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Transplant immunology I: mechanisms of rejection in solid organ transplants

Abstract

Non-identical transplants (allogeneic) have been a modern medicine milestone; however, the major pitfall for completed succeed is the recognition of foreign organ by the immune system. The myriad variations in sequence of the molecules of the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) between individuals are the major cause of allograft rejection. Thus, the recognition by the B or T lymphocytes of the receptor occurs in the hypervariable regions of the HLA molecules that triggers to the graft 3 types of rejection: hyperacute, acute, and chronic. In addition, the rejection could be cause antibody-mediated (ABMR), T-cell-mediated (TCMR), or both, which depends on the main branch is cause of rejection. This review will explore the mechanisms mentioned above and give an introductory insight into transplant immunology; thus, preparer the reader to delve into further reviews in a Histocompatibility or Immunogenetics laboratory purpose.

Keywords: Donor specific antibody, antibody mediated rejection, T-cell mediated rejection, human leucocyte antigen

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Introduction

The immune system (IS) evolved into a complex and efficient machinery to recognize molecules from foreign of the self (antigens). Thus, our body can recognize and commonly eliminate the deleterious microorganisms and tumors cells with minimal damage to the host cells.[1,2] In 1960s, the discovery of highly polymorphic genes tightly clustered (loci) explained how the T cells elicit a specific Immune response against to foreign antigens (alloreactivity) in specific cells.[3-5]

The genes mentioned previously are termed as the Major Histocompatibility Complex (MHC) or Human Leukocyte Antigens (HLA) in *Homo Sapiens*. The molecule coded by MHC behaves as a platform for peptides processed the cells (antigenic presentation); thus, this allows the training of T lymphocytes for their selective recognition.[6] Solid organ transplants, unfortunately, follow the same principle of alloreactivity; therefore, a tissue graft eventually will be destroyed by the recipient's immune system (rejection). Depending on the timing of their development, the rejection has been classified in hyperacute, acute, and chronic.[7] This article will explore the immune response behind organ rejection; besides, the emphasis will be placed on some details of this rejection. This is important for the study in a histocompatibility or immunogenetics laboratory.

MHC role in the organ rejection

HLA region is located on the short arm of chromosome 6 and it is divided into several classes. Their proximity causes all loci undergo low recombination rates during meiosis (linkage disequilibrium), thus these genes are inherited as a haplotype.[8]

The quaternary structure of class I has been displayed as polypeptide (α chain) associated with β 2 microglobulin (non-polymorphic), which is coded in another chromosome. The HLA class I (A-C) appears in all nucleated cells; in addition, there are other loci expressed on few cells (E, F, G) with specialized functions. The loci A, B and C are the most polymorphic, also they usually display the antigenic presentation of endogenous peptides for CD8+ T cells. For that reason, A, B and to a lesser extent C are the most involved in the pathogenesis of graft rejection.[9,10]

The HLA Class II possesses the DR, DQ, and DP as heterodimer protein (α, β chains) for antigenic presentation of exogenous peptides for CD4+ T cells. However, there are individuals which carried more copies of the DR β chain gene (DRB3,4 and 5); hence it creates a greater combination of sets for antigen presentation. Likewise, HLA class II loci possess lesser polymorphic genes (HLA-DM, DO) with regulatory functions of antigenic presentation. Historically, the most important locus in graft rejection has been DRB; although new findings have revealed other loci play an important role in acute rejection and graft survival.[11-14]

Those polymorphisms in HLA molecules rise the chances to harbor differences alleles among individuals in a population. With the mentioned previously, the donor variable regions, different from recipient, can be recognized by recipient B cells. This recognition, therefore, produce donor specific antibodies (DSA) which have been involved in graft rejection due various effector mechanisms.[6,15]

On the other hand, there is a paradox of T cell recognition between self and foreign. T lymphocytes are trained by positive and negative selection in the thymus; thus, the identification only from recipient MHC molecules has been assumed.[16] Three mechanisms have been postulated to explain the recognition of allogeneic MHC by T cells.[17,18]

Direct recognition: It consists in the recognition of a donor antigen-presenting cell (APC) located in the transplanted organ, which migrates to the lymph nodes and interacts either with the allogeneic MHC-peptide or MHC itself with the recipient's T lymphocytes.

Indirect recognition: It involves uptake of donor cell debris by recipient APCs; this causes a processing of proteins to allogeneic peptides and carried out on their own MHC complexes. This mechanism has been seen important in the activation of B lymphocytes.

Semidirect recognition: The recipient antigen-presenting cells can capture vesicles of apoptotic debris from donor cells and expose intact allogeneic MHC-peptide complexes to T lymphocytes on their surface.

Hyperacute Rejection

With the origin of the immune response synthesized above, the types of rejection could be explained better. Hyperacute rejection

occurs very early after the organ graft; it has been caused by ABO antibodies or preformed DSAs (e.g., previous transfusions, pregnancies, or transplants) in the recipient. Those antibodies interact with cognate-antigens of the endothelial cells located in the transplant vessels. Thus, the union and activation of the complement cascade are launched, where the C3a and C5a residues have proinflammatory functions and lead leucocyte migration. By other hand, C4b2A3b complex accomplishes the assemble of the membrane attack complex and destroy the cell.[7,16,19]

As a result of the inflammatory process and endothelial injury, the coagulation cascade is promoted, which generates the formation of clots in the capillary vessels (microtrombosis) with their subsequent occlusion. Therefore, adequate oxygenation of the organ is impaired, and it causes necrosis. Given the speed of the pathophysiological mechanism, there is no treatment for hyperacute rejection. For that reason, the transplant evaluation including the ABO matching; as well as the detection DSAs against the HLA molecules and the assessment if they match the donor´s HLA alleles to avoid them.[20]

Acute Rejection

This type of rejection appears weeks or months after the organ transplant because it requires the sensibilization recipient´s immune system. To reach this, the activation innate system is essential. This occurs by releasing molecules from damaged cells during ischemia-reperfusion of the graft (inflammation), termed as damage associated molecular patterns (DAMPs). The event described before, allows the maturation of APCs, especially dendritic cells whom activating the adaptive immune system; therefore, it induces a lymphocytic infiltrate in the tissue.[21]

On the other hand, according with the pathological changes, the rejection could be classified by the branch of adaptive immune system is involved in the organ damage; nevertheless, it is important keep in mind that both are activated for the sensibilization.[22] Antibody mediated rejection (ABMR) is characterized by *de novo* DSAs development with the complement process triggering (detected by C4d deposits) as was described above. Moreover, there is other relevant effector mechanism in ABMR, the NK cells and to a lesser extent macrophages activation. Those leucocytes attack cells by function-dependent cytotoxicity (ADCC) in the endothelium of the transplanted organ (capillaritis and/or glomerulitis). In addition, migrating leukocytes release proinflammatory cytokines that amplify the damage and lead the arrival of more cells of the immune system.[18,23,24] According to the modern views, ABMR continues having the most important role in rejection and, due to the mechanism triggering, take together hyperacute and AMBR as a single process.[25]

Conversely, T-cell mediated rejection (TCMR) occurs when the recipient's T cells are activated against allogeneic peptides or allogenic HLA-peptide complexes as described previously. This interaction allows the differentiation of CD4+ lymphocytes into a Th1 subset, which produce INF-ɣ and activation of cytotoxic CD8+ lymphocytes (CTL) for the induction of cell apoptosis (caspase mediated) in the tubular and arteriolar zone. CTLs exert their function mediated whether Fas-Fas ligand union or by granzymes releasing to the target cell.[16] In addition, there is evidence that a percentage of cases in kidney (around 30%) both branches directly cause graft injury. According with Banff classification, this type of rejection is termed borderline.[22,26]

Nowadays, the acute rejection has been managed with immunosuppressive treatment (e.g., calcineurin inhibitors). However, on some circumstances, such non-adherence to treatment, more aggressive drugs should be placed by the physician. Nonetheless, the continuous biochemical follow-up and detection of *de novo* DSAs in the recipient is required for differential diagnosis of acute rejection from other pathologies and establish the correct management.[27] Therapeutic approach is more extensive than described previously; it shall be studied for further reviews.

Chronic Rejection

In this case, there is a combination of immune and non-immune mechanisms (e.g., cytotoxicity to calcineurin inhibitors). Histologically, rejection is characterized by hypertrophy of the smooth muscle cells of the capillary vessel wall and presence of scar tissue (fibrosis) at the interstitial level. This process leads gradual occlusion of the capillary vessel, glomerulopathy and tubular atrophy in kidney transplants. In the heart and lung transplant chronic rejection has been described obliterating vasculopathy (obstruction of the vessel lumen) and *Brochiolitis obliterans* syndrome, respectively.[28-30]

From the immune perspective, the graft undergoes delayed hypersensitivity response (DTH) and repeated episodes of acute rejection caused by HLA and non-HLA DSAs (autoimmune manner) such as Anti-MICA (MHC peptide-related sequence A) or anti-ATR1 (angiotensin II receptor 1). These events induce interstitial scar formation, smooth muscle cells proliferation and the activation of the endothelium on the vessel which produce his occlusion. Furthermore, the activation of endothelium triggers growth factors onset (PDGF, TGF-β) that induce the myofibroblasts development into *tunica intima* and cause fibrosis into arterioles.[16,31,32]

Additionally, this type of rejection could be showing a lymphoid tissue in the graft (tertiary lymphoid tissue), which creates its own nodules with anti-donor specific B and T cells. However, depending on the resident population (e.g., Tregs), the tertiary lymphoid tissue also plays a role in tolerance of graft.[33] Finally, there is no effective treatment for chronic rejection, and it is major the cause of poor graft survival many years after the transplant.[31]

Conclusion

Understanding of transplant rejection mechanisms and development of its treatment to avoid them have been a modern medicine succeed. However, as detailed in this review, the immune response against the graft still having issues to resolve. Consequently, a series of tests have been developed in the histocompatibility or immunogenetics laboratory to prevent hyperacute rejection and monitoring *de novo* DSAs after engraftment. The typing of the donor/recipient haplotype, the physical/virtual crossmatch, as well as studies at different sensitivities and specificities of DSAs are examples of current analyses for guaranteed transplant safety.[34] The study of these tests will be addressed in a second part of the Transplantation immunology review.

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Conflicts of interest

The authors declares that there is no conflict of interest.

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