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Immunology of Liver Transplantation

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1. Introduction

The past four decades have witnessed the evolution of liver transplantation exploration procedures, and whilst they had witnessed a high mortality and morbidity they now serve as a successful therapeutic measure for end-stage liver disease. Nowadays, one year and five years survival for elective cases are often in excess of 85%-88% and 70%-75% and with an excellent quality of life (Annals of Hepatology, 2010). The remarkable success of liver transplantation is due largely to the development of immunosuppressive regimens that are highly effective at protecting allografts from acute rejection, and which ensure their survival in most cases. Interestingly, early liver transplantation studies with out-bred swine demonstrated that a high percentage of recipients maintained their graft in the absence of immunosuppression (Calne R Y et al., 1969). Subsequently, the spontaneous tolerance of liver allografts was also shown in liver transplantation in several allogeneic rat strain combinations and in most allogeneic mouse strain combinations (Farges O et al., 1995; Dresske B et al., 2002). As such, and compared with other solid-organ transplants, liver allografts have long been considered to be immunologically privileged, as manifest by an absence of hyperacute rejection despite a positive T cell cross-match, a low incidence of graft loss due to chronic rejection, and the potential for hepatocyte regeneration after tissue injury. Finally, in clinical transplantation, there is increasing evidence that some liver transplant recipients who cease taking immunosuppressive drugs maintain allograft function. Despite this special status, the liver can display destructive immunologic processes, since acute liver allograft rejection occurs in approximately 50% to 75% of liver transplant recipients (although in the majority of cases it is readily reversed with immunosuppressive approaches tailored to treat cellular rejection) (covered in a separate CAQ corner). Immunosuppressive drugs, however, also produce significant toxic effects that increase patient morbidity and mortality (Lechler R I et al., 2005; Sayegh M H et al., 2004). Moreover, the current immunosuppressive regimens do not prevent the development of chronic rejection, which is a major cause of graft loss. Most studies have also shown that a variety of autoimmune diseases with unknown aetiologies target the liver, including primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and biliary atresia (Duclos-Vallee J C et al., 2009; Schramm C et al., 2010; Guichelaar MM et al., 2003). As such, compared with other solid-organ transplants, liver transplantation is complex, having a sometimes paradoxical interaction with the host immune system. Understanding

these mechanisms is important, as it aids in the understanding of the clinical features of rejection and – hence – in making an early diagnosis and delivering appropriate treatment. Knowledge of these mechanisms is also critical in developing strategies to minimise rejection and in developing new drugs and treatments that blunt the effects of the immune system on transplanted organs, thereby ensuring the longer survival of these organs. The next chapter will elaborate on various aspects of liver transplantation immunology.

2. Types of grafts

Grafts of different species can cause different degrees of immune response to recipients. Generally, the greater the difference between the species, the more likely that it is that there will be a stronger immunological rejection. Accordingly, this section will discuss the types of graft. Liver grafts often mainly consist of four types: autograft, isograft, allograft and xenograft (Figure 1). The definitions and features of all grafts will be now be described in detail and the effects of different grafts on the body's immune system also will be introduced.
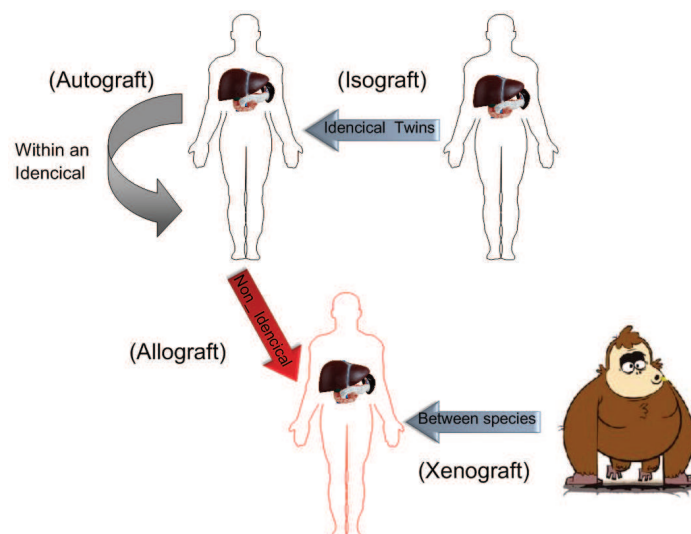

Fig. 1. Types of grafts

2.1 Autograft and isograft

Autograft means 'self-tissue' and refers to where on organ is transferred from one body site to another within the same individual. In recent years, auto-liver transplantation has been operated in some centres, but the number does not exceed one hundred because the operation technique is very complex and difficult. The autograft is a promising graft and has two advantages: (1) the graft is a tissue or organ already belong to the recipient who has spontaneous tolerance to the graft and so may avoid taking immunosuppressive drugs; (2) liver shortage is rapidly becoming a major restricting factor on the development of liver transplantation, and autografts avoid this problem. An isograft is a tissue or organ which is transferred between genetically identical individuals, e.g., liver transplantation between identical twins or grafts between mice of the same in-bred strain. This graft has the same advantages as the autograft, and it is not necessary to apply immunosuppressive regimens to the recipients. In particular, with the development of living donor liver transplantation,

this is an excellent graft. Nevertheless, the isograft is fairly uncommon and far from universal.

2.2 Allograft

An allograft is a tissue or organ which has been transferred between genetically different members of the same species. Allografts account for many human transplants, including those from cadaveric, living-related and living-unrelated donors. It is also called an allogeneic graft or a homograft. With regard to liver transplantation, most grafts are allografts. The graft may cause acute rejection and chronic rejection, and as such surgeons have to select the optimal match so as to reduce the occurrence of rejection by the ABO group and the HLA system.

2.3 Xenograft

A xenograft is a tissue or organ which has been transferred between different species. Donor shortage imposes the main restricting factor on liver transplantation and the continual growth of transplantation has led to significant organ shortages for a long time. At present in China – which is a country with a high incidence of liver disease – almost 3,000,000 patients develop some degree of liver cirrhosis, and about 10% of patients deteriorate to end-stage liver cirrhosis or liver cancer. As such, clinicians are often faced with the difficult prospect of rationing organs. Furthermore, liver transplantation in urgent cases is usually delayed – occasionally with fatal outcomes – until a suitable liver becomes available. Using animals as liver donors is a theoretically attractive solution, because it offers a potentially inexhaustible source of liver. This is of particular relevance for patients with fulminant liver failure who require urgent transplantation. Another potential use of xenografts lies in the fact that some animals are immune to certain viruses which may re-infect a human liver transplant (hepatitis being a case in point). Xenografts have been applied in the clinical region. Starzl's team transplanted two baboon livers into human subjects at Pittsburgh (Starzl et al., 1993). Although they did so with good graft function (and this may well result in the further development of this approach) the graft is confronted with some problems. The first is a problem of theory, such that only about fifty-percent of people support xenotransplantation. The second – and the biggest – problem is one of rejection, since xenotransplantation often causes hyperacute rejection and leads to graft dysfunction.

3. Immunological basis of allograft rejection

With regard to liver transplantation, grafts mainly originate from different members of the human species. The genetically encoded immunologically mediated barrier to transplantation was recognised and defined over the course of the last century. The immunological study of transplantation has played a pivotal role in the development of clinical transplantation. Although the first successful liver transplant was between identical twins, the development of transplantation as an important facet of modern medical therapy required the introduction of immunosuppression so as to prevent and treat the rejection of allografts (Liu L U et al., 2002; Yoshizawa A et al., 2006; Braillon A, 2009). The process of rejection is very complicated and has been shown to be caused by transplantation antigens, including major histocompatibility antigens, minor histocompatibility antigens and other

alloantigens. In addition, infiltrating leucocytes also launch the process, and it exhibits specificity and memory and is prevented by lymphocyte depletion (Gowans J L, 1962). The major histocompatibility complex (MHC) was identified as encoding the dominant transplantation antigens, and these were shown to be identical to serologically defined human leucocyte antigens (HLA), and subsequently to the elements responsible for the self-restriction of immunological responses to conventional antigens. The molecular and cellular basis of graft rejection will be described in the next section (Figure 2).
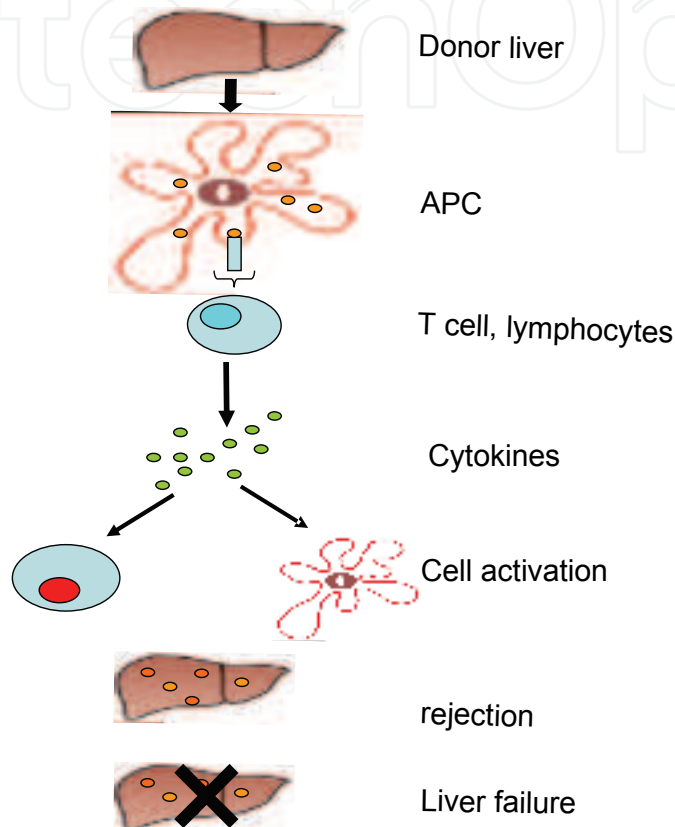

Fig. 2. The evolution of the immune response after liver transplantation. MHC, major histocompatibility complex; TCR, T cell receptor; APC, antigen presenting cell; IFN, interferon; TNF, tumour necrosis factor

3.1 Cell-mediated rejection of allografts

After liver transplantation, antibody-mediated, hyperacute vasculitic rejection can occur in individuals with preformed antibodies against the donor's MHC class I–encoded antigens. Under most other circumstances, acute allograft rejection is initiated by the large number of recipient T cells that recognise donor alloantigens (Stefanova I et al., 2003). Thus, the transplantation of MHC histoincompatible tissues elicits a strong, cytopathic, T cell-dependent immune response to donor tissues. By the T cell-dependent pathway to rejection, graft alloantigens are processed by specialised antigen presenting cells (APCs). Graft MHC molecules are internalised by donor and recipient APCs (Figure 3), following intracellular processing, and MHC peptide fragments are presented to the recipient's T cells (Watschinger B, 1995; Afzali B et al., 2008). Antigen presentation involves the engagement of these peptide antigenic fragments within a groove on the MHC molecules of the APC

surface. Acute cellular rejection is the best-characterised graft-specific form of immune rejection. Clinically apparent acute cellular rejection is defined by an often-sudden deterioration in allograft function; biopsy analysis of the transplanted tissue shows infiltration by host T cells and other mononuclear leucocytes and signs that these infiltrating cells have damaged the graft. Despite the routine use of immunosuppressive therapy, acute rejection is not rare. Studies show that CD4 and CD8 T cells both participate in acute rejection, although the rejection response is mediated primarily by CD4 T cells. CD4 T cells are activated by the above direct and indirect pathways, and primarily mediate the rejection response (Watschinger B., 1995). Although CD4 T cells are important in rejection, many activated CD8 T cells infiltrate the transplant tissue at the time of rejection, along with other mononuclear leucocytes (Strom TB et al., 1975). The cells of the innate immune system, such as natural killer (NK) cells, are also present in allografts during rejection. NK cells can recognise alloantigens because they constitutively express inhibitory receptors that are specific for self-MHC class I antigens; in addition, cytokines secreted by activated CD4 or CD8 T cells can promote the activation of NK cells, which can initiate and aggravate the rejection response (Dollinger MM et al., 1998).
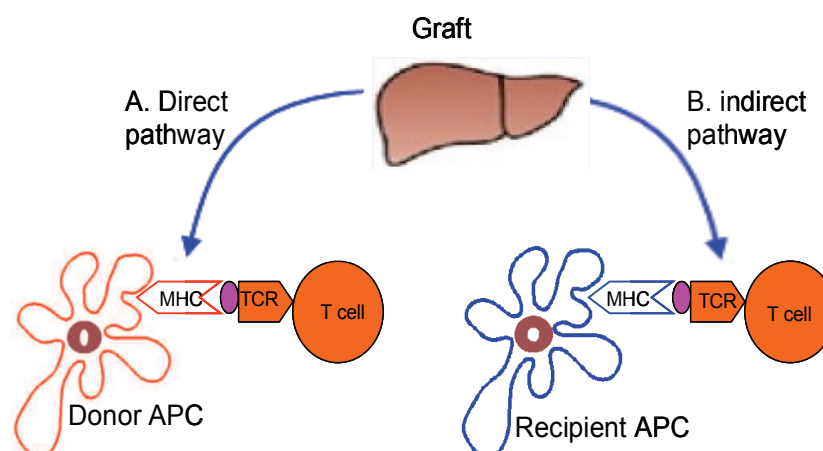

Fig. 3. Pathways of alloantigen presentation. (A) In the direct pathway, recipient T cells recognise intact allogeneic MHC molecules on the surface of donor APCs. The direct pathway is responsible for the large proportion of T cells that have reactivity against alloantigens due to the cross-reactivity of the T cell receptor (TCR) with self and foreign MHC molecules. (B) In the indirect pathway, recipient APCs trafficking through the allograft phagocytose allogeneic material are shed by donor cells (mostly peptides derived from allogeneic MHC molecules) and presented to the T cells on recipient MHC molecules

3.2 Humoral-mediated rejection of allografts

The humoral immune response is also important in the mediation of allograft rejection. The production of anti-donor MHC antibodies is associated with acute and chronic graft damage, usually in the form of graft vasculopathy. These antibodies can damage the graft by activating complement and mononuclear cells with Fc receptors that recognise the heavy chain of antibodies. Thus, Fc receptor–expressing leucocytes can be activated by antibody-coated donor cells. Anti-donor antibodies can also directly inhibit signalling cascades within endothelial cells (Li F et al., 2009). Humoral-mediated rejection of allografts is often observed following kidney, heart and lung transplantation, but liver allografts appear to

recover in relation to the development of humoral-mediated rejection. Most transplant organs manifest insidious and inexorable dysfunction as time passes. Although this process was formerly called 'chronic rejection', it is not clear that donor-specific immune rejection is the sole or even the primary cause in many conditions (Seetharam A et al., 2010). Pathology analysis often reveals fibrosis and atrophy in the absence of infiltration by T cells and other mononuclear leucocytes. Potential additional causes for chronic allograft failure include viral infection, recurrence of the original disease and drug toxicity. In general, humoral-mediated rejection of allografts is relatively uncommon in liver transplantation.

3.3 Memory T cell mediated rejection of allografts

Following T cell activation and proliferation, homeostasis of the adaptive immune system is restored by cell death – via "neglect" – of most antigen-specific T cells. A small number of T cells, however, survive and become long-lasting memory cells that ensure protective immunity against pathogens. Memory T cells can be divided into central memory and effector memory subsets, based on their circulation pattern and functional responsiveness. With regard to organ transplantation, upon re-exposure to donor antigens donor-reactive memory T cells are more sensitive to antigens, function more rapidly, produce effector cytokines, survive longer than naïve T cells and directly or indirectly produce cytolytic effects on the transplanted tissue (Ku C C et al., 2000; Sallusto F et al., 2000; Garcia S et al., 1999 & Barber DL et., 1999). Central memory T cells are responsible for recall antigen responses, and effector memory T cells survey peripheral tissues and immediately respond to invading pathogens (Sallusto F et al., 2004). As a consequence of continuous exposure to foreign antigens, memory T cells accumulate with time and represent approximately 50% of the total T cell pool in adults. Recipients who have not received a transplanted graft can still generate donor-reactive T cells, which can appear through immunisation by direct exposure to alloantigens via pregnancy or blood transfusion (Bingaman A W et., 2002). Furthermore, donor-reactive memory T cells can be generated in the absence of alloantigen exposure through heterologous immunity. Some memory T cells are therefore primed by an antigenic pathogen-derived peptides and cross-react with allogeneic peptides presented by the self or the donor MHC molecules. Alloreactive naïve T cells can acquire a memory phenotype and generate a substantial pool of donor-reactive memory T cells after transplantation, even when a recipient is under immunosuppressive therapy. Furthermore, the use of antibodies that deplete host T cells can amplify this phenomenon by inducing homeostatic T cell proliferation in response to lymphopenia (Wu Z et al., 2004). Because of their capacity to rapidly generate effector immune responses upon rechallenge, memory T cells appear to be particularly efficient at mediating allograft rejection (Zheng X X et al., 1999 & Schenk A D et al., 2008). In addition, memory T cells are less sensitive than naïve T cells to many immunosuppressive strategies. Compared with conventional T cells, memory T cells are less sensitive to T cell-depleting antibodies and therapeutics that block the CD28 and CD154 co-stimulatory signallers which inhibit the mammalian target of rapamycin (Pearl J P et al., 2005; Vu M D et al., 2006; Adams A B et al., 2003 & Araki K et al., 2009). The effects of memory T cells on the allograft response have been well delineated in animal models of allograft tolerance, wherein the generation of memory T cells by pre-sensitisation, heterologous immunity or homeostatic proliferation prevents the graft-protecting effects of most tolerising therapeutic strategies (Koyama I et al., 2007 & Valujskikh A et al., 2002). In contrast to human recipients, animals live in the protected environments of transplantation

laboratories and do not usually contain substantial numbers of memory T cells. This is one of the reasons that may explain the difficulties of translating into the clinic the results of protocols capable of creating allograft tolerance in rodent models. But the results cannot be applied in clinical conditions. Given the lower efficacy of conventional immunosuppressive drugs on activated memory lymphocytes, it is not surprising that memory T cells also exert harmful effects in clinical transplantation. In transplant studies, it is clearly understood that memory T cells – however they are generated – pose a significant barrier to inducing tolerance to allografts (Chalasani G et al., 2002; Zhai Y et al., 2002 & Adams AB et al., 2003). Thus, a better understanding of how to target this cell population and the designing novel of therapies that inhibit these cells would be beneficial.

3.4 Co-stimulatory pathways and the immunology of allografts

Evidently, T cells must receive two distinct but coordinated signals in order to achieve optimal activation. The first signal is provided by the TCR engagement with recognition of peptide/ MHC I or II on APCs, and the second signal is achieved by the interaction of co-stimulatory molecules on the T cells and their ligands on APCs. The importance of co-stimulation was found through experimental models in which its inhibition was achieved by some means, Signal 1 in the absence of signal 2 – as likely occurs in the liver – leads to a state of T cell non-responsiveness (or anergy) in which T cells can recognise cognate antigens through the TCR, but fail to mount a functional response upon reencounters with the antigen. So, there have been significant efforts to inhibit or block co-stimulatory pathways as a means of achieving allograft tolerance. There are two co-stimulatory pathways that are important in the generation of a complete T cell response are CD28/B7 and CD40/CD154 in the co-stimulatory field.

The role of CD28 has perhaps been that most intensively investigated in the co-stimulatory field. CD28 represents the prototypical T cell co-stimulatory molecule. In humans, CD28 is expressed on 90% of CD4 T cells and 50% of CD8 T cells; moreover, ligands for CD28, B7-1 (CD80) and B7-2 (CD86) are found on a variety of APCs including DCs, B cells and macrophages. The expression of CD86 is greater than for CD80 on APCs, although CD80 expression is enhanced during APC activation. The expression of CD80 and CD86 has been examined by immunohistochemistry or real-time polymerase chain reaction in livers following transplantation (Kwekkeboom J et al., 2003). CD80 was expressed only sporadically on normal liver but was present on at least 25% of the Kupffer cells in 45% of the transplanted livers. CD86 was found on the majority of Kupffer cells in all transplanted liver tissue and in normal liver tissue. The effect of ligation of CD28 by either CD86 or CD80 appears to be increased cytokine synthesis and proliferation by various intracellular signalling. Immunohistochemical analysis of CD86 expression in biopsies of liver recipients demonstrated an association with the increased expression of CD86 in the graft during severe acute cellular rejection (Bartlett A S et al., 2003). CTLA4 (CD152) is a CD28-related protein that binds to CD86 and CD80. Whereas CD28 delivers a positive co-stimulatory signal to T cells, CD152 delivers a negative signal that attenuates T cell function. CD152 expression is enhanced after T cell activation, and it has a higher affinity for CD86 or CD80 than does CD28; it has been proposed that the physiologic function of CD152 is to downregulate T cell responses. Therefore, specific activation of CD152 could potentially yield immunoinhibitory function and achieve allograft tolerance, but this ideal approach has been reached by the lack of suitable reagents.

The CD40/CD154 co-stimulatory pathway is a second important co-stimulatory pathway that is critical in the immune response of allotransplantation. CD40 is mainly expressed on APCs (including DCs, B cells, and macrophages) but it can also be expressed on nonimmune cells (including endothelial cells, mast cells, platelets and epithelial cells). However, CD154 is mainly expressed on CD4 T cells following activation, and to a lesser extent on NK cells, B cells, and CD8 T cells. CD154 combines with CD40, which is critical for the activation of DCs, B cells, and macrophages. In DCs, CD40 upregulates interleukin12 (IL-12) production, and in macrophages it results in the production of various proinflammatory cytokines. CD154 was also detected on Kupffer cells and on sinusoidal macrophages in livers during chronic rejection, but not in stable liver allografts or normal liver (Gaweco A S et al., 1999).

The most widely-used measure to block CD28-B7 interactions has been CTLA-immunoglobulin (Ig). In the orthotopic rat liver transplantation model, repeated administration of CTLA-Ig – beginning with CTLA-Ig in combination with donor splenocytes – leads to extended graft survival of >100 days, whereas the delayed administration of CTLA4-Ig alone or donor splenocytes alone did not (Neumann U P, et al., 2002). In recent years, many studies have shown that B7 cross-linking on APCs by CTLA4-Ig induces indoleamine 2, 3-dioxygenase (IDO), which itself inhibits local T cell activation (Mellor A L et al., 2003; Li W et al., 2009). Gene therapy approaches to deliver CTLA4-Ig to liver allografts have been successfully used in some animal experiments. Adenoviral-mediated gene delivery of CTLA4-Ig through ex vivo perfusion of cold preserved livers resulted in indefinite survival of rat liver allografts and in the generation of donor-specific unresponsiveness (Olthoff K et al., 1998). An interesting report suggests that CD154/CD40 interaction plays a role in promoting dendritic cell-maturation in the absence of CD4+CD25+ regulatory lymphocytes, whilst these cells promote the maintenance of immaturity (Serra P et al., 2003; Misra N et al., 2004). This accounts for the importance of DC activation, not only by innate immune mechanisms but also by activated T cells. The efficacy of anti-CD154 in a rat liver allograft model not only prolongs allograft survival but it was also associated with fewer complications (Bartlett AS et al., 2002). These roles underline the significant beneficial effects of CTLA4-Ig and anti-CD154 in pre-clinical models of transplantation; however, its clinical application has a long way to go for liver transplantation.

4. Classification and effector mechanisms of allograft rejection

Allograft rejection mainly involves host-versus-graft reaction in liver transplantation, which is the rejection of the transplant by the recipient's body. The recipient's lymphocyte mediated reactions to allogeneic or xenogeneic cells – acquired as a graft or otherwise –lead to damage and/or the destruction of the grafted cells. The graft rejection has been divided into three groups: hyperacute rejection, acute rejection and chronic rejection (Table 1).

Type of rejection	Time taken	Cause
Hyperacute	Minutes-hours	Pre-existing anti-donor antibodies and complement activation
Acute	Days – weeks	Primary activation of T cells
Chronic	Months – years	Causes unclear: antibodies, slow cellular reactions, immune complexes, recurrence of disease.

Table 1. Different types of graft rejection

4.1 Hyperacute rejection

Hyperacute rejection often occurs within minutes to hours after the host blood vessels are anastomosed to graft vessels. The rejection is mediated by pre-existing antibodies specific to the graft antigens (including ABO blood type antigens, VEC antigens and HLA antigens). Furthermore, these different antigens can activate the complement of the host and lead to damage to the endothelial cell. Studies have reported that the process is often accompanied with platelets activation and results in thrombosis and vascular occlusion (Fiane A E et al., 1999). In addition, the massive recruitment of neutrophils occurs, followed by rapid inflammation after transplantation. The pathological changes of hyperacute rejection are thrombotic occlusion of the graft vasculature ischemia, denaturation and necrosis (Figure 4). This rejection is relatively rare in liver transplantation.
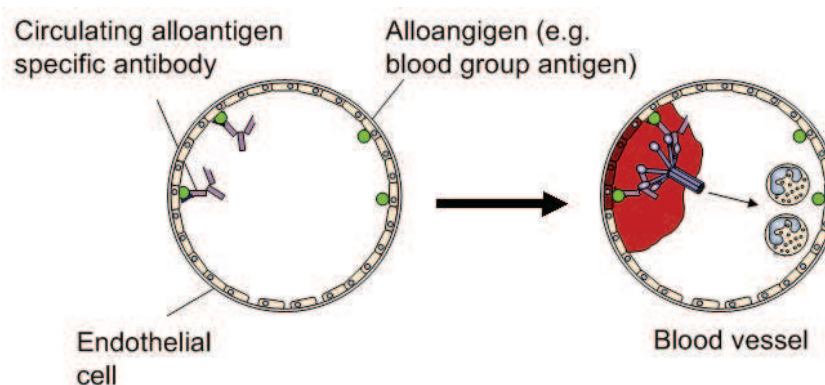

Fig. 4. Hyperacute rejection: complement activation, endothelial damage, inflammation, thrombosis and vascular occlusion

4.2 Acute rejection

Acute rejection occurs within days and up to three months after transplantation (80-90% of cases occur within one month). The rejection occurs due to donor HLA interaction with the host T cells, creating a cascade of immune responses initiated by that interface. After a solid organ transplant, there is an immunological milieu of activity. The mechanisms of the process involve abundant immune factors, such as humoral and/or cellular mechanisms (Figure 5). Antibodies can injure the graft by activating complement and mononuclear cells with Fc receptors that recognise alloantigens on the endothelial cell, resulting in vasculitis. Cytotoxic T cells (CD8+) will recognise alloantigens on an antigen presenting cell (APC) by direct presentation on the donor tissue and endothelial cells, which promotes the apoptosis of transplanted tissue. It has been shown that CD8+ cells alone are sufficient for the mediation of acute allograft rejection, but with the help of CD4+ cytokines secretion – such as IL-2 – clonal expansion and the expression of cytotoxic attack molecules will be upregulated (Kreisel D et al., 2002). The Fas/Fas ligand (FasL) pathway is another death-inducing pathway which is utilised by CD8+ cells. Whereas FasL is specifically induced upon CD8+ cells' activation, Fas is ubiquitously expressed on lymphoid and non-lymphoid tissue, including the liver. The Fas/FasL pathway is thought to play an important role in a variety of hepatic pathologies, and there is evidence that this pathway is also active during liver allograft rejection (Tannapel A et al., 1999; Ogura Y et al., 2001). Delayed hypersensitivity also has an important role in acute rejection, being initiated by alloantigen-

primed CD4+ cells specific to the donor class II (Carrodeguas L et., 1999). CD4+ cells release IFN-γ by re-exposure to specific alloantigens, a proinflammatory cytokine that can cause the activation of macrophages and the subsequent release of a variety of inflammatory mediators. These inflammatory mediators can augment the cellular anti-graft response or else can cause direct tissue damage. The acute rejection relatively occurs after liver transplantation is rare. But it has been a challenging process to try to unravel the participation of specific effector pathways and their interrelationships in the acute rejection of liver transplantation. The pathological features of acute rejection are acute vasculitis and parenchymal cell necrosis, along with the infiltration of lymphocytes and marophages (Figure 6).
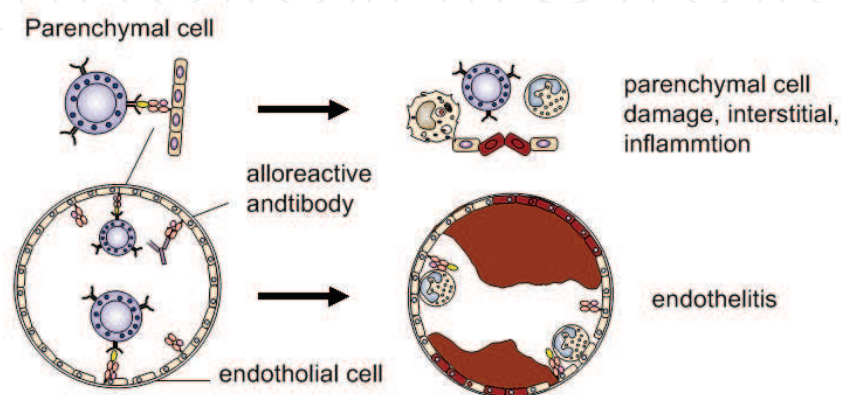

Fig. 5. Acute rejection: parenchymal cell damage and endotheliitis
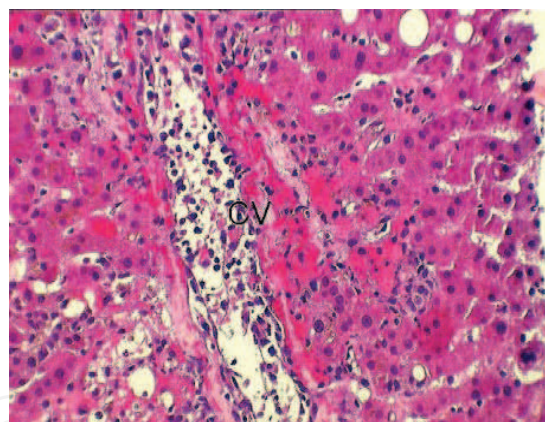

Fig. 6. A higher magnification of the previous photomicrograph details the subendothelial localisation of lymphocytes and the slight extension of the infiltrate into the perivenular hepatic parenchyma (http://tpis.upmc.com/TPIShome/)

4.3 Chronic rejection

Chronic rejection is less well-defined than either hyperacute or acute rejection, developing months or years after acute rejection reactions have subsided. Chronic rejection is an indolent but progressive form of allograft injury that is usually irreversible and which eventually results in the failure of most vascularised solid organ allografts. It is the single most significant obstacle to morbidity-free long-term survival. By five years after transplantation, it affects as many as 30-50% of heart, lung, pancreas and kidney allograft recipients, but only 4-8% of patients who undergo liver replacement (Demetris, A J et al.,

1997). Liver allografts differ from other solid organs in that chronic rejection is potentially reversible. This feature has been mainly attributed to its unique immunobiological privilege and the regenerative capacity of the process. Livers with chronic rejection have a decreased number of bile ducts on biopsy. This is referred to as "vanishing bile duct syndrome" (Demetris A et al., 2000). Chronic rejection is characterised by vasculopathy, fibrosis and a progressive loss of organ function. It is probably caused by multiple factors, viz., antibodies as well as lymphocytes (Figure 7). Chronic rejection may be mediated by a low-grade, persistent, delayed hypersensitivity response in which activated macrophages secrete mesenchymal cell-growth factors. Of potential importance are the persistent viral infections which induce cellular immune responses which in turn may synergise with donor-specific alloreactive T cells within the allograft. Chronic rejection may also reflect chronic ischemia secondary to the injury of blood vessels by antibody or cell-mediated mechanisms. Vascular occlusion may also occur as a result of smooth muscle cell proliferation in the intimae of arterial walls.
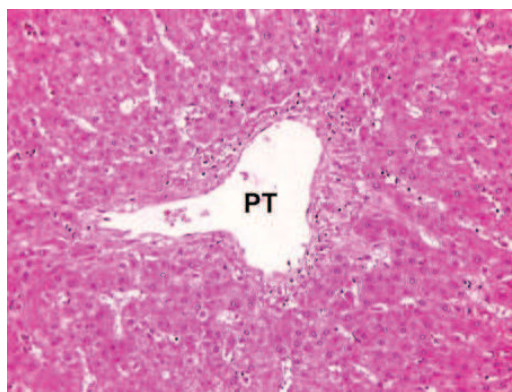

Fig. 7. Severe or very late-stage chronic rejection can result in the loss of the small branches of the hepatic artery, in addition to the loss of bile ducts. Note the lack of bile ducts and lack of hepatic artery branches in this portal tract (http://tpis.upmc.com/TPIShome/)

5. Prevention and treatment of allograft rejection

Allograft rejection is prevented by graft selection before transplantation, such as ABO blood group and HLA matching. Treatment of allograft rejection refers to immunosuppressive therapy, involving an immunosuppressive drugs selection and regimen, molecular therapy and cellular therapy. These related factors will be briefly described in this section.

5.1 Graft selection

The majority of liver transplant centres regard blood group compatibility as the primarily immunological selection criterion. A liver from a donor with a compatible ABO and Rh blood group is easy and feasible, with well-documented reports of this being performed in urgent situations (Gordon R D et al., 1986). In recent years, many transplantation centres have also carried out the operation with ABO-incompatible grafts, and the outcomes of ABO-incompatible liver transplantations have been similar to that of blood-type-matched transplantations in some centres. However, infection is the major cause of morbidity and mortality after ABO-incompatible liver transplantation (Tanabe M et al., 2010). At present, the transplantation of compatible but not identical livers is common practice, especially for

recipients with the less common blood groups. Interestingly, the results of ABO identical grafts were slightly better than the ABO compatible but non-identical grafts (Gugenheim J et al., 1990). An occasional complication with compatible, non-identical grafts is the occurrence of allograft rejection, due to the immunocompetent passenger lymphocytes within the transplanted liver producing antibodies against the recipient erythrocytes. It is well-established that renal transplantation in the presence of donor-specific cytotoxic antibodies – demonstrated by a positive cross-match – will result in rapid graft loss. However, the liver behaves in a totally contrary manner. In addition, the major histocompatibility antigens have a well-documented role in renal transplantation. However, early studies of liver transplantation in pigs implied that the liver may be a privileged organ exhibiting minimal rejection, with some grafts surviving without immunosuppression. This special feature prompted surgeons to ignore HLA-matching in patient selection for donor shortages. Retrospective data has not shown any clear survival advantages associated with good HLA-matching (Navarro V et al., 2006). Interestingly, some studies suggest that there is a clear disadvantage with certain aspects of HLA-matching. The largest series from Pittsburgh, involving more than 500 transplants, concludes that overall graft survival is actually reduced in grafts matched for HLA (Markus BH et al., 1988).

5.2 Immunosuppressive therapy

The liver is a privileged organ with a lower incidence of rejection than other organs, but immunosuppressive regimens are nonetheless required to control the alloreactive T-lymphocyte response after transplantation. In the 1990s, acute liver rejection occurred in up to 60% [1] of patients, without compromising graft or and patient survival (Neuberger J, 1999). Since 2000, the incidence of acute liver rejection has decreased to 15% of recipients. The incidence of chronic rejection is also declining, and most centres report current rates of 4% to 8%, whereas in the 1990s, rates of 15% to 20% were observed (Neuberger J, 1999).This decrease correlated with the use of new immunosuppressive drugs and improvements in treatment-management.

Over the last three decades, the number and types of immunosuppressive agents available to clinicians have increased considerably. The immunosuppressive therapy used in liver transplantation includes agents such as corticosteroids, calcineurin inhibitor (CNI), antimetabolites, inhibitors of TOR, and monoclonal and polyclonal antibodies which have different patterns of action (Figure 9) (Beaudreuil S et al., 2007). Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of physiological systems, including stress-response, immune-response and the regulation of inflammation. The drugs are hydrophobic, which enables them to enter the cell by membrane diffusion. They then form complexes with cytosolic receptors, leading to their translocation to the nucleus where they bind to glucocorticoid-response elements in the promoter regions of cytokine genes, thereby blocking T cell-mediated cytokine expression. Thus, corticosteroids have been a mainstay of treatment during the early days after transplantation, but as immunosuppressive agents they are often accompanied by many side-effects within a few years. Calcineurin inhibitor is the first routinely employed immunosuppressive agent, including cyclosporine A (CyA) and tacrolimus (FK-506). CyA selectively inhibits T lymphocyte proliferation by forming a complex with cyclophilin. This complex can inhibit the calcium and calmodulin-dependent phosphatase calcineurin.
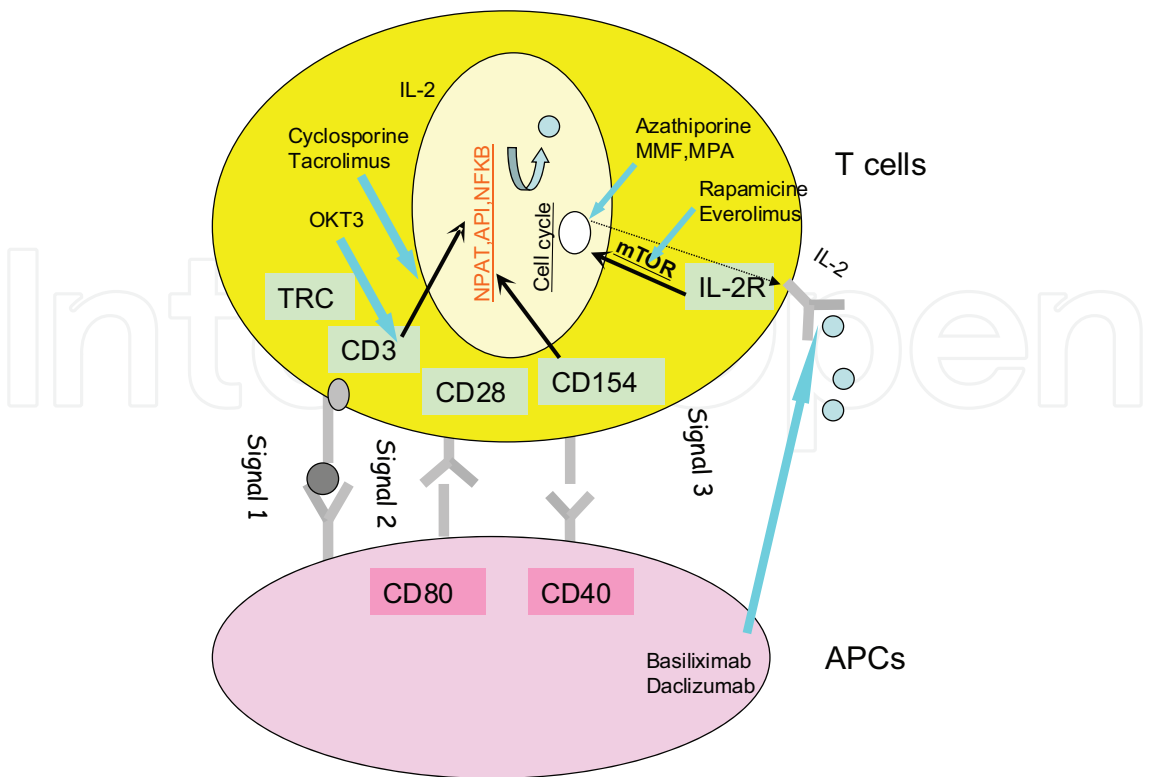
Fig. 9. Pattern of T cell activation and targeting of mainly immunosuppressors. Signals 1, 2 and 3 for T cell activation are shown with a number. The drug targets used in tolerance protocols are shown with blue arrow

Calcineurin is a key enzyme involved in controlling the transcription of IL-2 and other cytokines (Friman S et al., 1996). Therefore, impairing IL-2 transduction has a profound effect on the immune process of rejection by inhibiting calcineurin. However, the CyA metabolism is complex in liver transplant patients. Because it is metabolised primarily in the intestine and the liver, it increases the burden on the liver and even results in liver failure. Fk506 is very similar in action to CyA, but it is substantially more potent. It acts by binding to the FK-binding protein 12. The complex formed inhibits calcineurin, which regulates the transcription of the genes encoding IL-2, IL-3, IL-4, IL-8, as well as various chemotactic factors (Komolmit P et al., 1999). The side-effects of Fk506 are similar to those of CyA. In clinical practice, given the initial impairment of liver function and the frequent renal failure observed in the postoperative period, physicians should delay the administration of CyA or FK-506, with no impact on the outcome of liver transplantation or the occurrence of allograft rejection. Antimetabolites were not initially used in liver transplantation. Mycophenolate mofetil (MMF) – as a new antimetabolite molecule – has been shown to inhibit T and B cell proliferation, making it possible to reduce the rate of acute rejection in renal transplantation. These antimetabolites can be used together with an antibody against the IL2 receptor, delaying the introduction of CINs. These findings rapidly led to the use of these drugs in liver transplantation. Combination therapy with tacrolimus and MMF may significantly reduce the incidence of acute liver allograft rejection, allow a significant reduction in tacrolimus dosage, and decrease the incidence of nephrotoxicity (Eckhoff D E et al., 1998). In addition, the side-effects of MMF were relatively few. Inhibitors of TOR mainly include Rapamicine and Everolimus. Rapamicine is a macrocyclic triene antibiotic that is

structurally similar to tacrolimus. It forms a complex with the FK506-binding protein but it does not inhibit calcineurin. The complex blocks the cytokine response to T cell and B cell activation, preventing cell cycle progression and proliferation. Its principal side-effects are leukopenia, thrombocytopenia, high serum cholesterol and triglyceride levels, anaemia, lymphocele, wound dehiscence and mouth ulcers (Levitsky J., 2011). The biggest advantage of Rapamicine is associated with the lack of any significant nephrotoxicity (Vivarelli M et al., 2010). Compared with Rapamicine, Everolimus has greater bioavailability and a shorter half-life. The antibodies used in transplantation may be monoclonal or polyclonal. At present, monoclonal antibodies primarily include IL-2R antibodies and anti-CD52 antibodies. Two humanised IL-2R antibodies have been put on the market: basiliximab and daclizumab, which inhibit T cell proliferation by the competitive antagonism of IL-2-induced T cell proliferation, and they are accompanied with very few side-effects. OK3 is also currently the most widely-used monoclonal antibody, which binds to part of the T cell receptor (CD3) complex. The major impact of OK3 has been in the reversal of steroid-resistant, acute rejection (Cosimi A B et al., 1981). Polyclonal antibodies are IgG fractions from animals inoculated with human lymphocytes, thymocytes or cultured lymphoblast. Polyclonal antibodies have more profound and long-lasting biological depleting effects than other antibodies (Rebellato L M). However, polyclonal antibodies often induce the over-suppression of the immune system, increasing the risk of infectious diseases, lymphoproliferative syndrome and tumours.

There are significant variations in the regimens for immunosuppressive therapy used by different liver transplant centres. In general, most regimens include corticosteroids plus one calcineurin inhibitor, such as CyA or FK506. Anti-proliferative agents are often used in the first few months, with the patients also receiving bitoherapy with low doses of CIN and steroids. In liver transplantation, physicians tend to withdraw steroids within a few years due to their many side-effects. In addition, a study compared two groups of patients, one given induction therapy based on anti-thymocyte globulin (ATG) and FK506 without steroids, and the other treated with FK506, MMF and steroids. A graft survival of one-and-a-half years was 89% in both groups. However, rejection-rates were significantly lower in the group that was treated without steroids than in the group that was treated with steroids (Eason JD et al., 2001). Calcineurin inhibitor treatment often caused renal failure by nephrotoxicity. Studies have shown that up to 21% of patients were found to have developed chronic renal failure within five years of receiving a non renal transplant (Ojo AO et al.,2003). A recent report has shown that Sirolimus-based immunosuppressive therapy is a safe, effective replacement agent for primary immunosuppressive therapy in liver transplant recipients with FK506-related chronic renal insufficiency (Yang YJ et al., 2008). Furthermore, the addition of MMF to the regimen, and the reduction of the dose of calcineurin inhibitor by more than 50%, has been shown to improve renal function.

5.3 Prospective of using recipients T regulatory cell

In fact, the immunosuppression regimens used in liver transplantation were historically derived from those used in renal transplantation. Immunosuppressive regimens are required to control the allogeneic response in clinical liver transplantation, but they may also lead to severe complications, such as infectious diseases, cancers, cardiovascular diseases and – for treatments involving calcineurin inhibitors – chronic renal insufficiency.

T regulatory cells (Tregs), a subset of CD4+CD25+Foxp3+ lymphocytes, have the functional ability to suppress alloimmune responses both *in vitro* and *in vivo*. Increasing evidence from animal transplant research shows that Tregs can play a key role in promoting immunological unresponsiveness to allograft transplants (Pilat N et al., 2010; Webster KE et al., 2009). Regulatory T cells are the key cell-types in the induction of immune tolerance, and so the modulation of such cells may provide new strategies in creating transplant tolerance. However, there are several challenges to translating Tregs into the clinic. Tregs only account for about 5-10% of the total CD4+ T cells in the periphery, the limitation of cell number restricted the clinical application. There are a number of studies demonstrating the functional instability of Tregs *in vivo*, which can become IL-17 producing T effector cells in the presence of IL-6 (Yang XO et al., 2008). Furthermore, T effector cells activated under inflammatory conditions are highly resistant to Tregs-mediated suppression (Korn T et al., 2007). Concerning the Tregs, there are two broad approaches to the use of Tregs to promote transplant tolerance. The first is to expand Tregs *in vitro* and then apply expanded Tregs as a cell therapy *in vivo*. The advantage of this approach is that antigen-specific Tregs can be created *in vitro* using donor antigens. The second approach is to selectively and specifically stimulate *in vivo*, by taking advantage of fundamental differences between the biology of Tregs and T effector cells. In general, Tregs are a promising substance for the achievement of transplant tolerance.

6. Conclusion

The remarkable success of liver transplantation over the last four decades is due largely to the development of immunosuppressive regimens that are highly effective in protecting allografts from acute rejection, and that ensure their survival with a high quality of life in most cases. However, current immunosuppressive regimens do not prevent the development of chronic rejection, which constitutes a major cause of graft loss. In addition, these regimens may also lead to severe complications. This chapter mainly describe s the basic concepts of transplant immunology, the immunological basis of allograft rejection and the prevention and treatment of allograft rejection. In general, the immunological system of liver transplantation is very complex, and allograft tolerance has been well-established in experimental transplantation models; however, clinical operational tolerance will need to be further developed. Fortunately, Tregs may constitute a promising substance for achieving clinical operational tolerance by various modes of analysis. Furthermore, the clinical assessment of tolerance has been limited to laboratory-based evaluations of liver function and immunosuppressive agents' levels, and more precise clinical assessments should have been well-established.

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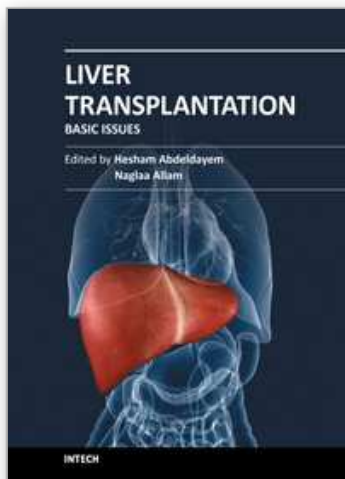
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