a) Mechanism of Action

HAR occurs within the first 48 hours following transplantation. This rapid response is triggered by cytotoxic antibodies targeting the donor's HLA or ABO antigens. HAR symptoms include high fever, swelling, activation of complement proteins, and issues related to blood coagulation. The coagulation complications arise from damage to endothelial cells, potentially leading to severe conditions such as heart attacks, strokes, pulmonary embolisms, and thrombosis. In the event of HAR, antibody-mediated rejection (AMR) takes place as antibodies induced by the donor's antigens attack, including those directed against ABO antigen carbohydrates, donor-specific HLA proteins, endothelial cell antigens, or surface antigens found on porcine cells. During this process, thrombus formation in blood vessels can cause injury to endothelial cells and disrupt normal blood flow (Kim, 2024).

b) Role of ABO and HLA Incompatibility

Both humoral sensitization to HLAs and ABO present significant immunological challenges in transplantation. The activation of B cells and plasma cells leads to the formation of donor-specific antibodies (DSA), which attach to HLA or non-HLA antigens on endothelial cells. This antibody binding triggers cellular activation through both complement-dependent and independent pathways, recruiting NK cells, neutrophils, and macrophages, all of which contribute to capillaritis and subsequent tissue damage. The structural manifestation of endothelial cell injury in acute AMR is characterized by platelet clumping, thrombotic microangiopathy (TMA), and a buildup of neutrophils, resulting in an initial pattern of cellular necrosis and a relatively swift deterioration in allograft function (Djamali et al., 2014).

ii. Acute Rejection

Acute rejection (AR) occurs due to differences in highly polymorphic HLA and is mainly driven by T cells. Upon activation, T cells release cytokines that attract inflammatory cells, ultimately resulting in the deterioration of the transplanted tissue. Currently, AR can be effectively managed using immunosuppressive treatments.

a) Mechanism of Acute Rejection

Without immunosuppressive therapy, transplant recipients have a vigorous immune response against the allograft, primarily due to T-cell recognition of foreign MHC proteins, referred as HLA in humans. Initially, donor dendritic cells within the transplanted tissue present foreign MHC to the recipient's T-cells through what is known as direct pathway. As these donor antigen-presenting cells (APCs) perish or are eliminated, recipient dendritic cells take over, processing and presenting the alloantigens to the T-cells via the indirect pathway.

The HLA genes are situated on the short arm of chromosome 6 and are categorized into two classes on basis of traditional criteria. The classical HLA class I genes consist of the A, B, and Cw loci found on nucleated cells. In contrast, the classical HLA class II genes include DR, DQ, and DP, normally expressed on B-cells, monocytes, dendritic cells, and other APCs, but may also be upregulated on a variety of other cell types in response to inflammatory signals (Fig. 1). The remarkable genetic diversity of HLA polymorphisms poses a significant challenge for transplantation, as discrepancies in HLA between the donor organ and recipient result in rapid recognition of the graft as foreign (Martinu et al., 2011).

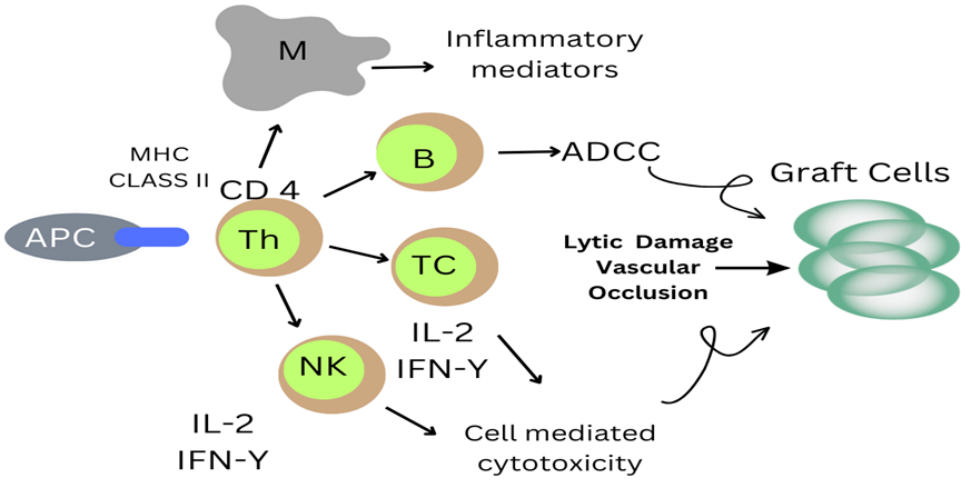

Fig. 1: Immunologic Mechanism of Acute Allograft Rejection (Retrieved from Canva Pro).

b) Clinical Signs of Acute Rejection

Clinical indicators like erythema or edema can be useful in identifying AR during the early stages following a transplant. However, it is unclear whether these signs continue to be dependable indicators of AR after the second year following the transplant (Haug et al., 2019).

iii. Chronic Rejection

Chronic rejection is a subtle and gradual process marked by the development of obstructive blood vessel changes and fibrosis in the tissue. This progression ultimately results in the gradual loss of function of the transplanted graft (Chalasani et al., 2004). CR typically occurs months to years following transplantation and is the primary reason for long-term graft failure. A key characteristic of CR is the rapid progression of arteriosclerosis or the narrowing of blood vessels in the graft known as vasculopathy or graft vascular disease. This condition is often associated with fibrosis in the graft tissue, leading to ischemia, cellular death, and ultimately, failure of the graft.

a) Pathogenesis of Chronic Rejection

Chronic allograft nephropathy (CAN) is a major cause of kidney transplant failure, ranking just after recipient death when the graft is still functioning. This condition is marked by a decline in renal function and the gradual replacement of kidney tissue with fibrotic material. While the exact mechanisms underlying CAN are not fully understood, it is believed to result from various factors operating both shortly after and long after the transplant procedure. Alloantigen-dependent processes play a major role in the onset of CR (Joosten et al., 2003).

b) Role of Macrophages

Transplanted organs contain macrophages from two primary sources those that are donor derived, which are present within the organ at the time of transplantation, and those that are recipient derived, which infiltrate the graft following the procedure. In the initial weeks after transplantation, the donor derived macrophages undergo proliferation, but their numbers gradually decrease in non-rejecting grafts over time.

Recent research examining the function of macrophages in chronic rejection has utilized a rat cardiac allograft model and non-invasive MRI techniques to monitor macrophages labeled with micron sized paramagnetic iron oxide particles. Findings indicate that the population of recipient derived macrophages increases as CR develops. Furthermore, sustained accumulation of these macrophages after the AR phase may serve as a marker for the onset of CR (Kloc & Ghobrial, 2014).

2. Cellular Mechanisms of Allograft Rejection

i. Direct Allorecognition: Donor APCs

Host T cells can identify MHC antigens through two distinct but related pathways. In the indirect pathway, donor MHC alloantigens, which can be either class I or class II, are internalized by recipient APCs. These cells process the alloantigens and subsequently present them as peptides derived from MHC to CD4+ T cells using the recipient's MHC class II molecules. This process resembles the normal function of APCs that constantly process soluble extracellular proteins (Figure 2).

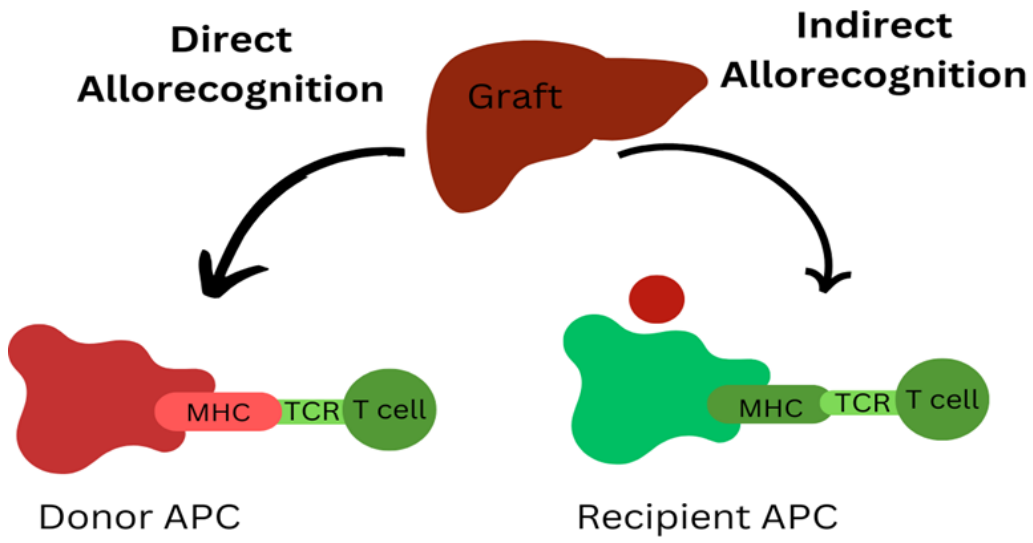

Fig. 2: Direct and Indirect Pathway of Allorecognition (Retrieved from Canva Pro).

Indirect Allorecognition: Recipient APCs

Conversely, the direct pathway of alloantigen recognition is specific to transplantation scenarios. In this case, the TCR recognizes an intact allo-MHC molecule present on donor cells directly. The TCRs of CD8+ T cells detect Allo-MHC class I antigens, while CD4+ T lymphocytes recognize allo-MHC class II antigens. Consequently, the T cell populations engaged in the direct versus indirect recognition of MHC alloantigens are entirely separate and do not overlap.

3. Activation of T Lymphocytes

i. Signal 1: Antigen Recognition

Transplantation presents a distinct immunological challenge where recipient T cells can be primed by three different mechanisms. The first mechanism is direct allorecognition, where recipient T cells use their TCR to engage with complete allogeneic MHC peptide complexes displayed by donor derived APCs, specifically dendritic cells. The second mechanism, indirect allorecognition, involves the processing of donor MHC or minor histocompatibility antigens by recipient APCs, which display derived peptides. In this pathway, the predominant antigenic peptides presented are those that come from the highly variable regions of allogeneic MHC molecules. The third pathway, semi direct allorecognition, occurs when host APCs capture MHC peptide complexes from donor cells. This process involves the transfer of membrane fragments between interacting cells, a phenomenon well established in cellular biology (Wood & Goto, 2012).

ii. Signal 2: Costimulatory Pathways (CD28, CTLA-4)

In untreated hosts, directly activated CD4+ T cells play a role in facilitating the production of alloantibodies and provide essential signals for the activation of CD8+ cytotoxic T lymphocytes, both of which can contribute to graft damage. Importantly, these activated CD4+ and CD8+

T cells decrease their levels of CD62L, a receptor involved in lymph node homing, while increasing CD44, a molecule associated with activation and adhesion. They then exit the secondary lymphoid organs and travel through the peripheral circulation, where they can encounter their specific antigens presented by the graft cells in the transplanted tissue. Although CD4+ T cells that specifically recognize donor antigens on donor cells are capable of causing acute graft rejection, there is some indication that the likelihood of this response may depend on their frequency (Heeger, 2003).

4. Effector Functions of T Cells

i. Cytotoxic T Cells (CTLs) and Apoptosis Induction

Apoptosis plays a major role in the process of allograft rejection, as observed in both animal studies and human transplant scenarios. Research conducted in vitro indicates that CTL is the main effector involved in alloreactivity. CD8+, CTLs can trigger apoptosis in target cells through two primary pathways: the perforin mediated granule exocytosis pathway and the Fas-mediated pathway. In the granule exocytosis mechanism, activation of the T-cell receptor leads to the discharge of lytic granules that contain perforin and proteases known as granzymes. Once the CTL makes direct contact with the target cell, perforin and granzymes are released into the space between the cells. When calcium ions (Ca^{2+}) are present, perforin proteins assemble to create pores in the target cell's membrane. This allows granzymes to enter and initiate the apoptotic process, including the fragmentation of DNA. Granzyme B, in particular, has demonstrated the ability to cleave and activate components of the caspase cascade, specifically caspases 3, 7, and 10 (Ogura et al., 2001).

ii. Helper T Cells (Th1 vs. Th17 Responses)

CD40 ligand (CD40L), also referred to as CD154 is a protein mainly found on activated Th1 cells and is part of the TNF-TNFR superfamily. It acts as a co-stimulatory molecule; when it binds to CD40 on APCs, it triggers T cells to secrete inflammatory cytokines such as TNF and IL-12. This interaction enhances the activation of APCs by increasing the expression of molecules like MHC, CD80, and CD86 on their surfaces. CD40 expression is also elevated in macrophages, dendritic cells, and B cells, creating a positive feedback loop that amplifies antigen specific signalling. Given the pivotal role of CD40L in Th1 immune responses, disrupting the CD40-CD40L pathway can hinder Th1-mediated inflammation. Research demonstrates that anti-CD40L monoclonal antibodies (mAbs) or genetic knockout of CD40L significantly improve graft survival and prevent acute rejection in both rodent and primate studies. Furthermore, anti-CD40L mAbs have shown efficacy when used alongside CTLA-4-Ig therapy and donor specific transfusions, contributing to immune tolerance (Abdoli & Najafian, 2014).

Th17 cells can initiate a rejection response in transplantation without relying on Th1 pro-inflammatory lymphocytes or the IL-17A cytokine. The CD28 co-stimulatory signal is essential for the differentiation of Th17 cells, just like it is for other helper T cell subsets. The administration of anti-CTLA-4 and CTLA-4-Ig, which enhance and inhibit the CD28 co-stimulatory signal respectively, results in either an increase or a reduction in Th17 cell differentiation.

5. Role of Natural Killer Cells

NK cells exist in various subpopulations, each with unique roles. In rodents, their subsets can be distinguished by the different expressions of killer cell lectin-like receptors (KLRs) that recognize MHC class I. Some of the KLR families are grouped within the NK cell complex (NKC) and include both inhibitory and activating members. NK cells that exhibit a combination of the inhibitory Ly49i2, the activating Ly49s3, and the inhibitory KLR subfamily H, member 1 (KLRH1) show a strong reactivity toward allogeneic target cells with foreign MHC class I in laboratory settings (Smelt et al., 2014).

6. Role of Chemokines in Immune Cell Recruitment

Chemokines were initially identified for their role in promoting the movement of white blood cells. Over time, this group of chemotactic cytokines has been recognized for its significant functions in regulating the recruitment, activation, and functioning of leukocytes. They also contribute to haematopoiesis, influence angiogenesis, and play important roles in adaptive immunity. In conditions of stress, such as within kidney transplants, cells generate increased levels of oxygen and nitric oxide radicals. This process release platelet activating factor and tumour necrosis factor, and also escalates the expression of adhesion molecules that facilitate the rolling and stable adhesion of leukocytes to the blood vessel lining. When leukocytes roll along this lining, their integrins and the endothelial cell adhesion molecules remain unactivated. Activated endothelial cells or those responding to platelet activation present specific chemokines that interact with the endothelial surface. The endothelium serves as an initial gatekeeper for leukocyte infiltration, as different types of endothelial cells have varying capacities to present specific chemokines. Consequently, chemokines displayed on the endothelial surface are crucial for directing and sorting leukocytes within the allograft tissue, promoting the activation of integrins on leukocytes, and ensuring their firm adhesion to the endothelium despite the shear forces in circulation (Nelson & Krensky, 2001).

7. Role of Dendritic Cells in Immune Cell Recruitment

Dendritic cells are specialized APCs that play an important role in triggering an acute immune response against transplanted organs. In their immature form, these cells are found in various peripheral tissues and organs, enabling them to effectively capture antigens. When they detect inflammatory signals, such as specific cytokines, they undergo a process of maturation and migrate to the lymph nodes, particularly to areas populated by naïve and central memory T cells. Unlike macrophages and B cells, dendritic cells are highly effective at stimulating naïve T cells due to their abundance of MHC molecules and costimulatory signals. Once T cells become activated, they move into the transplanted organ where they can identify foreign antigens present in the tissue. Over time, the donor's antigen-presenting cells diminish in number, and the immune response shifts to being led by recipient dendritic cells that enter the transplanted tissue, capturing antigens and presenting processed fragments to T cells through an indirect mechanism (Ingulli, 2010).

8. Role of Complement System

The role of the complement system in mediating injury, particularly in cases of chronic active AMR, remains a topic of debate. While earlier studies indicated that targeting C5 with treatments like the anti-C5 antibody eculizumab was effective in managing acute AMR, addressing chronic injury has proven to be more complex. Trials that focused on inhibiting the classical pathway, such as BIVV009, did not show significant improvement in microvascular inflammation or a reduction in markers associated with rejection. Moreover, the presence of C4d in capillaries, which suggests activation of the classical pathway, does not consistently align with graft dysfunction, particularly in cases of ABO-incompatible transplants. Additionally, numerous AMR instances do not show C4d deposition, hinting at the involvement of mechanisms that do not rely on complement activation. Although some research has linked ex vivo complement fixation by donor specific antibodies to transplant outcomes, it could be argued that complement fixation is more reflective of the strong antibody binding that leads to transplant injury through different pathways, such as the activation of natural killer cells via Fc receptor interactions (Diebold et al., 2024).

9. Immune Regulation in Allograft Tolerance

Immunological tolerance refers to a condition in which the immune system does not react negatively to specific antigens in the absence of any external immunosuppressive treatment, while still being able to respond to other antigens. The elimination of alloreactive T cell clones may play a vital role in achieving this tolerant state. However, sustaining peripheral tolerance over the long term is thought to rely on self-sustaining regulatory mechanisms that actively inhibit aggressive immune responses directed against foreign tissues (Sánchez-Fueyo et al., 2002).

10. Clinical and Therapeutic Implications

i. Immunosuppressive Therapies

The immune response against transplanted tissues can be suppressed by using immunosuppressive medications. Antithymocyte globulins (ATGs), derived from the serum of immunized horses or rabbits, are a type of polyclonal antibody that targets various T cell surface proteins. This action results in the inactivation and reduction of T cell activity, as well as modulation of their ability to migrate and exert cytotoxic effects. Moreover, ATGs also affect B cells, dendritic cells, and NK T cells.

Belatacept is a fusion protein combining a modified version of the extracellular domain of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) with the Fc region of human immunoglobulin IgG. It inhibits co-stimulation by binding to the CD80 and CD86 receptors on antigen-presenting cells preventing the interaction with CD28 on T cells. Belatacept is typically used alongside other immunosuppressive agents as part of a maintenance treatment regimen (Claeys & Vermeire, 2019).

ii. Role of Biomarkers

Numerous innovative biomarkers have emerged to evaluate allograft health, anticipate rejection before changes in GFR occur, and forecast long-term graft outcomes. However, a limited number are presently utilized in clinical settings. One promising early indicator of allograft damage and failure is the presence of donor derived cell free DNA in the bloodstream of transplant recipients. This indicator measures as a percentage of the recipient's total circulating DNA an increase in this fraction serves as a sensitive marker for allograft injury. Three assays utilizing next-generation sequencing technology namely Allosure, TRAC, and Prospera are commercially available and have been validated, proving particularly effective for the detection of acute cellular rejection. Additionally, a gene expression profiling based test called TRUGRAF has been validated for identifying subclinical rejection (Moll & Beilhack, 2024).

Conclusion

Grasping the intricacies of allograft rejection is vital for progressing in transplantation medicine. The rejection of allografts is a complex process featuring various immunological responses that unfold through different stages. Hyperacute rejection, which arises from pre existing antibodies, emphasizes the need for thorough pre transplant assessments to prevent immediate graft failure. Meanwhile, acute rejection is largely driven by T-cell responses, highlighting the critical role of precise immunosuppressive treatments to manage inflammatory processes. Chronic rejection poses significant difficulties due to its gradual development, which includes vascular changes, fibrosis, and eventual failure of the graft. The involvement of immune cells such as T cells, macrophages, dendritic cells, and natural killer cells, as well as key molecular processes like allorecognition and chemokine mediated cell recruitment, offers valuable insights into the rejection mechanism. New developments in biomarkers and immunosuppressive therapies including donor derived cell free DNA and targeted co-stimulation inhibitors have opened up novel avenues for earlier detection and more personalized treatment options. Looking ahead, a collaborative approach that integrates immunology, molecular biology, and clinical practice is crucial for reducing rejection rates and improving long-term graft success. Ongoing exploration of the immune system's complexities will lead to more effective and customized strategies, ultimately enhancing outcomes for transplant patients and fostering the overall progress of organ transplantation.

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