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The Immunology of Allograft Rejection: A Survey of Current Knowledge and a Discussion of Peptide-Specific Anti-Rejection Strategies

The goal of transplantation immunology is to develop strategies for antigen-specific inhibition of transplant rejection. The immune response triggered in the host by the MHC-incompatible organ transplant can lead to the loss of organ function. The MHC peptides created by antigen processing of the donor- or allo-MHC molecules of the transplant are a major stimulus for activation of alloreactive CD4+ T cells in the recipient. The T cells activated via this pathway of indirect alloantigen recognition are among the determining factors in the pathogenesis of both acute and chronic rejection. Since activated CD4+ T cells control by means of their cytokines both the cellular and humoral arms of the adaptive immune response, they are a key element in the search for effective immunomodulating therapeutic strategies. According to current knowledge, regulatory T cells play a crucial role in the immune response. Even though antigen-independent factors, such as ischemia and reperfusion injury, also participate in the multifactorial process of rejection, the allogeneic immune response depends mainly on the MHC incompatibility between donor and host. It remains for future studies to determine the extent to which antigen-specific modulation of the allogeneic T cells is able to effectively control this multicellular process.

Key words:

alloantigen recognition, transplant rejection, alloantigen, peptide, T cells

Die Transplantatabstoßung: Eine Übersicht zur Immunologie und Anmerkungen zur antigenspezifischen Hemmung mit Peptiden

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Das Ziel der Transplantationsimmunologie ist die Entwicklung von Strategien zur antigenspezifischen Hemmung der Transplantatabstoßung. Das MHC-inkompatible Organtransplantat induziert eine zum Funktionsverlust führende Immunantwort im Transplantatempfänger. Die aus den Fremd- oder Allo-MHC-Molekülen des Transplantates durch Antigenprozessierung entstandenen MHC-Peptide stellen dabei einen wichtigen Stimulus zur Aktivierung alloreaktiver CD4+ T-Lymphozyten des Transplantatempfängers dar. Die über diesen Weg der indirekten Alloantigen-Erkennung aktivierten T-Lymphozyten sind mitentscheidend für die Pathogenese der akuten, aber auch der chronischen Abstoßung. Da die aktivierte CD4+ T-Zelle über ihre Cytokine beide

Arme der adaptiven Immunantwort, den zellulären und den humoralen, steuert, steht sie im Mittelpunkt möglicher immunmodulierender Therapieansätze. Nach gegenwärtigen Erkenntnissen spielen sehr wahrscheinlich regulatorische T-Lymphozyten hierbei eine große Rolle. Auch wenn zusätzlich antigenunabhängige Faktoren, wie Ischämie oder der Reperfusionsschaden, ebenfalls das multifaktorelle Geschehen der Abstoßung beeinflussen, so basiert die allogene Immunantwort doch in erster Linie auf der MHC-Inkompatibilität zwischen Spender und Empfänger. Inwieweit die antigenspezifische Modulation der alloenen T-Lymphozyten ausreicht, um dieses multizelluläre Geschehen effektiv kontrollieren zu können, bedarf weiterer Untersuchungen.

Schlüsselwörter:

Alloantigenerkennung, Transplantatabstoßung, Alloantigen, Peptide, T-Lymphozyten

1. Introduction

An understanding of the immunology of transplantation is essential for effective treatment of the recipient's complex response to donor tissue. This type of immune response, called rejection, remains one of the major obstacles to successful transplantation of vascularized organs. Transplantation remains, despite its shortcomings, the therapy of choice for end-stage organ failure. Major improvements in surgical techniques, MHC matching and immunosuppressive drugs have increased the one-year survival rate for most solid organ grafts to over 90% (1).

The advances in transplantation medicine have led to a growing need for donor organs. More than any other medical discipline, transplantation medicine depends on the active support of society: only the willingness of people to donate organs makes this form of therapy possible. In Germany, for example, only 3,200 donors were available for the 11,000 patients who needed a transplant in 2001 (2). Physicians and scientists are searching for alternatives to donations from deceased donors in order to increase the pool of suitable organs. Among the alternatives are living organ donation (3), xenotransplantation (4, 5), the use of artificial organs (6) and tissue and organ regeneration (7, 8). Evaluation of allograft rejection is difficult because of the complexity and characteristics of this type of immune

response. Our understanding of the basic mechanisms of transplant rejection are based on the pioneering studies of Peter Brian Medawar and Frank Macfarlane Burnet on immunological tolerance (9); the discovery and characterisation of the major histocompatibility complex (MHC) by Georg D. Snell, Jean Dausset, and Beruj Benacerraf (9); and on the investigations into the MHC-restricted mechanisms of T-cell recognition by Rolf M. Zinkernagel and Peter C. Doherty (9). Numerous questions remain unanswered and are in need of further investigation.

Transplantation between genetically different individuals evokes a rapid and destructive immune response that in the absence of immunosuppression leads to graft destruction. The knowledge that the recipient's immune system mediates this destruction has prompted a search for new ways to manipulate or control the immune system. The success of clinical transplantation depends largely on successful suppression of the unwanted immune response with immunosuppressive agents. Since T cells are the central players in graft rejection, most current immunosuppressive drugs target T-cell activation and clonal expansion. The clinical introduction of cyclosporine A (CsA) initiated a dramatic revolution in transplantation medicine (10). Transplant survival rates have increased, and the promise of improved immunosuppression encouraged transplant centers around the world to

begin grafting not only kidney, liver and heart, but also lung, small bowel, and pancreas. New drugs and improved formulas for established drugs continue to improve the prognosis for transplant patients (11).

To minimize the risk of allograft rejection, transplant recipients require life-long immunosuppression. Several immunosuppressive drugs introduced in the past two decades have helped to avert tissue damage and disruption of organ function, decreased the rate of acute graft rejection, and improved one-year graft survival. However, these agents lack specificity and are associated with severe side-effects such as reduced immunity to infections and malignant diseases as well as drug-related adverse effects like nephrotoxicity, hypertension, diabetes and hyperlipidaemia (12). With regard to long-term immunosuppressive therapy, the immunosuppressive drugs currently available do not definitively protect the patient against loss of the organ graft to rejection. Approximately 15% of all organ grafts are rejected within the first six months after transplantation. Should patients overcome this critical phase, they are threatened by the Damocles' sword of chronic rejection. In the case of a failed kidney allograft, the rejected organ can be removed and the patient returned to dialysis to await a second organ. Failure of other transplanted organs, such as the liver or heart, results in the death of the patient when a new organ is not immediately available. For these and other reasons, physicians and scientists are making every effort to decrease the side effects of immunosuppression (13).

2. The Immunology of Allograft Rejection

The basic guidelines for tissue grafting were first worked out for skin transplantation. During the early stages of the Second World War, the United Kingdom's Medical Research Council asked Peter Medawar to investigate why skin grafts from unrelated donors were consistently rejected by burn patient hosts. This work enabled him to establish theorems of transplantation immunity (14). Medawar observed that initial skin grafts transplanted from one animal to another survived for 7 to 10

days. When the recipient was regrafted with skin from the same donor, the second graft was rejected in only 2 to 4 days. This accelerated response, called "second set rejection", is due to a secondary immune response. When the same animal was given a skin graft from a donor unrelated to the first graft donor, the graft elicited only a first set rejection. Medawar's findings indicate that the phenomenon of second set rejection is due to immunologic memory and specificity, both cardinal features of the adaptive immune system. The primary or first set rejection is mainly caused by naïve alloreactive lymphocytes, whereas the second set rejection is mediated by sensitized alloreactive lymphocytes. This can be shown by transferring lymphocytes from an individual previously exposed to a skin graft into a naïve individual from the same strain. If this naïve individual is then given the same skin graft as the individual from whom it received the sensitized lymphocytes, the transferred lymphocytes will induce a second set rejection. T cells are the most important cells in allograft rejection. *Nude* mice that lack T cells, for example, do not reject skin grafts. The transfer of normal T cells restores the ability to reject allografts. These observations show that graft rejection results from a specific, lymphocyte-mediated immune response to alloantigens that ultimately leads to the destruction of the transplanted tissue. The alloimmune response, which involves both cellular and humoral immunity, has two stages: stage I, the sensitization stage, which is characterized by allorecognition and activation of alloreactive CD4+ T cells, CD8+ T cells and B cells, and stage II, the effector or destruction phase, in which the graft is destroyed.

3. Passenger Leukocytes

Organ grafts usually contain numerous hematopoietic cells, such as monocytes/macrophages, dendritic cells and lymphocytes. These donor-derived leukocytes harbored within the graft are called passenger leukocytes. They can be detected after transplantation in blood and peripheral organs of the recipient and play an important role in the activation of the recipient's immune system against the allograft (15). Their

depletion reduces or eliminates the graft's immunogenicity and prolongs graft survival (16). The graft's immunogenicity is largely determined by the antigen-presenting cells within the graft, such as B cells, macrophages and, especially, dendritic cells (17). The finding that donor antigen-presenting cells are present in recipient lymphoid tissue after transplantation (18) suggests that the initial step for the priming of naïve T cells occurs in lymphoid tissues. This hypothesis is supported by the experiments of Inoue et al. in which T-cell activation and therefore graft rejection did not occur when secondary lymphoid organs were absent (19). These experimental data indicate that passenger leukocytes participate in host T-cell priming by migrating from the graft to the host's lymph nodes and/or spleen, where they activate alloreactive host T cells in the direct pathway of allorecognition (20). Host T cells can recognize allo-MHC molecules directly on the surface of these cells. Full activation requires appropriate costimulatory signals mediated by molecules such as CD80, CD86 and CD40 (21). Such primed T cells circulate and target MHC molecules expressed by cells of the graft.

4. Microchimerism

What is the fate of passenger leukocytes in the recipient? Studies have shown that their quantity decreases continuously, but small numbers (<1%) remain in blood or various organs years after transplantation and are detectable with molecular biological methods (22). This organ graft-induced coexistence of donor and recipient hematopoietic cells is defined as microchimerism (23). It has been argued that a persistent microchimerism may be essential for sustained survival of allografts (24). The describer of microchimerism hypothesized that the coexistence of donor and recipient immune cells causes peripheral clonal deletion of alloreactive T cells (25). This is interesting, but difficult to validate experimentally. Recent results suggest that passenger leukocytes play an as yet incompletely understood role as immunomodulators in the induction phase of graft acceptance (26). Most clinical data on organ graft-induced microchimerism are controver-

sial and its functional relevance for stable graft acceptance or even tolerance is unclear (27).

5. Mixed Allogeneic Chimerism

Mixed allogeneic chimerism has been induced by bone marrow transplantation in various animal models with a lifelong, donor-specific tolerance to organ grafts sharing the same MHC subtype with the hematopoietic cells (28). To date, however, its clinical application has failed because of the potential toxicity of the necessary host conditioning. In contrast to microchimerism, the number of donor hematopoietic cells in mixed allogeneic chimerism is usually >1%. Both microchimerism and mixed allogeneic chimerism are based on David Owen's observation in 1945 that fraternal bovine twins that shared a common placental circulation exhibited a state of mixed chimerism (29). Medawar showed that these chimeric twins were tolerant to skin grafts from each other (30). Medawar's group was later able to induce neonatal tolerance experimentally for the first time by injecting a cell suspension containing hematopoietic cells into neonatal mice (31). Once acquired tolerance had been achieved in neonatal mice, the ultimate challenge for generations of transplantation immunologists has been to establish tolerance in an adult human immune system (Fig. 1) with reproducible and safe clinical protocols.

6. Non-Alloimmune Mechanisms of Allograft Failure

It should not be forgotten that in addition to the aforementioned antigen-specific mechanisms, ischemia/reperfusion injury and the surgical trauma imposed on the graft can induce inflammatory responses in the graft by the innate immune system which in turn trigger and amplify antigen-specific adaptive immune responses. This injury response can lead not only to acute graft rejection, but may influence chronic processes. Ischemia/reperfusion injury alters the expression of adhesion molecules and thus influences the infiltration of inflammatory cells (32). Cel-

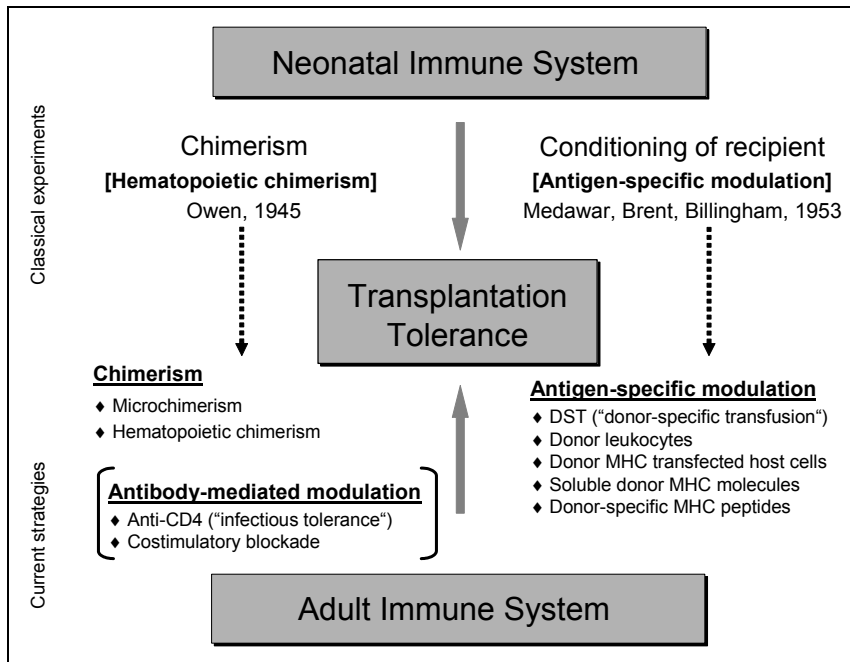


Fig. 1: All current strategies for induction of transplant-specific tolerance are based on observations and experiments from the first half of the 20th century. The major challenge since then has been the successful application of these basic principles (hematopoietic chimerism and antigen-specific modulation) to the adult human immune system.

lular components of the innate immune system are detectable in injured organ grafts. In addition to professional antigen-presenting cells, natural killer cells can be cytolytic and produce proinflammatory cytokines, monocytes/macrophages can activate complement and the coagulation cascade, present antigens, and serve as effectors of tissue injury (33).

7. Cellular Basis of Allograft Rejection

Immunological responses against allo- or xenografts remain the major cause of allograft injury and loss. The innate and adaptive immune systems are variously involved in rejection. Two factors determine the strength and nature of the alloimmune response: 1) the nature of the foreign graft, i.e. whether it is an allograft or xenograft, a vascularised or non-vascularised organ graft (34), untreated or pre-treated to reduce immunogenicity, or consists of tissues and cells; and 2) the nature of the host response, i.e. whether the rejection is hyperacute, acute, or chronic as determined by its histopathology and/or time course.

7.1 Hyperacute Rejection

Hyperacute rejection is characterised in most cases by haemorrhage and thrombotic occlusion of the graft's vascular vessels. Vascularised grafts are therefore affected by this most violent form of rejection, which occurs within minutes to hours after transplantation, with the organ quickly becoming pale and undergoing necrosis. In the blood stream circulating antibodies bind to endothelial alloantigens and trigger the complement system which promotes intravascular thrombosis and irreversible ischemic damage on the grafted organ. The antibodies are of the following subclasses: (I) preformed IgG antibodies. These are most common in sensitized individuals, e.g. after transplantation, repeated transfusions, or multiple pregnancies. In most cases these preformed IgG antibodies react against MHC class I molecules (35). Hyperacute rejection caused by preformed IgG antibodies can be prevented by cross-matching prior to transplantation. (II) Pre-existing "natural" IgM alloantibodies to nonself carbohydrate determinants. The best characterised alloantibodies are those directed against ABO blood group antigens. Hyperacute rejection by anti-ABO antibodies is not a

clinical problem because all donors and recipients are screened for identical ABO type. (III) Preexisting "natural" IgM human anti-pig antibodies in the case of xenogeneic transplantation. The majority of these antibodies are directed to α 1,3-galactose, a ubiquitous endothelial carbohydrate determinant. This antigen seems to be the major xenoantigen causing hyperacute rejection in pig-to-human xenotransplantation (36), but it is not expressed by humans and old world monkeys that produce high titers of antibodies against it. After transplantation of a vascularised xenograft, these preformed antibodies recognize and engage with the α 1,3-galactose antigen, thus triggering reactions in the xenograft vessels (fixation of complement, recruitment of the coagulation cascade and platelet aggregation and neutrophil adherence and infiltration) that lead within minutes to hyperacute rejection (37).

The search for a solution to the problem of hyperacute rejection in xenotransplantation has focused largely on genetically engineered pigs (38, 39). In transgenic pigs expressing the human decay-accelerating factor (hDAF), the injurious effect of antibody-mediated complement activation on the vascularised pig organ is greatly inhibited (40). Transplantation of such transgenic pig organs into non-human primates results in a dramatically reduced rate of hyperacute rejection (41). A further step forward is doubtless the ability to prevent the expression of α 1,3-galactose epitopes on pig endothelium by knocking out the gene that encodes the enzyme α 1,3-galactosyltransferase responsible for production of α 1,3-galactose epitopes (42). Since both copies of the gene have been inactivated, organ grafts from these pigs should not cause hyperacute rejection.

7.2 Acute Rejection

Acute rejection, which occurs typically after the first week following transplantation, is characterised by vascular and parenchymal injury. It involves both humoral and cell-mediated immune reactions. T cells play a central role in acute rejection by responding to alloantigens, predominantly MHC molecules, presented on vascular endothelial and parenchymal cells. Both CD4+ and CD8+ T cells contribute to acute rejection.

tion. CD4+ T cells mediate acute rejection by secreting cytokines and inducing delayed-type hypersensitivity-like reactions in grafts. Recognition and lysis of foreign cells by alloreactive cytotoxic CD8+ T cells is an important mechanism of acute rejection. Similar to hyperacute rejection, antibodies can mediate a humoral immune response to the vessel wall and activate complement. Krieger et al. used gene knockout mice to demonstrate the paramount role of CD4+ T cells in initiating rejection of allografts (43). They can both initiate and mediate allograft rejection, whereas CD8+ T cells are primarily mediators (44). There are two distinct mechanisms for the activation of alloreactive T cells that differ mainly in the route by which they recognize alloantigens: the direct and indirect pathways of allorecognition (Fig. 2). Since this topic has been dealt with in detail in recent overviews (e.g. 45), we will only discuss some of the more important aspects.

7.2.1 The Direct Pathway of Allorecognition

Direct recognition of allogeneic MHC antigens by T cells is the primary cause of acute rejection of transplanted organs. This pathway involves recognition by recipient T cells of donor allogeneic MHC class I and class II molecules, resulting in the generation of cytotoxic and helper T cells which play a pivotal role in the rejection process. Direct recognition of allogeneic MHC molecules may be thought of as a cross-reaction in which a T cell with the appropriate T-cell receptor specific for the complex of self-MHC and peptide also recognises the allogeneic MHC molecules. Evidence that self-restricted T-cell clones recognise allogeneic MHC/peptide complexes comes from a variety of sources (46, 47). Recent structural analysis of an alloreactive T-cell receptor confirmed that it interacted with an allogeneic MHC/peptide complex in a mode similar to its interaction with self-MHC molecules (48). In an allogeneic situation where the peptide and the presenting MHC are foreign for the alloreactive T cells, differences may derive either from polymorphic residues of the MHC and/or from the allogeneic peptide bound by the allogeneic MHC (49). This means that the nature of the peptide in the binding groove is not

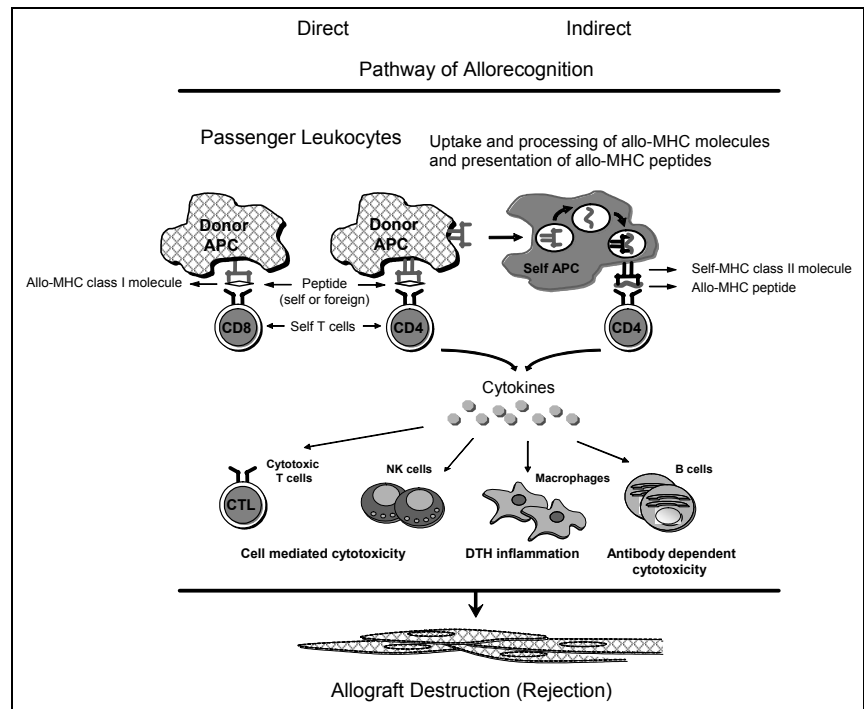


Fig. 2: *The direct and indirect pathways of allorecognition. In the direct pathway, passenger leukocytes transferred with the organ transplant directly activate alloreactive CD4+ and CD8+ T cells. In the indirect pathway of allorecognition, the recipient's antigen-presenting cells uptake allo-MHC molecules, process them into allo-MHC peptides, and present them in self-MHC class-II molecules to "self" T cells. Alloreactive CD4+ T cells that recognise these allo-MHC peptides are activated to secrete interleukins that control the various effector cells taking part in the rejection, such as natural killer cells, macrophages and B cells.*

necessarily relevant for the direct alloresponse (50). The consequence is that all MHC molecules on the surface of an antigen-presenting cell (more than 10^5 copies) are potential targets for alloreactive T cells independent of the presented peptide. Between 0.1% and 10% of an individual's T-cell repertoire are capable of directly recognising allo-MHC molecules, a very high percentage when compared to the less than 0.001% of T cells responding to a "normal" non-allogeneic peptide (51). This appears to be one reason for the extraordinary strength of the alloimmune response. In conclusion, several factors account for why so many recipient T cells with defined specificity for foreign peptides recognize the allogeneic MHC molecules after transplantation as an initial and central step towards graft rejection.

7.2.2 The Indirect Pathway of Allorecognition

In the indirect pathway of allorecognition, MHC molecules are recognised as

conventional peptide antigens by alloreactive T cells. This pathway became the focus of research early in the 1980s and results from self-MHC-restricted presentation of donor MHC peptides. It occurs when the allogeneic MHC molecules shed by the donor tissue (52) are taken up and processed by recipient antigen-presenting cells. This pathway was recently implicated in the chronic rejection of transplanted organs (53). While the direct pathway depends on the limited presence of passenger leukocytes and leads to an activation of CD4+ and CD8+ T cells, the indirect pathway depends on the continuous supply of alloantigens from the graft and usually involves allorecognition of CD4+ T cells (Fig. 3). Phagocytosis by host antigen-presenting cells results in the presentation of allopeptides by self-MHC class II molecules. However, it is possible that some antigens of phagocytosed graft cells enter the MHC class I pathway and are indirectly recognised by CD8+ T cells, a phenomenon known as "cross-priming" (54). The percentage of alloreactive T cells primed by the indirect pathway of allorecognition is

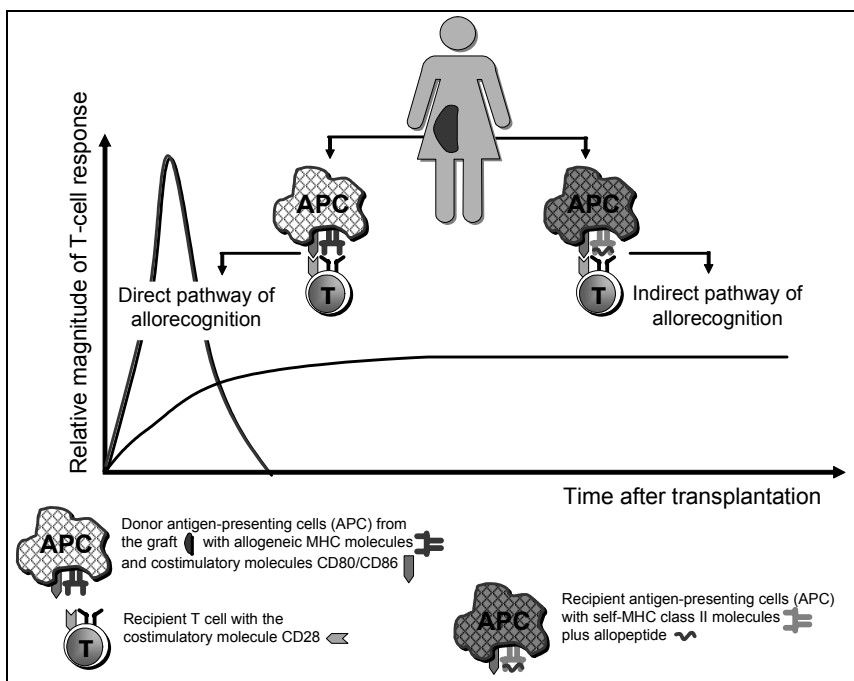


Fig. 3: The immunological situation following organ transplantation. Shown is the relationship between the type of T-cell activation, its relative magnitude and the duration of the resulting alloimmune response leading to rejection. Since the indirect pathway of alloantigen recognition (Fig. 2) is dependent on allo-MHC peptides, it offers special opportunities for influencing both the activation and function of alloreactive T cells using modified peptide antigens (Fig. 4).

about 100-fold lower than that of T cells participating in the direct pathway (55). Since MHC molecules are highly polymorphic in nature, they are responsible for allograft rejection. Transplantation between individuals with identical MHC molecules may also fail in the late phase after transplantation because at this time the so-called minor histocompatibility antigens, for example the H-Y antigens, come into play. These are polymorphic alloantigens that generally produce weak or slower rejection reactions (56).

Because MHC molecules are the most polymorphic proteins involved in T-cell activation, each allogeneic MHC molecule may give rise to multiple allogeneic peptides. Analysis of the immunobiological characteristics of MHC-derived peptides is based on sequences stored in databanks, which facilitate the generation of selected peptides. Many of these peptides derive from the polymorphic regions of the donor MHC molecules (57, 58, 59). The theory that these MHC molecules are also subject to the process of antigen processing and presentation is supported by sequence analysis of peptides eluted by the binding grooves of MHC class-II molecules.

The majority of these peptides derive from processed self-MHC molecules (60) and their presentation is thought to be important for maintenance of the immune system's ability to distinguish between "self" and "nonself" (61). It can be assumed therefore that allo-MHC molecules are processed and presented as well. Such membrane-bound molecules are either released by destroyed cells or shed from the cell surface of intact cells. Allogeneic MHC molecules have been detected circulating in the blood of renal transplant recipients (62).

In principle both allogeneic MHC class I and class II molecules can be processed by antigen-presenting cells of the recipient and presented as peptide fragments. Like all extracellular proteins, they reach the interior of the cell by endocytosis where they are broken down by proteases in vesicles (so-called endosomes). MHC class II molecules synthesized in the endoplasmic reticulum are transported via Golgi vesicles to these endosomes, with which they then fuse. Here the MHC class II molecules are loaded with the peptide and the resulting complex is transported to the cell surface (63). Naturally proc-

essed peptides bound by MHC class II molecules are between 13 and 24 amino acids long and are positioned lengthwise in the binding groove (64). Synthetic peptides, which are nine or less amino acids long, are also bound. The binding groove of the MHC class II molecule is open laterally, allowing the peptides to stick out at both ends (65).

7.3 Chronic Rejection

Chronic rejection (66), which occurs months or years after transplantation, is characterised by irreversible fibrosis with loss of normal organ structure and is the main cause of late graft rejection. The pathogenesis of chronic rejection is less well understood than that of acute rejection. It is likely that most of the adaptive and innate immune systems are involved in this process. Many risk factors may increase the incidence of chronic rejection: HLA incompatibility, ischemic injury, and the number and severity of acute rejection episodes and infections. One outstanding morphological sign in many cases is the occlusion of blood vessels, usually arteries, as a result of the proliferation of intimal smooth muscle cells. This graft vascular remodeling, which ultimately leads to ischemia and graft failure, is called graft arteriosclerosis or transplant-associated vasculopathy and is often seen in failed cardiac and renal allografts. Activated lymphocytes in the graft vessel wall participate in this process by inducing macrophage recruitment. Macrophages localized in the perivascular areas appear to be central to the initiation of fibrosis because they produce and secrete a variety of fibrogenic factors, matrix proteins, and growth factors for smooth muscles (33). Different upregulated cytokines have been demonstrated, including those associated with macrophage activation such as MCP-1 (33). IFN- γ in particular seems to play a key role in the development of transplant-associated vasculopathy (67). Chronic rejection cannot be prevented with current immunosuppressive drugs, so the present strategy is to limit the number of acute rejection episodes. The best prospects for overcoming late graft loss due to chronic rejection may reside in a new generation of immunosuppressive agents (68), in drugs with vasculoprotective effects to prevent neointima formation (69), and

in the promotion of clinically feasible strategies for induction of tolerance (70).

8. Antigen-Specific Therapy to Prevent Allograft Rejection

The underlying strategy of immunosuppression is the deliberate suppression of the host's immune system so as to prevent rejection of the transplant. This is not without danger, for long-term suppression of the immune system increases the patient's susceptibility to infection and risk of malignancy. These serious drawbacks underscore the need to develop strategies for antigen-specific suppression of the alloimmune response (Fig. 4). Improved understanding of the immunological processes underlying transplant rejection should open up new prospects for preventing it over the long term or even the induction of tolerance, the holy grail of transplantation medicine (71). The present survey does not add to our understanding of immunological tolerance nor does it discuss the various experimental approaches for induction of tolerance. Rather, it provides an overview of therapeutic approaches that employ synthetic peptides to prevent transplant rejection. Although recognition of alloantigen can lead to deleterious effects on a graft, the literature contains several examples of tolerance induction following exposure of the recipient to donor alloantigens prior to transplantation, either by infusion with whole cells or by treatment with MHC-derived synthetic peptides. This was first observed after blood transfusions (72). The success of this strategy depends on the nature and dose of the antigen as well as the route of administration.

T cell-mediated immunity occurs if T cells encounter their specific antigen in the form of a peptide/MHC complex on the surface of activated antigen-presenting cells. Since the donor MHC peptides are the principal antigens in the initiation and maintenance of the alloimmune response, it is not surprising that most experimental studies have focused on modulation of the alloimmune response using MHC allopeptides (73, 74). Some allopeptides have been shown to have potential immunomodulatory capacities when administered in-

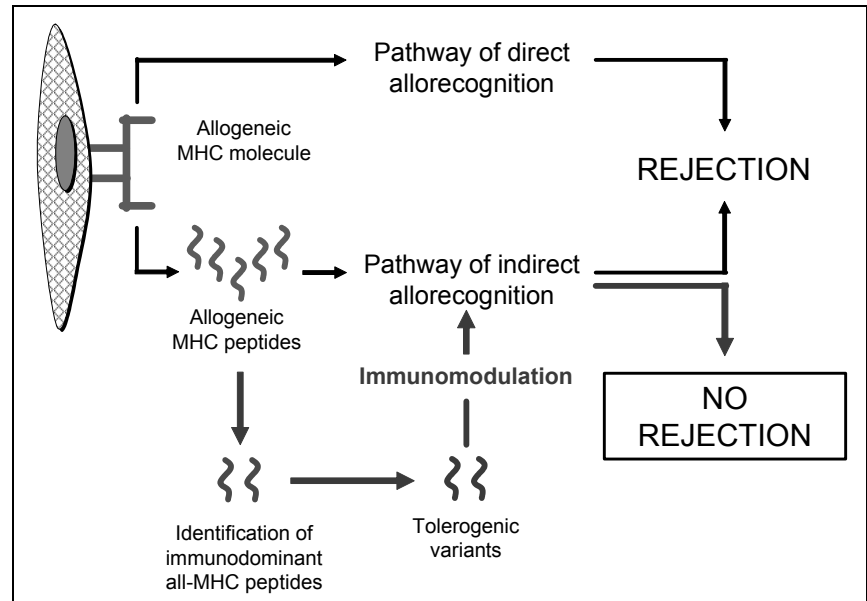


Fig. 4: The indirect pathway of alloantigen recognition is of special importance for peptide therapy. Along this pathway, immunomodulation of peptide variants could inhibit transplant rejection in an antigen-specific manner. It remains unclear whether this would allow effective control of the reactivity of alloreactive T cells. Shown here is a cell of the transplant with an alloantigen which can represent both an allo-MHC class I and an allo-MHC class II molecule.

trathymically (75), orally (76), or as peptide-pulsed recipient dendritic cells (77). The mechanism underlying this antigen-specific suppression of T-cell activity (78) appears to involve the switch from a Th1- to a Th2-dominated cytokine pattern ("immune deviation") (79). The development of tolerance observed after the application of MHC class-I peptides is also accompanied by upregulation of Th2-cytokines (80). A further strategy of possible clinical relevance is the application of such peptides in combination with short-term immunosuppression using calcineurin inhibitors. Thus transplant-specific tolerance was observed following combined application of MHC class I peptides and CsA (81). Our group achieved similar results administering a combination of allo-MHC class II peptides and CsA following small bowel transplantation (82). This protocol is based on the so-called "linked unresponsiveness" phenomenon and cannot achieve its result if the two substances are applied separately. It is not yet known under which conditions the inhibitory properties of such peptides come into play. Since all of these studies were performed in animal models and the responsible mechanisms must be further investigated and elucidated, their clinical applicability remains unclear.

A better approach may be to alter the alloreactive T-cell recognition by subtle changes in the sequence of the alloantigens (83). Peptides with modifications on the T-cell receptor contact sites are generally termed altered peptide ligands (84). Altered peptide ligands appear to influence the type and/or effectiveness of the T-cell response by modulating the intracellular signal transduction pathways and phosphorylation of proteins involved in T-cell activation (85). Altered peptide ligands have been studied in different murine models of autoimmune diseases because the dominant antigens are well characterized for most autoimmune diseases. Their use has highlighted the possibility of inducing a variety of biological activities, such as cytokine production without proliferation, changes in cytokine profile, and induction of anergy (86). Although the therapeutic use of altered peptide ligands has been well studied in experimental autoimmune diseases, very few data are yet available on the application of altered peptide ligands in the transplantation situation. Present data show that such peptides can indeed inhibit the activation of alloreactive T cells *in vitro* by the indirect pathway of allorecognition (87).

As stated above, allo-MHC molecules are the main stimulus of alloreactive T

cells after transplantation. The cytokines released by activated CD4⁺ T cells play a central role in the pathogenesis of acute and chronic rejection. According to current knowledge, after transplantation only a limited number of immunodominant peptides are presented to the recipient's T cells via the indirect pathway of alloantigen recognition (88). More importantly, no indication has yet been found of toxic reactions following application of peptides. Especially attractive is the connection between alloantigens and the induction of regulatory T cells (89). Regulatory T cells are currently regarded as a promising mediator of transplant-specific tolerance. Lechler et al. successfully demonstrated the *ex vivo* induction of allopeptide-specific human CD4⁺ CD25⁺ regulatory T cells (90). Not yet explained is whether such regulatory T cells generated *ex vivo* exert a regulatory function *in vivo* as well. It is also conceivable that regulatory peptides could be applied directly *in vivo* to induce regulatory T cells.

Clonal deletion is an extremely important mechanism for inhibiting the formation of autoreactive T cells (91). It is also vital for the induction of transplant-specific tolerance. At present, however, so-called active mechanisms are preferred, such as regulatory T cells (92). These require that an altered immunological status (possibly tolerance) can be demonstrated following transplantation by the detection of such cells and/or by the interleukins they secrete. This new approach can help in solving one of the basic problems of transplantation, namely the lack of markers of tolerance. Molecular-immunological markers for reliable demonstration of transplant tolerance are of paramount importance in clinical practice. The currently available *in vitro* assays do not always allow unequivocal verification of stable tolerance (93). This is due in part to our incomplete understanding of the mechanisms that determine whether a T cell is alloreactive or tolerant during activation. Such understanding though is a basic requirement for successful establishment of such assays. Since the immunodominant peptide and/or the corresponding altered peptide ligands must be identified for each donor-recipient combination, it is likely that this method will first be applied clinically in cases allowing lengthy preparation for the transplantation. Among

such cases are living donations and cell transplantation of parathyroid glands (94) or islets of Langerhans (95). This could ultimately form the basis for an extensive databank containing the immunodominant peptides and/or even their altered peptide ligands for the most common HLA donor-recipient combinations. Antigen-specific modulation of T-cell recognition following transplantation could in all likelihood also reinforce the cellular and molecular mechanisms leading to tolerance, and thus achieve the ultimate goal of transplantation research, the induction of transplant-specific tolerance. That this continues to be so highly relevant is attested to by the founding of the International Immune Tolerance Network for the initiation and coordination of promising clinical studies on the induction of tolerance (96).

9. Conclusions

Despite the dramatic improvement in early graft survival, overcoming late graft loss caused by chronic rejection and the lethal consequences of long-term immunosuppression, such as infection and cancer, requires the continued efforts of the transplantation community. The ability to reduce, temporally limit or even eliminate altogether the need for conventional immunosuppressive drugs without provoking rejection is the holy grail of transplantation medicine. Induction of tolerance is a promising approach to achieving these aims. At present, strategies based on immunomodulation with regulatory T cells appear very attractive. Of particular interest is whether such therapies can postpone or even prevent chronic transplant rejection, an unresolved problem of transplantation medicine. Even though the clinical application of peptide-based therapies is still some time away, the promise they hold is so great as to warrant continued research. Already their contribution to our understanding of the complex phenomenon of "alloreactivity" and the possibilities of targeted manipulation of alloreactive T cells makes the analysis of synthetic allo-MHC peptides of inestimable value.

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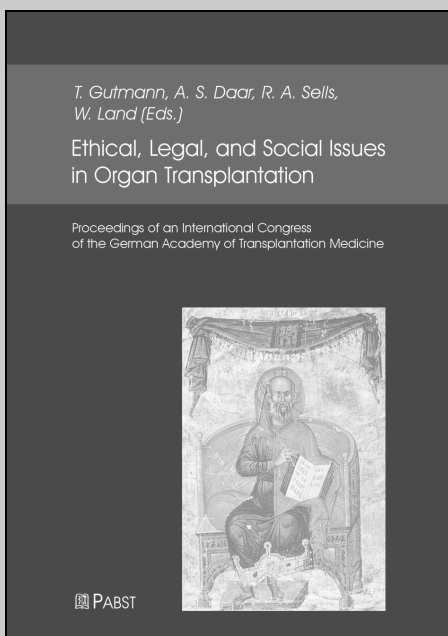
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