

Old game, new players: Linking classical theories to new trends in transplant immunology

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Abstract

The evolutionary emergence of an efficient immune system has a fundamental role in our survival against pathogenic attacks. Nevertheless, this same protective mechanism may also establish a negative consequence in the setting of disorders such as autoimmunity and transplant rejection. In light of the latter, although research has long uncovered main concepts of allogeneic recognition, immune rejection is still the main obstacle to long-term graft survival. Therefore, in order to define effective therapies that prolong graft viability, it is essential that we understand the underlying mediators and mechanisms that participate in transplant rejection. This multifaceted process is characterized by diverse cellular and humoral participants with innate and adaptive functions that can determine the type of rejection or promote graft acceptance. Although a number of mediators of graft recognition have been described in traditional immunology, recent studies indicate that defining rigid roles for certain immune cells and factors may be more complicated than originally conceived. Current research has also targeted specific cells and drugs that regulate immune activation and induce tolerance. This review will give a broad view of the most recent understanding of the allogeneic inflammatory/tolerogenic response and current insights into cellular and drug therapies that modulate immune activation that may prove to be useful in the induction of tolerance in the clinical setting.

Key words: Transplant immunology; Immune rejection; Inflammation; Adaptive immunity; Innate immunity; Graft

tolerance

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Core tip: Although the basic mechanisms of transplant allorecognition have been the object of intense study for the last 80 years, graft rejection is still an important obstacle in clinical practice. This review focuses on the principal concepts of transplant immunology and how they apply to the most recent discoveries in the field. It also reviews current treatments used to prolong graft survival and recent approach trends toward tolerance induction in the translational setting.

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INTRODUCTION

Although the first attempts at organ and tissue transplantation date to many centuries ago, knowledge of the underlying principles that orchestrate the immune response to this surgical procedure only began to be understood in the mid-twentieth century. Initial studies by Medawar and Gibson in the 1940's showed that allogeneic skin rejection resulted from a response of the recipient to the graft^[1,2], and years later, further studies demonstrated the characteristics mediated by cells in this response^[3,4]. Since then, great advances have surged as further studies determined the role of different components of the immune system, such as antibodies, antigen-presenting cells (APCs) and T lymphocyte subpopulations, in allograft rejection and tolerance. Nevertheless, rejection is still the main barrier to the success of transplantation, and the development of agents that interfere with the alloimmune response and graft rejection has played a crucial role in the success of organ transplantation. This review will discuss the basic mediators that determine graft rejection and focus on the current immunobiology underlying transplantation research in this area.

ALLOANTIGENS

Major histocompatibility complex/human leukocyte antigens and non-human leukocyte antigens

Classically, transplantation is classified into four categories according to the origin of material to be grafted: Autologous, syngeneic, allogeneic or xenogeneic. Autologous transplantation occurs when cells, tissues or organs originate from the same individual, or in other words, a patient's own tissue or organ is transferred. Syngeneic transplantation, in turn, occurs between two

syngeneic or genetically identical individuals. A third type, which is the most common in the clinical setting, is allogeneic transplantation, which is performed between individuals of the same species that are genetically different, while xenogeneic transplantation occurs when the donor graft originates from a different species of the recipient.

The immune system has the intrinsic ability to distinguish between self and foreign (non-self) antigens, which allow it to develop a response against foreign organisms in order to destroy them. Specifically, in the context of transplants, this capacity is termed allorecognition and refers to the phenomenon by which the recipient's immune system recognizes and reacts against donor antigens^[5-7]. Thus, the transplantation of tissues or cells between genetically different individuals invariably triggers an immune response that may manifest itself as rejection depending on the magnitude of this response^[8-10].

The success of solid organ transplants depends fundamentally on the control of the immune response to foreign molecules that differ among the same species, better known as alloantigens. Currently, a variety of relevant antigens have been described in the context of transplantation, including major histocompatibility complex (MHC) molecules, minor histocompatibility antigens (mHAg), ABO antigens and endothelial/monocytic cell antigens.

In 1950, Snell^[11] and Gorer^[7] characterized and determined various antigens responsible for rejection not only in allogeneic tumors but also in healthy allogeneic tissue. Because they were the first antigens discovered regarding the rejection process, these were termed the MHC and are currently known to be the main targets of immune recognition of the surface of donor cells.

This group of genes is common among all vertebrates, and it has an important role in the immune system, mainly in determining the biological identity of individuals. In humans, it is termed human leukocyte antigen (HLA), and it is contained in the short arm of chromosome 6, which is a large chromosomal region with more than 200 coding loci. Based on structural and functional differences as well as on tissue distribution, the HLA products have been divided into three classes (I, II and III), with only classes I and II encoding HLA surface antigens, whereas class III encodes the components C2, C4 and factor B of the complement system^[12-14]. These antigens are encoded by different genes inherited from both parents, which are expressed in a codominant fashion^[15]. In addition to this, HLA surface antigens are extremely polymorphic^[14], which contributes to numerous possible combinations and explains the difficulty in finding close compatibility between individuals. These codominant polymorphic genes influence, among other things, how the immune system responds to the graft recipient. Considering the differential immunogenicity of HLA mismatches observed in epidemiological studies^[16], there are some acceptable mismatches, in which the recipient immune system could only weakly react to the donor, enabling longer graft survival. A greater impact of

HLA-DR, HLA-A and HLA-B antigens has been observed in renal graft rejection^[17], with a much larger effect of DR matching than the others^[18,19]. Retrospective analysis of graft survival data also showed that certain HLA mismatch combinations are linked to increased allograft rejection^[16,20].

MHC molecules play a critical role in the immune system, which corresponds to the presentation of peptides in a form that allows them to be recognized by T cells. Their highly polymorphic genes encode for cell surface receptors that have a central role in the control of immune recognition of self and non-self as well as subsequent tissue rejection, autoimmunity and immune responses to infectious diseases. Among all genes included in this region, two highly variable groups (MHC class I and class II) with differences in structure and presentation function are central in allorecognition.

In humans, MHC class I molecules have three loci (HLA-A, HLA-B and HLA-C) and their products result in the classical class I molecules, which are expressed codominantly on all nucleated cells. Structurally, these molecules are formed by a heavy α chain (domains $\alpha 1$, $\alpha 2$ and $\alpha 3$), which is non-covalently associated with a light chain ($\beta 2$ -microglobulin) encoded by a gene located on chromosome 15^[12]. These molecules have a groove formed by domains $\alpha 1$ and $\alpha 2$, to which endogenous peptides with length of 8 to 11 amino acids from the cytosol, intracellular parasites or tumors are attached, allowing their presentation on the cell surface of MHC class I-expressing cells, especially to cytotoxic CD8⁺ T cells^[21-23] (Figure 1).

MHC class II molecules, which are encoded by three polymorphic genes (HLA-DR, HLA-DQ and HLA-DP), are constitutively expressed only on APCs, such as macrophages, dendritic cells (DCs), B cells and also thymic epithelial cells, although they may also be induced in other cells such as fibroblasts and endothelial cells under specific stimuli^[12]. These molecules consist of a non-covalent association of the α and β polypeptide heterodimer chains, which are encoded by genes of the HLA-D region. Moreover, on class II molecules, the groove region consists of the $\alpha 1$ and $\beta 1$ domains, and it is slightly larger than in class I molecules, allowing the binding of peptides between 13 and 18 amino acids. These molecules present exogenous peptides (*via* the endosome) on the surface of APCs^[24], especially to helper CD4⁺ T cells^[21-23] (Figure 1).

The MHC is the densest region of the human genome, and it is also one of the most variable, contributing to differences among individuals in immune responsiveness. It is well-known that MHC variants confer susceptibility to many chronic inflammatory and autoimmune conditions, including multiple sclerosis, type I diabetes and Crohn's disease, as well as infectious diseases such as malaria and HIV^[25-27]. Analysis of MHC variants has facilitated the localization of susceptibility loci for autoimmune diseases; however, for most genetic diseases, the specific loci involved remain undefined, and

the mechanisms underlying the association of the MHC in autoimmune diseases remains poorly understood.

In 1994, a new group of polymorphic genes located near the HLA-B locus on chromosome 6, termed MHC class I chain-related genes (*MIC* genes), was described^[28]. Only two members of the *MIC* gene family encode functional proteins, MHC class I chain-related protein A (MICA) and B (MICB), which are highly polymorphic^[29]. The expression of these genes are induced by stress, encoding cell-surface glycoproteins that do not associate with $\beta 2$ -microglobulin and are unable to bind peptides for presentation to T cells^[30,31], in contrast to MHC class I molecules. MIC antigens bind to the NKG2D receptor present on NK cells, $\gamma \delta$ and CD8 T lymphocytes^[29,30], resulting in a cytotoxic response against cells expressing these MIC genes^[32]. Moreover, the expression of the *MIC* gene family in an allograft can generate anti-MIC antibodies, which can lead to cell destruction and progressively to graft failure, as observed in renal allografts^[33-35].

Several molecules encoded outside the MHC loci, such as the CD1 family, are structurally and functionally similar to classical MHC molecules and are therefore termed MHC-like molecules. The CD1 family consists of five glycoproteins coding for MHC-like molecules that associate with $\beta 2$ -microglobulin but have a deeper groove that is more hydrophobic than classical MHC molecules; this hydrophobic groove binds to lipid fragments and glycolipid antigens^[36,37]. These molecules can present endogenous or exogenous lipid antigens to natural killer T (NKT) cells *via* the CD1d isoform. NKT cells are essential for cornea allograft survival because they are required for the induction of allospecific T regulatory cells^[38]. Furthermore, human CD1d has been identified as a transplantation antigen that mediates a transplantation rejection response in a skin graft mouse model^[39].

Acute and hyperacute rejection^[40-42] may also occur in the absence of detectable HLA antibodies, suggesting that non-HLA molecules also play roles in rejection. One of these are mHAg^[43], which are peptides presented by MHC class I and II molecules with discrete polymorphisms and considerable allogeneic properties^[44]. These antigens were initially characterized to possess a weaker potential to induce rejection in comparison to MHC antigens, although it has been shown that in MHC-compatible transplanted tissues, recognition of mHAg^[43] may also lead to early rejection. This may result from the principle that any polymorphic protein within a species can become a mHAg, thus expanding the possible number of mHAg between non-identical individuals with compatible MHC. Nevertheless, mHAg-related rejection appears to be restricted to only some immunodominant epitopes^[44,45]. Although the molecular basis of this phenomenon is not completely understood^[46], these antigens may be encoded by sex chromosomes (the most widely studied are present in the Y chromosome), autosomal chromosomes (with various origins, such as myosin and the *BCL2A1*

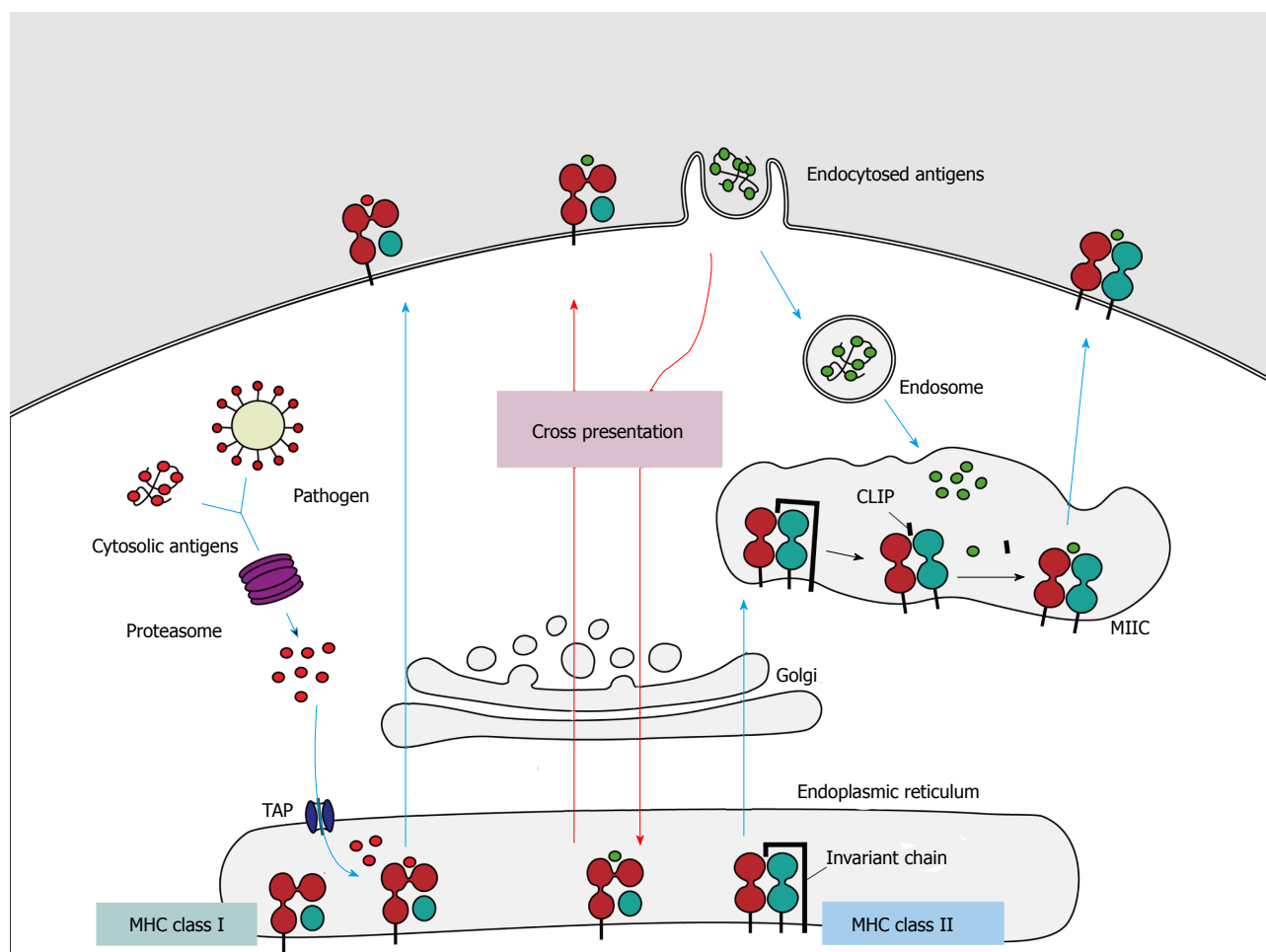


Figure 1 Major histocompatibility complex class I and II pathways. (1) MHC class I molecules present peptides derived from proteins presented in the cytosol of endogenous or pathogen origin. The proteasome breaks down these proteins into peptides, which are then translocated to ER by the transporter associated with antigen processing (TAP) to access the MHC class I molecules. In absence of peptides, MHC class I molecule is stabilized by ER chaperones (calreticulin, PDIA3, PDI and tapasin), but when peptides with sufficient affinity bind to class I molecules, these chaperones are released and the peptide: MHC complex leaves the ER for presentation on cell surface of CD8⁺ T cells; (2) MHC class II molecules present peptides derived from proteins that enter the cell through endocytosis. The chains α and β are assembled in the endoplasmic reticulum associated with the invariant-chain (Ii) to prevent binding of endogenous proteins. This complex (MHC:II) is translocated to MHC class II compartment (MIIC) where Ii is degraded to class II-associated invariant chain (CLIP). In the MIIC the MHC class II molecules acquire HLA-DM to facilitate the exchange of CLIP to specific antigen derived from degraded protein on the endosomal pathway, thus the complexes are transported to the plasma membrane to present the peptide to CD4⁺ T cells; (3) Cross presentation involves dendritic cells with the unique ability to present exogenous antigens via MHC class I (by a mechanism not completely understood). MHC: Major histocompatibility complex.

and *LBC* oncogenes), and ultimately, mitochondrial DNA^[47-50]. Additionally, immunity against these antigens is a significant clinical problem, as evidenced by the need for immunosuppression, even in the setting of HLA-identical transplantation, and the incidence of graft-vs-host disease (GVHD) following HLA-identical stem cell transplantation^[51].

In addition, there are many other non-HLA antigenic determinants that are expressed on endothelial cells and monocytes that may also be potential targets in allorecognition^[33], and non-HLA antibodies reactive with these cells appear to have a deleterious effect in several transplant models^[46,52-54]. Moreover, ABO incompatibility arising from differences between the antigens of the ABO system, in turn, has less relevance in graft survival, but may also result in the hyperacute rejection of vascularized grafts such as kidney and heart grafts^[55,56].

ANTIGEN PRESENTATION IN TRANSPLANTATION

Antigen presentation is the primary component linking the innate and adaptive immune systems. It does so by permitting lymphocytes to establish effective immune surveillance of their environment through APCs and consequently mounting strong cellular and humoral responses. Nevertheless, this same process, which is essential for the detection of pathogens and potential tumor cells, is also responsible for the recognition of allogeneic antigens in a transplant setting. Thus, the allospecific immune response is mediated mainly by recipient lymphoid cell adaptive responses, which are orchestrated by T and B cells specific for MHC

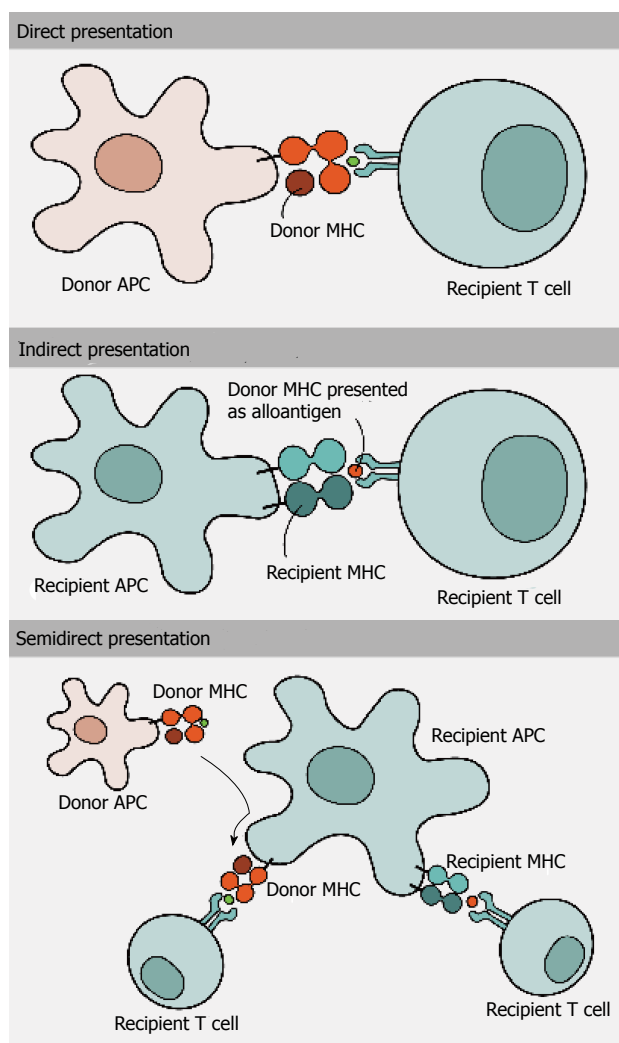


Figure 2 Antigen presentation and allorecognition. T cells can recognize alloantigens by three different pathways of allorecognition: (1) Direct pathway involves the recognition of intact donor MHC molecules on the cell surface of donor APCs by recipient T cells; (2) In contrast, in indirect pathway donor MHC molecules are processed and presented as peptides by recipient MHC molecules to recipient T cells; and (3) Semi-direct pathway, in turn, involves the transfer of intact donor MHC molecules to recipient APCs, being presented to recipient T cells. MHC: Major histocompatibility complex; APCs: Antigen-presenting cells.

alloantigens expressed by the donor.

To achieve appropriate naïve T cell activation responses, a series of sequential signals are required consisting of: (1) T cell receptor (TCR) recognition; (2) costimulatory molecule signaling; and (3) cytokine activation. Each T lymphocyte has a unique and highly specific TCR on its surface that binds to the peptide-MHC complex on APCs, allowing their recognition as self or non-self. In the context of transplant rejection, this occurs as T cells specific for MHC antigens recognize foreign MHC-peptide complexes, which elicit a highly efficient response. Indeed, it is estimated that the frequency of alloreactive precursor T cells may be up to one thousand times greater than that of common antigens, demonstrating the efficiency of allogeneic immune responses^[57]. If a lymphocyte recognizes the complex as non-self, it then

becomes activated and begins to proliferate, adopting effector and memory functions that contribute to the response against the graft, which are detailed further in later sections.

B cells also play a major role in adaptive responses by producing antibodies directed against the graft. In this case, antigen presentation occurs when B-cell antigen receptors (BCRs), which consist of cell-surface immunoglobulins, recognize antigens either directly or through MHC presentation. Importantly, in the first setting, direct recognition induces antigen internalization and consequent MHC class II-peptide presentation to T cells, which in turn, along with co-stimulatory activation, drives B cell differentiation into antibody-producing plasma cells and memory B cells^[58-60].

Allogeneic MHC molecules may be presented for recognition by TCRs via four fundamentally different, though not exclusive, pathways and thus may be involved in mediating allograft rejection simultaneously or in different contexts^[51] (Figures 1 and 2). With direct presentation, recipient alloreactive T cells are directly activated after the recognition of allogeneic/non-self intact MHC class I and II molecules on the surface of donor APCs^[5,61-63]. The presence of APCs in transplanted donor tissue dictates a strong anti-donor response early after engraftment, which decreases over time due to the eventual death and removal of these donor APCs^[64]. Indirect presentation, on the other hand, involves the capture and processing of allogeneic MHC class I and II donor molecules by recipient APCs^[65,66], generating small peptides that are later presented by MHC class II molecules. This presentation results in alloresponses led by CD4⁺ T cells^[67,68] and corresponds to slower responses than those generated via the direct route. The lower frequency of T cells with indirect allospecificity (compared to direct) in the normal repertoire suggests that the direct response dominates the early post-transplant period, while the indirect response develops a role in long-term alloantigen presentation, when donor APCs are already dead^[69-71]. Semi-direct presentation, in turn, comprises the interaction between the recipient T cells and APCs, involving the exchange of intact peptide: MHC complexes by direct cell-to-cell contact^[72-74] or by the release of small vesicles called exosomes^[75,76]. Thus, the recipient APCs are able to present alloantigens directly to recipient T cells, allowing donor MHC and self MHC with donor peptide to be presented on the surface of the same cell. Even so, the precise role of this type of allorecognition in transplant rejection and tolerance remains to be fully elucidated^[10].

The fourth type of presentation, cross-presentation, results from the ability of certain APCs to carry peptides that are derived from exogenous antigens on MHC class I molecules, an atypical characteristic, as endogenous antigens are commonly expressed on class I molecules and exogenous are expressed on class II. This type of presentation allows responses to pathogens that do not infect directly or replicate little within the APC^[77]; however, this mechanism is not

exclusive of infectious diseases, and the efficient priming of CD8⁺ T cells can occur after allogeneic transplantation as a consequence of cross-presentation of proteins derived from the donor by the recipient DCs^[78].

ALLOGENEIC REJECTION: THE CLASSICAL VIEW

Rejection can be divided into three main types: Hyperacute, acute or chronic, according to the cells and mechanisms involved in tissue damage and the consequent time course of graft loss.

Hyperacute rejection occurs due to the presence of preexisting antibodies towards graft antigens, caused by previous sensitization, which occurs in blood transfusions, organ transplant or even pregnancies. This recognition usually happens as soon as the organ is perfused, and widespread vascular injury associated with thrombosis prevents blood flow, leading to tissue necrosis and consequent graft loss within minutes to hours after the transplant. Nevertheless, this type of rejection is rarely observed in modern medicine due to pre-transplant CDC crossmatch exams that preemptively detect receptor reactivity to donor antigens.

Acute and chronic rejection are more difficult to prevent and less predictable. Acute rejection happens in the first weeks after transplant and is mainly associated with direct antigen presentation pathways, which activate CD4⁺ T lymphocytes to produce cytokines that amplify inflammation, and CD8⁺ T lymphocytes, which differentiate into cytotoxic cells upon activation and mediate direct graft cell destruction. These, in turn, also promote monocyte activation at graft sites, which also mediates the balance between tissue damage and repair^[79-81].

Moreover, as donor APCs disappear with time, chronic rejection is mainly driven by indirect antigen presentation, where graft antigens are presented by recipient APCs^[82,83]. In parallel, various studies also indicate that initial ischemia/reperfusion injury plays an important part in chronic graft rejection, and with time, together these factors ultimately culminate in a particular type of immune activation that causes progressive arterial damage and tissue fibrosis^[84,85].

All these types of rejection simply establish a didactic form of characterizing the complex and often concomitant forms of graft rejection. The following portion of the review will approach the main cells mediating the sensitization and effector phases of graft rejection, focusing on the most recent data in literature.

ALLOGENEIC REJECTION: AN UPDATED VIEW

Innate immunity in graft rejection

Since the beginning of transplant immunology, scientists have always focused on the adaptive mechanisms responsible for graft rejection and immunological memory, and until recently, little emphasis has been placed on the role of innate cells in allogeneic transplantation. Nonetheless, more recent research has noted that innate

immune cells have a crucial role in triggering initial signals in transplant rejection and play an active role in establishing tolerance in transplantation (Figure 3).

The first immunological trigger to unfold during transplantation is almost always of innate origin due to the inevitable physical and ischemia-reperfusion (I/R) injury to solid organs during transplantation in addition to common conditioning regimens, such as chemotherapy, before bone marrow transplantation (BMT). This is particularly important, as it is responsible for the initial activation of innate cells and maturation of APCs to efficiently present antigens to T cells. These signals are expressed as damage-associated molecular patterns (DAMPs), such as heat shock proteins, heparin sulfate and reactive oxygen species (ROS), and activate pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), leading to innate cell activation. These cells, in turn, secrete cytokines and chemokines such as TNF- α and IL-6, which give way to a cascade of events that amplify inflammation and attract further immune cell infiltration. Moreover, some reports have even suggested that innate cells may be able to distinguish allogeneic antigens, putting into question the lasting paradigms that divide the innate and adaptive responses^[86,87]. This idea is defended by reports showing differential, memory-like recognition of alloantigens in RAG^{-/-} mice. Some of these reports suggest that NK cells may participate in this phenomenon, showing that these cells develop a stronger IFN- γ response to a secondary stimulus^[88]. NK cell-independent recall responses have also been shown in these mice, suggesting that other innate immune cells may also play a bigger role in adaptive immunity than first imagined. Nevertheless, recent research has also suggested that this recognition alone is insufficient to initiate alloimmunity, indicating that effective rejection can take place even in the absence of an innate response^[89,90].

As cited previously, lymphocyte activation depends not only on an appropriate peptide presentation to antigen-specific T lymphocytes but also on the presence of efficient co-stimulatory signals. Therefore, there are two main signals needed for T cell activation: A first signal, involving antigen-specific MHC-peptide complex interaction to TCR molecules present in T cells, and a second signal, which consists of antigen-non-specific co-stimulation receptors on APCs and T cells that in turn drive intracellular activation signals with IL-2 production, T cell differentiation and survival. The basic literature usually describes main APC co-receptors such as B7 (CD80 and CD86), which interact with CD28 on T cells. However, a diverse number of other co-receptors are also known to have positive and negative effects on T cell activation (Figure 4), acting simultaneously at the immune synapse to effect cell activation or inhibition. The majority of known receptors belong to the immunoglobulin superfamily (IgSF) or the tumor necrosis factor receptor superfamily (TNFRSF), including OX40, CD40 and 4-1BB. Without the appropriate stimuli, T cells become anergic or enter apoptosis, and thus, these molecules are important targets

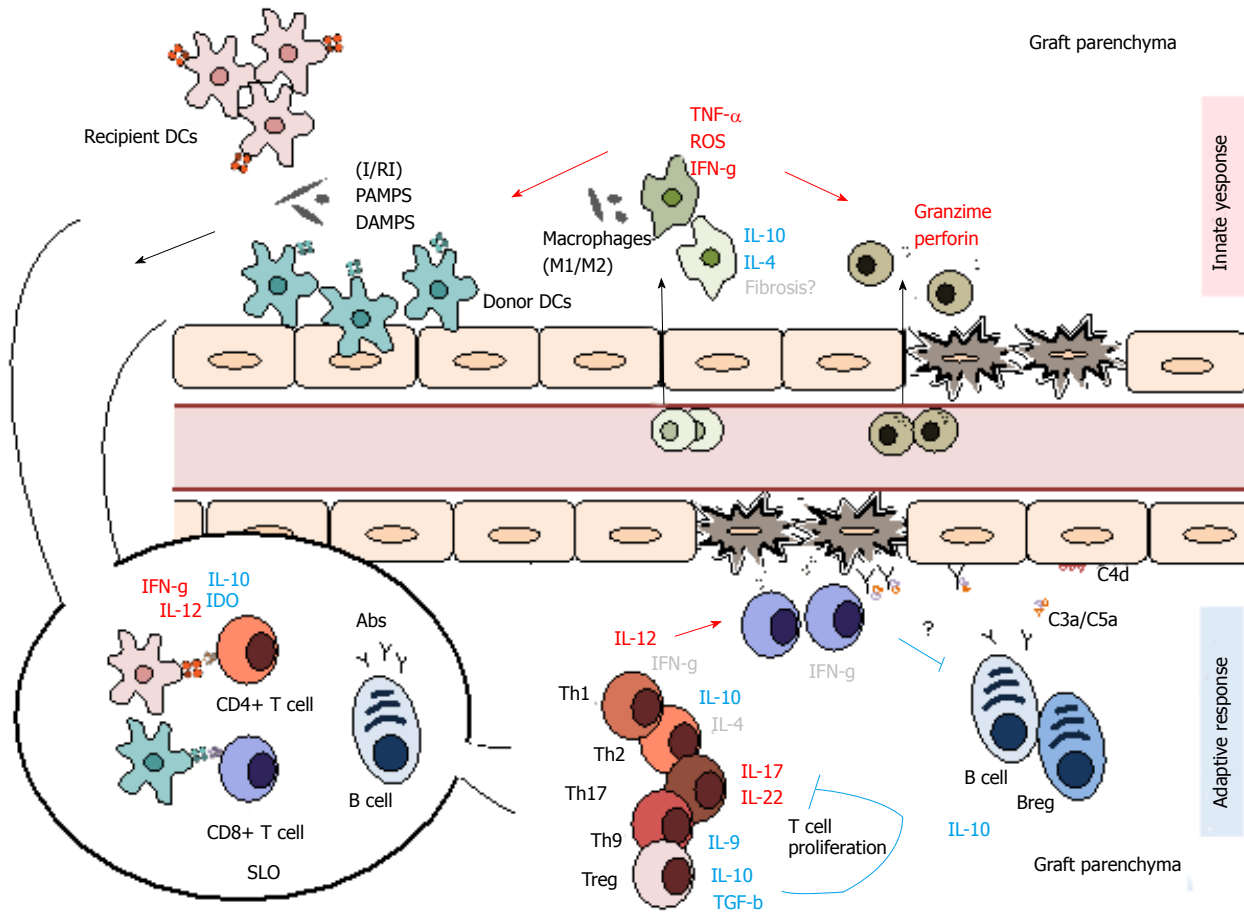


Figure 3 Summary of the main innate and adaptive mediators of graft rejection. Alloimmune rejection is a multifaceted process that involves both innate and adaptive mediators. Initial tissue damage is mostly mediated by innate participants as macrophages and NK cells along with dendritic cells, which link the both innate and adaptive responses. With time, these gradually give way to more adaptive mediators as T and B lymphocytes and antibody production. I/R: Ischemia/reperfusion injury; PAMPs: Pathogen-associated molecular patterns; DAMPs: Danger-associated molecular patterns; IDO: Indoleamine 2,3-dioxygenase; Abs: Antibodies; DC: Dendritic cells; SLO: Secondary lymphoid organ; ROS: Reactive oxygen species; TNF: Tumor necrosis factor. Mediator roles are represented in red (pro-inflammatory), blue (regulatory) and grey (indetermined).

for immunosuppression and cancer therapy, which will be detailed further on. Moreover, many different cells, such as DCs, macrophages and even B-lymphocytes, serve as APCs, as they all express both MHC and co-stimulatory molecules. These cells are considered professional APCs, and each have important roles in different contexts of graft allorecognition. It is also important to highlight that non-APCs also regulate lymphocyte activation, as is the case for apoptotic cells that express phosphatidylserine^[91-94].

Macrophages

Macrophages are also important mediators of graft rejection, playing a part in antigen presentation and tissue inflammation and damage. These cells have been suggested as predictors of graft failure and are considered by some researchers to be even more reliable predictors than T cell infiltrates^[95,96]. Macrophages originate from circulating monocytes, which infiltrate the graft due to multiple chemotactic factors and receptors, such as monocyte chemoattractant protein-1 (MCP-1), macrophage colony-stimulating factor (M-CSF)^[97-100], and CX3C chemokine receptor 1 (CX3CR1). Some of

these molecules have also been linked to kidney graft infiltration^[101,102], differentiating into active mature cells that promote tissue injury. Accordingly, some studies even suggest a central role for CD68 monocytes in allograft dysfunction^[103]. Studies assessing the preoperative Campath-1H (Alemtuzumab) treatment of renal recipients demonstrate the effects of monocytes in mediating acute rejection. Because Campath-1H depletes more T lymphocytes than monocytes, this study showed that CD68 monocytes were a dominant population in acute rejection^[79,104].

In addition, mature monocytes are especially responsive to I/R injury and are activated soon after DAMP and PAMP stimuli, thereby secreting a range of cytokines that further activate other innate immune cells and also promote lymphocyte activation^[105]. Macrophages are also prominent producers of ROS and eicosanoids that induce tissue damage and amplify the inflammatory cascade after tissue engraftment^[106]. There are numerous subtypes of macrophages, ranging from inflammatory M1 cells, which produce increased amounts of TNF-α and IFN-γ, to more tolerogenic M2 macrophages, which secrete

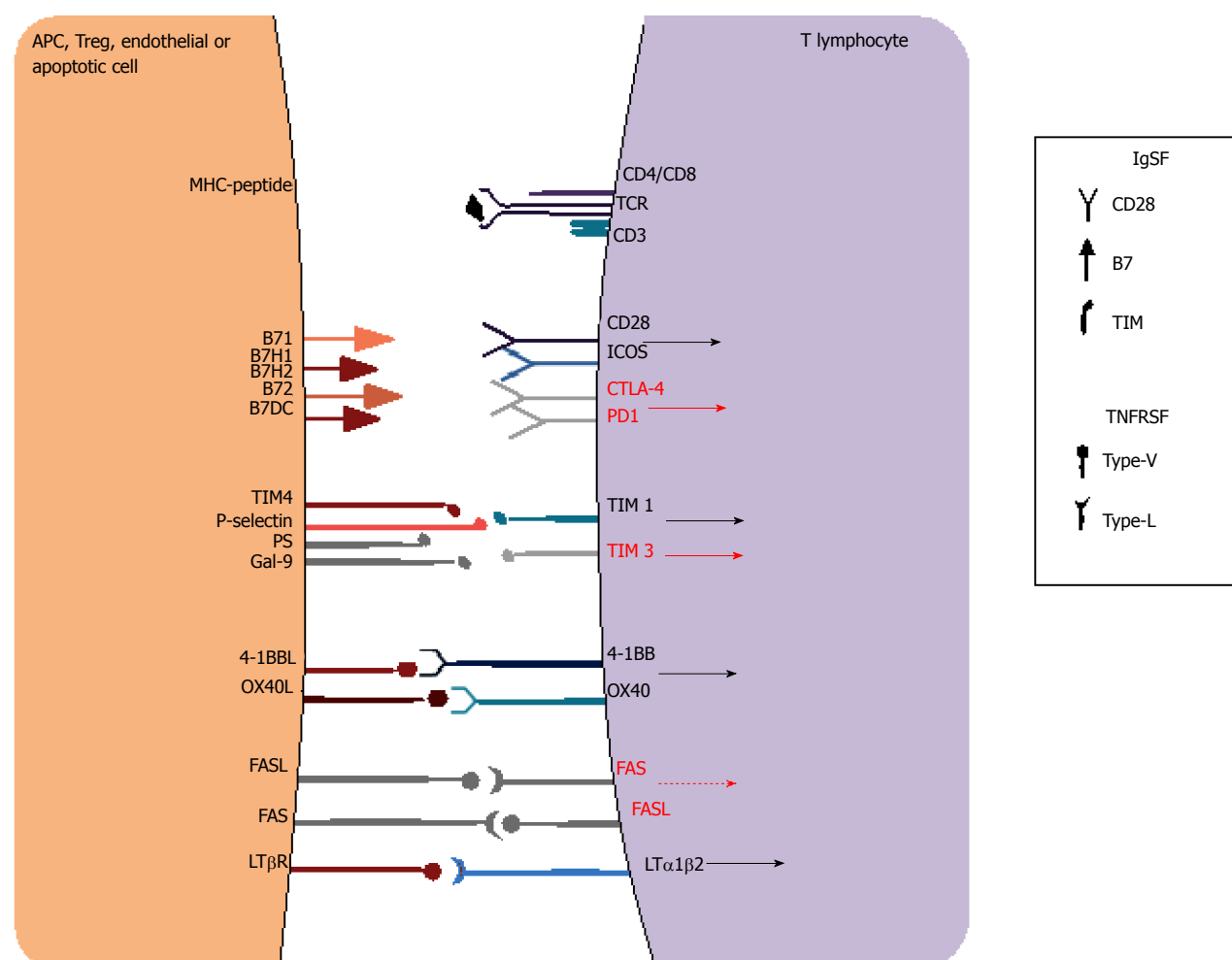


Figure 4 Examples of co-stimulatory receptors in immune synapse interactions. T cell activation depends not only on the antigen-specific signals provided by MHC-TCR signaling but also on a complex balance of co-stimulatory signals that may enhance or inhibit activation. These receptors are mainly classified into the immunoglobulin superfamily (IgSF) or the tumor necrosis factor receptor superfamily (TNFRSF) and may provide positive (black arrows) or negative signals (red arrows), or even apoptotic signals (red dashed arrow), which in turn decide cell fate. MHC: Major histocompatibility complex; TCR: T cell receptor.

cytokines such as IL-4 and IL-10 and are associated with wound-healing and regulatory properties^[107]. One study has indicated that the transfer of human regulatory macrophages ($CD14^{-/low}HLA-DR^{+}CD80^{-/low}CD86^{+}CD16^{-}CD64^{+}TLR2^{-}$ and $CD163^{-/low}$) induces protection after renal transplant^[108]. However, some studies have also associated M2 macrophages with increased allograft fibrosis^[109-111]. However, this might depend on the time course of cell activation and the type of macrophage present, as DAMP, PAMP and dead cell clearance also reduces cell stimulation and innate immune activation.

NK cells

Classically, NK cells are lymphocytes that respond to signals provided by tumor cells or virally infected cells. However, other stress-related signals can activate NK cells^[112] through an unbalanced positive signal *via* membrane receptors. Although these cells share many characteristics with classical lymphoid cells, their activation takes shape through antigen-independent signals and does not produce immunological memory, falling therefore into the category of innate immunity.

These cells recognize activating and inhibitory cell surface receptors that indicate cell stress, such as TLRs, class I MHC binding inhibitor receptors (e.g., Ly49), MHC class I-related binding activating receptors (e.g., NKG2D) and Fc receptors (e.g., CD16)^[113,114]. In addition, NK cells are also activated by cytokines, such as IL-2, IL-15, IL-12 and IL-18^[115]. Moreover, after activation, NK cells go on to perform effector functions such as cytotoxicity (perforin and granzymes) and cytokine production ($IFN-\gamma$, $TNF-\alpha$, IL-22)^[116]. Because NK cell class I MHC inhibitory receptors are polymorphic and recognize self-MHC, these cells are readily capable of responding to allogeneic graft cells due to the "missing-self" principle, leading researchers to investigate these cells' role in graft rejection, especially after BMT. However, literature pertaining to NK cells in allorecognition is contradictory. Some authors demonstrated that these cells are important mediators in GVL (graft vs leukemia) effects, although they may accelerate graft failure due to an attack on donor cells^[116,117]. On the other hand, recent research has also indicated that donor cells may evade allorecognition by acquiring host MHC class I molecules

through the transfer of surface proteins from receptor cells, therefore inhibiting NK responses^[118]. Nonetheless, most articles have shown that NK cells may also facilitate bone marrow engraftment and regulate graft-vs-host disease by suppressing donor and host T cells^[119-122].

NKT cells

NKT cells are a heterogeneous population of T cells that express TCRs and NK markers and have properties of both T and NK cells. These cells recognize glycolipid antigens presented by CD1d on APCs instead of MHC molecules. They can be divided into two main subtypes depending on the TCR subchain expressed. Invariant or type I NKT cells express an invariant TCR β -chain (V α 14-J α 18 - mouse or V α 24-J α 18 - human) that is paired with a semi-invariant TCR β -chain (V β 11 - humans or V β 2, V β 7 or V β 8.2 - mice), while type II NKT cells include all other CD1d-dependent T cells^[123], with a very small frequency in the peripheral blood. After TCR activation, these cells can modulate the immune system by producing significant amount of Th1, Th2 and Th17 profile cytokines^[124-126] and by increasing the expression of co-stimulatory molecules^[127].

Recent studies indicate that these cells have tolerogenic effects and are crucial for the induction of peripheral tolerance. NKT cells induced transplantation tolerance towards allogeneic and xenogeneic islet cells transplanted into the liver and towards cardiac allografts^[128-130]. The presence of these cells suppresses GvHD and solid organ rejection, which seems to be mediated by the production of IL-4 and IL-10 and by Treg activation^[131-133].

DCs

DCs are the most prominent APCs involved in antigen presentation, mainly due to their particular ability to capture, process and express peptides *via* the MHC and their ability to migrate to T cell zones in lymph nodes, expressing high levels of co-stimulatory molecules along with peptides to T lymphocytes. These cells comprise an expressively diverse population that, after differentiating from the common DC precursor (CDP) or monocytes, when activated by danger signals as described above, transition from an immature state (iDCs) with low costimulatory receptor and MHC expression to a mature state (mDC), expressing high levels of costimulatory and MHC molecules.

DCs are classified into various subsets depending on their origin and the way they are activated, with the main types being plasmacytoid DCs (pDCs), conventional or classical DCs (cDCs) and inflammatory monocyte-derived dendritic cells (moDCs). The first population produces significant amounts of Type I and III IFN and diverse chemokines including CXCL1, CXCL3 and others^[134,135]. However, they are considered poor APCs and are considered important in the induction of tolerance to grafts, which will be detailed further on.

In contrast, cDCs are efficient APCs that, when mature, produce various cytokines, such as IFN- γ , IL-12

and IL-10, which can direct T-cell activation towards an immunogenic or tolerogenic profile. Research suggests that cDCs are the main APCs responsible for alloantigen presentation during GvHD early after BMT^[136]. cDCs are divided into CD8⁺ or CD8⁻ cells, and there are many different reports on their effects on graft rejection. CD8⁺ DCs are only expressed in mice (not in humans), but some reports suggest that they have a regulatory role in BMT and solid organ transplantation, where they suppress the activation of other inflammatory DCs by producing indoleamine 2,3-dioxygenase (IDO) and increase Treg numbers and Treg production of IL-10^[137-140].

Finally, moDCs possess strong inflammatory properties, differing from cDCs in that they originate from a monocyte precursor and express Gr-1/Ly6C. Although there are almost no *in vivo* data on the role of this specific population against other cells in graft rejection, some studies indicate that these cells have intense antigen-presenting functions, maybe even more than cDCs^[86,87,141,142]. Other studies have also shown that these cells can effectively activate NK cells^[143], which are discussed later. Future research shall elucidate the role of these cells in a transplantation setting.

ADAPTIVE IMMUNITY

The adaptive immune system has been recognized to have a critical response to organ transplantation. The rejection process is characterized by a highly complex series of cellular and humoral interactions in which T and B lymphocytes as well as DCs exhibit central and essential roles. Nevertheless, the immune response underlying allograft rejection is an ongoing dialogue between the innate and adaptive immune system, whereby innate immune cells modulate and direct the development of adaptive responses through pattern recognition receptor signaling (Figure 3).

T cells

To reduce transplant rejection, the biggest challenge faced is overcoming or suppressing adaptive immunity. T cells have a central role in adaptive effector responses due to their cytokine production and cytotoxic functions. After CD4⁺ T cell activation, the cells differentiate into subtypes, mainly including Th1, Th2, Treg, Th17 and Th9 cells, according to their signature cytokine production. Nevertheless, although these are some of the most studied mediators in transplantation, little consensus exists on their effects on graft rejection, with most of these cell types displaying dual roles in immune activation in transplantation.

In immunology, Th1 cells are considered classic pro-inflammatory actors. These cells are characterized by the expression of the T-bet transcription factor, along with the secretion of IFN- γ , TNF- α/β and IL-2, which in turn stimulate macrophages and lymphocytes towards enhanced effector functions associated with intracellular immunity. Specifically, IL-2 is essential to promoting T cell proliferation, while IFN- γ expression increases

CD8⁺ T cell activation^[144]. Many studies correlate IFN- γ expression to kidney graft rejection^[145,146]. However, there are also data that showing that IFN- γ may prolong survival by reducing tissue necrosis and local granzyme-perforin secretion^[147,148]. This has also been described in GvHD, whereas it prevented early onset of rejection^[149], although this effect may depend on conditioning regimens^[150]. In addition, IFN- γ expression by Tregs may also be important in reducing GvHD^[151].

In contrast to Th1 cells, Th2 cells are traditionally considered immunomodulatory cells associated with extra-cellular immunity. They express the Gata-3 transcription factor and secrete IL-4, IL-5, IL-10 and IL-13. However, in a transplantation context, some studies demonstrate that Th2 cells have limited immunomodulatory properties^[152-154]. Most recent data suggest that Th2 responses may have a negative role in transplant rejection^[155]. In addition, some reports also suggest that IL-4 production by Th2 cells may accelerate cardiac and kidney rejection^[156,157].

Th17 cells have also an important role in graft rejection. These cells express the transcription factor ROR γ T and are characterized by IL-17 and IL-22 production. Studies show that the absence of Th17 cells leads to prolonged renal graft survival with reduced IFN- γ and enhanced Treg function^[158]. In addition, IL-17/IL-22 levels correlate with acute liver, kidney, islet and lung rejection in addition to GvHD^[159-164]. However, the exact role of Th17 cells in transplant rejection may be more complex, as some studies have suggested that Th17 cells are more important for chronic rejection^[165].

Finally, there are little data on the role of the recently discovered Th9 cells, which express increased levels of IL-9, in allograft rejection. Two articles suggest that CD4⁺ T cells that were co-stimulated and polarized with TGF- β and IL-4 in the presence or absence of rapamycin yielded effector cells of the Th9 phenotype that secreted increased IL-9 and expressed a transcription factor profile characteristic of both Th9 and Th2 cells (high GATA-3/low T-bet). Another transcription factor that promotes Th9 is PU.1. Its epigenetic modifications are important for Th9 immunity regulation^[166]. These cells may have regulatory functions similar to Th2 cells by reducing IFN- γ alloreactivity and CD4⁺ and CD8⁺ T cell engraftment in BMT but also by inhibiting GVHD while increasing GVL^[167,168].

Cytotoxic T cells

CD8⁺ T cells have an important role in cell-mediated transplant rejection, with distinct cytotoxic effector functions, and were able to be activated even in the absence of CD4⁺ T cells^[169], promoting cellular damage through the secretion of granules containing perforin, granzyme and granulysin. While perforin polymerizes, forming transmembrane pores on target cells, granzymes consist of a class of proteases that cleave substrates in the cytoplasm of target cells, triggering rapid apoptosis. Moreover, granulysin also mediates cell death, inducing ionic unbalance and mitochondria-mediated cell apoptosis

in addition to facilitating intracellular bacterial killing^[170]. In addition, CD8⁺ T cells can also express FasL, which binds to Fas receptors on target cells, causing caspase activation and consequently also leading to cell apoptosis. It has also been reported that APO2L/TRAIL constitute an additional pathway of T cell-mediated cytotoxicity^[171,172], inducing apoptosis in a FasL- and perforin-independent manner.

In practice, there is no consensus on the specific importance of these cells in the context of allogeneic activation. Although CD8⁺ T cells may not be essential for some types of allograft rejection^[173], others correlate their presence with graft cytotoxicity^[174,175]. Recent data have shown that these cells may also inhibit alloantibody production by promoting alloprimed IgG1 (+), resulting in B cell death through FasL- and perforin-mediated apoptosis^[176]. Moreover, these cells can also secrete a range of cytokines and are divided into two subclasses, Tc1 or Tc2. Type 1 CD8⁺ T cells (Tc1) cells mainly secrete IFN- γ , which was recently shown to promote hematopoiesis *via* increased myeloid differentiation in order to reinforce target cell clearance^[177], and on the other hand also reduce IL-4-dependent IgG1 alloantibody production. In parallel, Tc2 cells mainly secrete IL-4 and IL-5 and have been shown to reduce GvHD^[178-180].

Memory T cells

Memory T cells represent a major challenge in the context of transplantation. Although they have an important role in defense against pathogens, especially in immunocompromised patients, they are also important in transplant rejection. These are very heterogeneous cells, both functionally and phenotypically, expressing different surface markers and residing in lymphoid and non-lymphoid tissues, such as the lung and liver^[181,182]. Memory T cells are different from naïve T cells because they are long-lasting cells, are antigen-independent persistent, and are capable of self-renewal^[183]. Furthermore, they are able to be activated more easily than naïve T cells because they are less dependent on TCR stimulation and on co-stimulatory molecules^[184]. These cells can be CD4⁺ or CD8⁺ cells, with the CD8⁺ subtype much more frequent and commonly studied^[185]. They are dependent on sensitization, are linked to adaptive immune responses, and are responsible for the recall response^[183]. These cells are also derived in an IL-7 dependent manner from effector T cells resistant to apoptosis^[186,187]. Memory T cells also have greater and faster responsiveness to antigens than naïve T cells because they are derived from effector T cells^[188] and are more effective in the immediate response against antigens^[189,190].

These cells are also expressly involved in transplant rejection^[191-194]. Analysis in patients showed that higher frequencies of memory T cells pre-transplantation are related to higher post-transplantation complications^[195,196]. Treatment with immunosuppressive drugs that reduce alloreactive T cells also favors the generation of memory

T cells because this generate homeostatic proliferation without antigen stimulation^[197], which causes naïve T cells to be converted into effector memory T cells^[198,199]. Memory T cells are also involved in heterologous immunity, a process whereby cells activated by pathogens cross-react against alloantigens^[200,201].

Memory T cells are also involved in tolerance resistance, mainly because they are highly reactive to donor antigens^[191,202,203]. These cells have the ability to break Treg-induced suppression^[193,204], constituting a barrier to treatments that aim to induce tolerance in transplantation. To circumvent this, studies have demonstrated that the depletion of memory T cells along with mixed chimerism through BMT after renal transplantation successfully induced a state of delayed tolerance^[205].

A recent study has demonstrated that the level of CD38 on CD8⁺ memory T cells in the peripheral blood can predict the occurrence of GVHD^[206]. Thus, the observation of T cell memory and its frequency in recipients may permit the establishment of a relative risk assessment of rejection mediated by these cells, or conversely, the possibility of establishing tolerance and the reduced probability of rejection.

B cells

B lymphoid cells are one of the main players in transplant rejection, and along with their antibody-producing properties, they also play an important part in allogeneic responses as APCs and cytokine producers. During B cell ontogeny, these cells go through different maturation stages, starting at the immature B cell stage and roaming to the spleen to complete their maturation. There, the majority of B cells become mature follicular B cells, which circulate between secondary lymphoid organs until they are activated, or marginal zone B cells, which continue in the spleen. Some articles have reported that B cells increase acute GvHD by accentuating T cell activation^[207,208]. Chronic GvHD has also been linked to B cell responses *via* a positive correlation with high levels of autoantibodies^[209,210]. Likewise, sex-mismatched BMT has also been associated with H-Y antibodies derived from donor B cells^[211]. In addition, B cells also promote T cell activation as a result of antigen presentation and are able to induce graft rejection, even in an antibody-independent manner^[212]. However, extensive literature has indicated that B cells may also have important tolerogenic properties in a transplantation setting, mainly *via* the suppression of T cells and DCs through cytokine production, which will be discussed in detail later in the review.

Antibody-mediated rejection and complement

Antibodies are one of the most important mediators in transplant rejection and play a key role in both acute and chronic rejection. They are produced by transient plasmablasts and long-lived memory plasma B cells resident in secondary lymphoid organs and bone marrow. After transplantation, patients may display pre-existing or

de novo donor-specific antibodies (DSAs) that target both HLA and non-HLA molecules. Data suggest that 20% of transplant patients will develop DSA within the first 5 years, and there are substantial data showing that these are responsible for accelerating graft rejection^[213,214]. In summary, antigen recognition by antibodies results in the formation of antigen-antibody complexes, which recruit inflammatory cells through Fc receptor recognition and activate the classical pathway of complement activation. This, in turn, leads to the formation of active soluble byproducts that activate inflammatory cells and also leads to the formation of the membrane attack complex (MAC), leading to pore formation and consequent allogeneic cell death. Many studies have demonstrated the important role of complement activation in graft rejection, and many of its byproducts correlate with graft rejection. Both CD3a and C5a have been shown to induce APC and T cell activation, with increased expression of IL-6, costimulatory molecules and MHC II along with reduced FOXP3⁺ Treg formation^[215-217]. In addition, C1q has also been shown to activate DCs, increasing TNF- α production and leading to a Th1 response^[218]. Due to the vast formation of byproducts of complement activation, many researchers have also aimed to use these as biomarkers of antibody-mediated rejection. Among these, C4d, which is a product of C4 breakdown and easily localizes to endothelial cells and the basement membrane, has been shown to be of great value^[219], although C4d-negative antibody-mediated rejection also exists.

IMMUNOSUPPRESSIVE DRUGS AND TOLERANCE

Immunosuppression

The use of immunosuppressive drugs is essential in cases of solid organ transplantation because it can avoid the immune response against the graft or delay the appearance of *de novo* baseline disease. Thus, the most frequently used drugs act on pathways that inhibit the proliferation and activation of T cells, the main mechanisms involved in rejection^[220]. Commonly, these drugs are used in combination, which can vary according to the patient, the type of transplant and also with the transplant center.

Azathioprine is the oldest immunosuppressive drug to be used in the prevention of rejection, and it was used with the first successful deceased kidney transplantation in 1962^[221]. Although currently, it has not been commonly used in transplants, it is still an important treatment for autoimmune and inflammatory diseases^[222-224].

Calcineurin inhibitors (CNIs), such as cyclosporin A and tacrolimus, are the most commonly used treatments. Cyclosporin A emerged as an alternative to azathioprine and triggered an important advance in medical transplants^[225,226]. Tacrolimus has been the first choice of treatment in most transplant centers in Europe and the United States^[223]. These drugs inhibit the calcineurin

pathway, avoiding the dephosphorylation of NFAT (nuclear factor of activated T lymphocytes) and its translocation to the nucleus, ultimately blocking the activation of genes involved in T cell activation and, consequently, the propagation of the immune response^[226,227]. However, the use of these drugs may induce nephrotoxicity^[228,229] and can cause diabetes, dyslipidemia, hypertension, cardiovascular and kidney disease^[230,231].

Everolimus and Sirolimus belong to another class of immunosuppressive drugs widely used in kidney transplantation in combination with other drugs. They inhibit mTOR (mammalian target of rapamycin), a kinase protein involved in the activation and proliferation of lymphocytes and tumor growth, among other functions^[232], that is also related to the expansion of Treg cells^[233,234].

Mycophenolate mofetil has been increasingly used as an initial immunosuppressive drug in recent years^[222]. After it is metabolized, it generates mycophenolic acid, which inhibits inosine-5-monophosphate dehydrogenase (IMPDH), an important enzyme involved in purine synthesis. By inhibiting this enzyme, the drug can reduce T and B cell proliferation, in addition to decreasing the recruitment of lymphocytes to sites of inflammation and inducing necrosis in activated lymphocytes^[235].

A more recent therapeutic option is Belatacept, a fusion receptor protein that blocks the CD80/CD86-CD28 co-stimulatory pathway, selectively inhibiting T cell activation^[236]. Clinical studies have demonstrated that continuous treatment with Belatacept was associated with a consistent improvement in renal function post-transplantation^[237-239].

Other treatment alternatives have also been tested. Studies have shown that the use of anti-CD40 can be effective^[240] at preventing acute renal transplant rejection^[241]. Clinical trials with a JAK3 (Janus kinase) inhibitor, Tofacitinib, in kidney transplantation showed low rates of rejection and a high graft survival, similar to cyclosporin, which was used as a control^[242,243]. Phase II studies with Sotrastaurin have also been carried out. This molecule selectively inhibits protein kinase C, blocking T cell activation, although contradictory results regarding its efficacy in preventing rejection have been obtained^[244,245].

Moreover, in some, cases, pre-treatment using monoclonal antibodies, such as Alemtuzumab, or polyclonal antibodies, such as anti-thymocyte globulin, can be used as induction therapy at the time of transplantation. This treatment depletes peripheral blood leukocytes, inducing lymphopenia^[190], and can stimulate Treg cells^[246,247] and regulatory B cells^[248], enabling a reduction in the use of other immunosuppressive drugs.

Another class of drugs, proteasome inhibitors, can act directly on T and DC cells. The proteasome is essential for the maintenance and regulation of basic cellular processes, including cell signaling and survival pathways. The inhibition of proteasomal proteolytic activity by proteasome inhibitors suppresses essential immune functions. They can inhibit the activation of

nuclear factor (NF)- κ B and the transcriptional regulation of pro-inflammatory cytokine release and/or induce the apoptosis of activated immune cells. They can affect T cell activation, function, proliferation, and viability and suppress DC maturation and inhibit DC function. For this reason, they have already been tested in diverse autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis^[249-252].

Tolerance

The use of immunosuppressive drugs has been the main option for transplant patients and has provided improvements in graft survival rates. However, many of these drugs present medical complications such as infections, nephrotoxicity, cardiovascular problems and cancer^[228,253,254]. Furthermore, the treatment is not able to prevent chronic rejection, and the rates of chronic allograft dysfunction are still very high^[255,256]. Additionally, the prolonged use and the high cost of immunosuppressors can lead to non-adherence to treatment^[257]. Therefore, alternative therapies are needed, and the induction of tolerance would be an ideal substitute for the use of immunosuppressive drugs^[258].

Immunological tolerance is an important mechanism to prevent anti-self immune responses and autoimmune diseases. In central tolerance, which occurs in the fetus thymus before T cell maturation, cells that react against self-antigens are deleted and regulatory T cells are expanded. On the other hand, peripheral tolerance, a secondary process of immunological tolerance, occurs in peripheral lymphoid organs, where there is induction of anergy and deletion of T cells that self-react against antigens that did not exist in the thymus or somehow escaped central deletion^[259].

In the context of transplantation, true tolerance is by definition a permanent state of acceptance of alloantigens without the use of immunosuppressive drugs^[260], given that in experimental models, animals must retain the ability to reject a third donor organ^[261].

The induction of chimeras, or mixed chimerism, is a situation in which donor cells and recipient cells co-exist in the immune system^[262], and it is an important technique to induce immunological tolerance. In chimera induction, hematopoietic cells from the donor are transferred to the recipient, and the recipient cells are retained, being only partially replaced by the donor^[260]. In parallel, host bone marrow and donor thymus cells cause the central deletion of donor alloreactive T and B cells^[260,263], allowing a new concept of what is self.

In experimental models, this method induces donor-specific tolerance and enables prolonged graft acceptance^[264]. In humans, Alexander *et al.*^[265] demonstrated in a patient who received liver transplantation that the induction of mixed chimerism promoted tolerance and prevented GVHD occurrence. This method has already been used in transplants with good results^[266] and is an important way to induce tolerance and prevent rejection or GVHD, allowing the long-term withdrawal of immunosuppressive drugs^[267-269].

Currently, the existence of cells capable of regulating the immune response, leading to a more tolerogenic and less inflammatory profile, and restoring the balance of the immune system is well established. In the transplantation context, these cells are responsible for the balance between the survival and rejection of the graft^[270]. Regulatory cells of the immune system, such as Tregs^[271], tolerogenic DCs^[272], and Bregs^[273,274], have been detected in recipients that have developed operational tolerance. Therefore, the direct use of these cells, or of elements that stimulate these cells, may be important tools for tolerance induction because they are able to prevent or minimize the use of immunosuppressive drugs and their adverse effects^[270,275-278].

Regulatory T cells

Regulatory T cells play an important role in regulating the immune response and are responsible for the balance between the inhibition of autoimmunity (acting in tolerance against self antigens) and preventing tissue damage (acting on innate and adaptive response against non-self antigens)^[259]. Two major subtypes of Tregs have been described. Naturally occurring Tregs are generated in the thymus from T-cell precursors expressing CD4, CD25 and the transcription factor Foxp3 and play an important role in maintaining tolerance to self-antigens or other antigens present in the thymus^[279,280]. Moreover, induced or adaptive Tregs (iTregs), which are induced in the periphery in various tissues^[281,282], express CD4 and Foxp3 and are responsible for the response against antigens not found in the thymus^[283]. Thus, both subtypes may be responsible for the recognition of donor alloantigens and for the immune tolerogenic response against them^[284].

Treg cells act through different mechanisms that can direct or indirectly inhibit T cell activation and proliferation. These cells can transmit inhibitory signals *via* cell-cell contact or secrete regulatory cytokines such as TGF- β , IL-10 or IL-35. In addition, they can also limit the availability of trophic factors, such as IL-2, to effector T cells, generate direct toxicity against target cells, or modulate APC functions. Moreover, these cells also act on other immune cells, such as B cells, NK, NKT and mast cells^[259,279,283,285].

The induction of operational tolerance to transplantation is strongly associated with Tregs^[270,283]. Therefore, the use of these cells has been tested in several ways. The use of these cells as a conditioning therapy before transplantation was able to induce tolerance^[286], as was the use of Tregs for the generation of mixed chimerism, where donor Tregs were essential for the suppression of immune response^[287,288]. The use of drugs or cytokines that induce Tregs *in vivo* also improve graft survival^[289-291] along with donor alloantigen inoculation pre-transplantation^[292], which promotes the expansion and proliferation of Tregs *in vivo*. Direct inoculation of Tregs or inoculation after *ex vivo* expansion was also effective in reducing rejection^[293-295] and in the prevention

of GVHD^[296,297]. In humans, clinical trials have also shown that the infusion of Tregs is able to reduce GVHD^[298,299]. Importantly, the immunosuppression generated is not global, as the injected Tregs retained the ability to respond to infections^[296,298], which was an important advantage in comparison to immunosuppressive drugs.

DCs

As described previously, DCs are APCs that participate in T cell activation and are crucial for the activation of the immune response, including the response against alloantigens. When they become mature, they express some co-stimulatory surface markers, such as CD80, CD86, CD40, and MHC II^[300]. Immature DCs have decreased expression of MHC II, CD86 and CD40, generating a more tolerogenic profile. Tolerogenic DCs have reduced production of cytokines such as IL-6 and IL-12 and increased IL-10 secretion^[301]. Thus, they are capable of inducing clonal deletion, inhibiting memory T cells and inducing or expanding Tregs^[277,302].

New therapies based on the transfer of tolerogenic DCs have been tested, especially for autoimmune diseases^[278]. Blockade of DC-T cell interactions *via* co-stimulatory receptors and T cell surface molecules impairs T cell proliferation, preventing an exacerbated immune response^[303]. Additionally, immature DCs are also able to promote tolerance in animal models of solid organ and BMT. Treatment with donor immature DCs^[304-306] or regulatory DCs^[307] in transplantation also prolongs graft survival and the development of GVHD. Moreover, DCs can also be conditioned to become tolerogenic through the use of cytokines, growth factors and drugs^[308], and the use of TGF- β ^[309], and rapamycin^[310], for example, were observed to prolong graft survival.

Regulatory B cells

The role of B cells has always been related to the activation of the immune response and transplant rejection, especially through the production of antibodies. However, some B cell subtypes with regulatory functions are also observed to produce regulatory cytokines^[311]. Many regulatory B cell subtypes (Bregs) have already been described, including the transitional cell (T1B and T2B), the marginal zone (MZ) B cell, the transitional 2 marginal zone precursor B cell (T2-MZP)^[312] and a rarer CD1d^{hi}CD5⁺ subtype, known as the B10 cell, that has received the most attention^[313,314]. MZ B lymphocytes have been shown to produce high levels of IL-10 after the anti-CD40-mediated induction of tolerance^[314]. In addition, B10 cells are found mainly in the spleen and also exert their actions exclusively *via* the production of IL-10, which regulates T-cell activation and inflammatory responses^[315]. In an EAE model, Matsushita *et al.*^[316] demonstrated that regulatory B cells (B10) exert their function by altering IFN- γ and TNF- α secretion and suppressing T cell proliferation and acting on DCs, downregulating their antigen-presenting ability. Furthermore, another study has also demonstrated that Breg cells play an important role in

the induction of Treg cells, maintaining high Treg levels in comparison to Th1 and Th17 cells^[317].

B cells are strongly related to operational tolerance. Studies involving transplant patients show an increased percentage of B cells in the blood of tolerant patients compared to patients treated with immunosuppressive drugs or those who have suffered rejection^[274,318,319]. B-cell-related genes are also differentially expressed in tolerant patients^[273,319]. In addition, when evaluated *in vitro*, B cells from tolerant patients produced a higher amount of IL10 compared to those from non-tolerant patients^[273]. Another study also showed that B cells from patients with chronic rejection do not inhibit autologous T cell proliferation, whereas B cells from healthy patients do^[320], confirming the involvement of Breg cells in the tolerance induction process.

Thus, research in recent years has also aimed towards the use of B cells as a cellular therapy to induce tolerance. To this end, Breg cells were shown to induce chimerism and tolerance to donor antigens^[321]. Likewise, studies in transplantation models indicated that Breg inoculation is effective towards prolonged graft acceptance^[322,323] and the suppression of T cell activation^[324], promoting the development of Treg cells, possibly *via* TGF- β production^[325].

Mesenchymal stromal cells

Mesenchymal stromal cells have known immunosuppressive properties and are capable of inhibiting T cell function and proliferation, inducing T cell apoptosis and inducing regulatory T cells^[326]. The use of MSCs in solid organ transplantation has had important results. MSCs attenuate ischemia-reperfusion injury^[327] and prevent graft rejection^[328,329]. These cells are able to inhibit the T cell response^[330,331] and inhibit the migration of activated T cells into the graft^[332,333] in addition to expanding Treg cells^[334-336] and tolerogenic DCs^[337-339], generating a state of tolerance^[326].

Based on evidence in experimental models that MSCs favor the development of tolerance and have demonstrated efficacy and safety, some clinical trials are in development^[340]. The infusion of these cells was able to maintain stable graft function *via* Treg expansion and the reduction of memory T cells^[341] and decrease the incidence of acute rejection^[342].

Fetal tolerance

Finally, the induction of tolerance is also essential to the fetus, which must tolerate maternal antigens, preventing an immune response against the mother. The immune environment of the developing fetus is specially prepared to generate immune tolerance, especially to non-inherited maternal antigens (NIMAs), protein products derived from polymorphic genes expressed by the mother. Fetal CD4⁺ T cells have a strong predisposition to differentiate into Tregs after activation by maternal antigens, which actively promotes tolerance to maternal cells residing in fetal tissues^[343]. Afterwards, shortly before birth, the fetal cells transition to a more defensive adult-type response,

with the ability to combat pathogens^[344]. Maternal cells also play an important role in fetal protection during pregnancy. Maternal Treg cells are involved in this process, as they are enriched in the decidua and return to normal levels after birth^[345], which does not occur in cases of miscarriage^[346,347].

The establishment of microchimerism is the primary factor responsible for the generation of Tregs because fetal cells also have access to the mother. This chimerism occurs both in the maternal tissues and in the fetal tissues, and maternal cells are often found in fetal tissues^[343,348], remaining for a long period after birth^[349]. Even after development, the ability to generate tolerance to antigens that have been in contact with the fetus is not lost, consisting in a postnatal tolerance. This fact was confirmed in a study by Burlingham *et al.*^[350], who showed that patients who received HLA-haploidentical sibling renal transplantation of which the mismatch corresponded to a NIMA had a significant increase in graft survival compared to those in which the mismatch was a non-inherited paternal antigen (NIPA), suggesting a relationship with the exposure to antigens during the fetal period. Other studies using a heart transplantation model also demonstrated that allografts expressing NIMAs were protected from rejection when implanted in offspring mice that had come into contact with the same NIMAs during pregnancy, therefore creating a predisposition to transplantation tolerance in mice as an adult^[351], mainly through the induction of NIMA-specific Treg cells^[352].

CONCLUSION

Although the basic mechanisms of transplant allorecognition have been the object of intense study for the last 80 years, graft rejection is still an important obstacle in clinical practice. Allorecognition is an unfortunate disadvantage to the evolution of more effective immunological surveillance and is therefore especially complex to surpass. Nonetheless, current advances have shed light on important mediators that fuel graft rejection, making the search for new therapies possible. In addition, promising discoveries have been made in the search for effective immunosuppressive regimens and, more importantly, the achievement of functional tolerance.

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