Review

Chemokine Receptors and Transplantation

Jinquan Tan[1, 2] and Gang Zhou[1]

A complex process including both the innate and acquired immune responses results in allograft rejection. Some chemokine receptors and their ligands play essential roles not only for leukocyte migration into the graft but also in facilitating dendritic and T cell trafficking between lymph nodes and the transplant in the early and late stage of the allogeneic response. This review focuses on the impact of these chemoattractant proteins on transplant outcome and novel diagnostic and therapeutic approaches for antirejection therapy based on targeting of chemokine receptors and/or their ligands. *Cellular & Molecular Immunology*. 2005;2(5):343-349.

Key Words: chemokine, receptor, transplant, allograft, rejection

Introduction

Chemokine receptors and their ligands control a wide variety of biological and pathological processes, ranging from immunosurveillance to inflammation, from viral infection to cancer, and from transplant rejection to transplant tolerance (1).

Allograft transplant rejection is mediated largely by circulating peripheral leukocytes induced to infiltrate into the graft by various inflammatory factors. Of these, chemokine receptors and their ligands, which are expressed by early innate responding leukocytes, as well as by inflamed graft tissues, are responsible for the recruitment and infiltration of alloreactive leukocytes.

Chemokine and chemokine receptor family

The term "chemokines", which is an abbreviation of "chemoattractant cytokines", was created to describe a family of around 50 related proteins that have roles in leukocyte activation, selectin/integrin up-regulation, hematopoiesis, angiogenesis, and adaptive immunity both during development and in the adult. However, they were originally discovered for their ability to function as chemoattractants (2, 3). Chemokines are low molecular weight proteins (8-12 kD), which usually contain four cysteine residues and are subdivided into four different families in terms of the arrangement of the first two N-terminal cysteine residues: the CXC (α), CC (β), C (γ) and CX3C (δ) families of chemokines (Table 1). Most chemokines belong to the CC and CXC families and they have received the greatest attention in experimental models of disease and inflammation (4, 5).

All known chemokines bind to seven-transmembrane G-protein-coupled receptors, *Bordetella pertussis* toxin-sensitive receptors. The ability of any particular chemokine to activate a given leukocyte is *via* the expression of corresponding receptors on the surface of the cell. The specificity and complexity of the chemokine system stem from the regulated expression of their receptors. Although the C and CX3C chemokines bind to only one receptor, the CC and CXC chemokines are promiscuous, with most binding to two or more receptors each, for instance CCL5 binds to CCR1, CCR3, and CCR5. Even in the case of a particular chemokine binding to only a single receptor, chemokine receptors also can bind more than one ligand, for example only CCR6 and CCR9 from CCR1-11 bind only one CC chemokine. Chemokine receptors are named after their specific chemokine preferences (Table 1): CCR1-11, CXCR1-6, XCR1, CX3CR1 and chemokine-binding proteins Duffy, D6 (6, 7).

Chemokine receptors and transplantation rejection

It is not surprising that chemokine receptors and their ligands may be involved in rejection of allogeneic transplants because the chemokine receptor system plays an essential role in host defense (11). Chemokine system could influence at least three aspects of allograft biology. First, chemokines recruit leukocytes in the process of ischemia-reperfusion injury, which could be led to by restoration of blood flow in the allograft. Second, chemokine receptors and their ligands mediate host responses to infection during immune

[1]Department of Immunology, Wuhan University School of Medicine, Wuhan, China;

[2]Corresponding to: Dr. Jinquan Tan, Department of Immunology, Wuhan University School of Medicine, Wuhan, China. Tel: +86-27-628-65893, Fax: +86-27-687-59039, E-mail: jinquan_tan@hotmail.com.

Received Oct 10, 2005. Accepted Oct 25, 2005.

Table 1. Classification of chemokines and chemokine receptors (8, 9, 10)

Ligands	Synonyms	Receptors
CXC (α)		
CXCL1	Groα	CXCR1, 2, Duffy
CXCL2	Groβ	CXCR2
CXCL3	Groγ	CXCR2
CXCL4	PF4	CXCR1, 2
CXCL5	ENA-78	CXCR2
CXCL6	GCP-2	CXCR1, 2
CXCL7	NAP-2	CXCR2, Duffy
CXCL8	IL-8	CXCR1, 2, Duffy
CXCL9	Mig	CXCR3
CXCL10	IP-10	CXCR3
CXCL11	I-TAC	CXCR3
CXCL12	SDF-1	CXCR4
CXCL13	BCA-1	CXCR5
CXCL14	Bolekine	ND
CXCL15	Lungkine	ND
CXCL16	SR-PSOX	CXCR6
CC (β)		
CCL1	I-309	CCR8, Duffy
CCL2	MCP-1	CCR2, D6
CCL3	MIP-1α	CCR1, 5
CCL4	MIP-1β	CCR5, D6
CCL5	RANTES	CCR1, 3, 5, Duffy, D6
CCL6	MRP-1	ND
CCL7	MCP-3	CCR1, 2
CCL8	MCP-2	CCR1, 2, 5, D6
CCL9	MRP-2	ND
CCL10	CCF18	ND
CCL11	Eotaxin	CCR3
CCL12	MCP-5	CCR2
CCL13	MCP-4	CCR1, 2, 3, D6
CCL14	HCC-1	CCR1, D6
CCL15	HCC-2	CCR1, D6
CCL16	HCC-4	CCR1, 8
CCL17	TARC	CCR4
CCL18	DC-CK1	ND
CCL19	ELC/MIP-3β	CCR7, 11
CCL20	LARC/MIP-3α	CCR6
CCL21	SLC/6Ckine	CCR7, 11
CCL22	MDC	CCR4
CCL23	MPIF-1	CCR1
CCL24	Eotaxin-2	CCR3
CCL25	TECK	CCR9, 11
CCL26	Eotaxin-3	CCR3
CCL27	CTAK/Eskine	CCR10
CCL28	MEC/CCK1	CCR10
C (γ)		
XCL1	Lymphotactin	XCR1
XCL2	SCM-1	XCR1
CX3C (δ)		
CX3CL1	Fractalkine	CX3CR1

ND, not determined.

suppression. Third, the inflammatory components of acute and chronic rejection are likely to be controlled by chemokines (5).

Analysis of mice with targeted deletions of certain chemokine receptors and their ligands has gradually clarified their relative importance in allograft rejection. Following we will discuss the relationship between some particular chemokine receptors and various tissue transplant.

Heart transplantation

Hancock et al. used three models *in vivo* to demonstrate a role for CXCR3 in the development of transplant rejection. It is concluded that CXCR3 plays a key role in T cell activation, recruitment, and human cardiac allograft destruction (12, 13). Interestingly, CXCR3 showed a unique pattern of expression by immunohistochemical staining: it was found the weak expression on cells in the outer layer of the neointima and adventitia and the strongest staining in the innermost layer of the neointima (14). In some patients, there was a trend for persistent expression of $CD3^+$ and $CXCR3^+$ expressing infiltrates in the later part of the first posttransplant year. The CXCL10, ligand of CXCR3, which was rarely expressed in normal biopsies, was markedly induced in acute rejection (15). The presence of $CXCR3^+$ T cells and CXCL10 within endomyocardial biopsies is strongly associated with acute rejection.

Just as CXCR3, CCR5 expression level was increased higher in the later than earlier biopsies despite no change in histologic rejection-grade status (16). This result demonstrates significantly increased expression of T-cell chemoattractants in heart allografts during later rejection when compared with episodes occurring shortly after transplantation, and also suggests increased intensity of inflammation in rejection occurring at later times posttransplant that are revealed by molecular analyses of the graft.

In addition, inbred mice with a targeted deletion of the CCR1 showed significant prolongation of cardiac allograft survival in different four models (17). The other study examined the effect of BX471, the CCR1 antagonist, in a rat heterotopic heart transplant rejection model. Treatment of animals with BX471 and a subtherapeutic dose of cyclosporin is much more efficacious in prolonging transplantation rejection than animals treated with either cyclosporin or BX471 alone (18). The mechanism of action of the CCR1 antagonist is that the antagonist blocks the firm adhesion of monocytes triggered by CCL5 on inflamed endothelium. These findings provide evidence that *in vivo* blockade of CCR1/ligand interactions is of therapeutic significance in preventing acute and chronic rejection clinically.

CXCR3, CCR5, CCR2, CCR3 genes and those of their corresponding ligands were selectively and strongly induced in grafts that develop transplant vasculopathy. The expression patterns of these receptors were similar in both cardiac and aortic allografts, although their induction and absolute expression levels were amplified several folds in the grafted aorta compared with heart grafts. The genes which were induced before morphologic changes became apparent, and then expression was sustained during the whole period of neointimal formation (14, 15).

All above studies suggested diagnostic as well as

potential therapeutic roles of the chemokine-receptor pairs CXCL10-CXCR3, CCL5-CCR5, CCL5-CCR1 and CCL2-CCR2 in patients or rat models of cardiac allograft transplant.

Kidney transplantation

Some chemokine receptors have been shown to play important roles in acute renal transplant rejection and chronic allograft nephropathy (19). Ischemia/reperfusion injury after organ transplantation is a major cause of delayed graft function. Following ischemia/reperfusion, CXCR2 produced in graft attracts and activates granulocytes in a rat model, which in turn promotes graft damage. It is effective that using repertaxin, a CXCR2 inhibitor, to treat the recipient animal can prevent granulocyte infiltration and renal function impairment in allogeneic transplantation (20). The possibility to modulate ischemia/reperfusion injury in this rat model opens new perspectives for preventing posttransplant delayed graft function in humans.

In addition, CXCL10, CCR1, CCL5, CCR2, and CCR5 express increased level in acute renal transplant rejection, but CCL2 shows a low expression. In particular, CCR1 and CXCL10, which show high expression prior to rejection and return to baseline levels with antirejection therapy, may have potential use in immunomonitoring in PBMCs and as predictive factors of rejection prior to its clinical manifestation (21). The levels of CXCL10, a CXCR3 ligand, in pretransplant serum represent a clinically useful parameter for the identification of subjects exhibiting high risk of acute rejection, chronic allograft nephropathy and graft failure (22). This result might be used to individualize immuno-suppressive therapies.

Compared to acute renal transplant rejection, biopsies with chronic allograft nephropathy revealed a lower but detectable expression of CCL2, CCL5, CCR1, CCR2 and CCR5 in tubulointerstitial cells, and a significantly lower infiltration with MRP14-positive monocytes/macrophages (23). However, there are other different findings that ligands for CCR5 are upregulated, and the graft is infiltrated by CCR5-positive mononuclear cells during acute and chronic transplant rejection. In 163 renal transplant recipients, some studies examined the association of human chemokine receptor genetic variants, CCR5delta32, CCR5-59029-A/G, CCR2-V64I, CX3CR1-V249I, and CX3CR1-T280M (24). The risk of acute renal transplant rejection was reduced significantly in recipients who possessed the CCR2-64I allele or who were homozygous for the 59029-A allele (25). Patients homozygous for CCR5delta32 show longer survival of renal transplants than in the control group, suggesting a pathophysiological role for CCR5 in transplant loss (26). It was concluded that the risk of acute rejection in renal transplantation is associated with genetic variation in the chemokine receptors CCR2 and CCR5. These two receptors may be a useful target for the prevention of transplant loss.

Some chemokine receptors and their ligands could have impact on the development of chronic allograft nephropathy because they are involved in tissue regeneration. The differences in the quantity of expression between the different chemokines and chemokine receptors point to a complex regulation of chemokine expression in renal allografts.

Pancreatic islet transplantation

Chemokine receptors and their ligands have a pivotal role in the mobilization and activation of specific leukocyte subsets in acute islet allograft rejection. Islet allograft rejection is associated with a steady increase in intragraft expression of the chemokine receptors CXCR3, CCR5, CCR2, CCR1 and their corresponding ligands CXCL9, CXCL10, CCL5, CCL8, CCL9 (27).

In comparison with untreated wild-type recipients, anti-CXCL10 treated wild-type recipients and $CXCR3^{-/-}$ recipients demonstrated the same degree of chemokine gene expression but less lymphocytic infiltrate. That is to say, CXCR3 gene deletion or anti-CXCL10 antibody therapy modulates lymphocytic graft infiltration and statistically prolongs graft survival in murine islet allograft recipients. The mean length of allograft survival was markedly increased from 12.7 ± 3.1 days in untreated WT to 19.7 ± 2.3 days for anti-CXCL10 treated WT and 20.2 ± 2.7 days for $CXCR3^{-/-}$ recipients (28). On the contrary, untreated WT recipients demonstrated increased graft-site gene expression for CXCL10, CCL5, CCL4 and heavy graft-site cell infiltrates at day 7.

CCR5 is expressed preferentially by $CD4^+$ Th1 cells. The same as CXCR3, CCR5 also plays a crucial role in islet allograft rejection in a streptozotocin-induced diabetic mouse model. BALB/c islet allografts transplanted into $CCR5^{-/-}$ recipients (C57BL/6) survived significantly longer compared with those transplanted into wild-type control mice. Furthermore, twenty percent of islet allografts in $CCR5^{-/-}$ animals without other treatment survived > 90 days (29). The possible mechanism is that intragraft mRNA expression of IL-4 and IL-5 was increased while IFN-γ was decreased in $CCR5^{-/-}$ mice. That means a Th2 pattern of T-cell activation in the target tissues versus a Th1 pattern observed in controls. A similar Th2 response pattern was also observed in the periphery (splenocytes responding to donor cells) (29). It can be concluded that CCR5 plays an important role in orchestrating the Th1 immune response which leads to islet allograft rejection.

According to above-mentioned findings, the effect of a novel, small-molecule compound TAK-779 by targeting CCR5 and CXCR3 in acute islet allograft rejection was tested *in vivo*. Treatment of TAK-779 significantly prolonged allograft survival across the MHC barrier in two distinct transplant models. Furthermore, TAK-779 treatment significantly attenuated the development of chronic vasculopathy, fibrosis and cellular infiltration (30). The treatment of anti-CCR5 and anti-CXCR3 has an evidently therapeutic effect on inhibiting both acute and chronic allograft rejection. Therefore, targeting the CCR5 and CXCR3 may provide a clinically useful strategy to prevent islet allograft rejection in the future.

Another important target is CCR2, which is highly induced and plays a specific role in early islet allograft rejection. In fully MHC mismatched transplant model, islet

allograft was transplanted from BALB/c mice into C57BL/6 wild-type and $CCR2^{-/-}$. The median survival time of islet allograft was prolonged obviously from 12 days for wild-type recipients to 24 days for $CCR2^{-/-}$ recipients. However, these changes were only transient in $CCR2^{-/-}$ recipients that ultimately rejected their grafts (27). In contrast to the islet transplants, CCR2 deficiency offered only marginal prolongation of heart allograft survival. This study highlights the tissue specificity of the chemokine receptor system *in vivo* in regulating allograft rejection.

Liver transplantation

Ischemic-type biliary lesions are a major complication following orthotopic liver transplantation. Unlike in renal transplants, the non-function CCR5delta32 polymorphism is a significant risk factor for the development of ischemic-type biliary lesions after liver transplantation. The incidence of ischemic-type biliary lesions in patients was increased from 12% with WT CCR5 to 31% with CCR5delta32. The rate of 5 year patient survival was decreased from 85% with WT CCR5 to 70% with CCR5delta32 (31). These results show that the CCR5 status should be screened prospectively before liver transplantation.

Besides CCR5, other chemokine receptors CCR6, CXCR3, CXCR4 and their ligands CCL20, CXCL9, CXCL10, CXCL11 and CXCL12 could be detected in normal liver tissue and in acute allograft rejection biopsy specimens by RT-PCR. CCL20 and CCR6 cells were detected in the portal fields of all acute allograft rejection biopsy specimens. The C4d deposits along the portal capillaries indicate a humoral mediated alloresponse caused by the accumulated B and plasma cells, which are promoted by the expression of B-cell activating chemokine receptor system in acute liver rejection (32).

Bone marrow transplantation

Graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplantation. It plays a critical role in the development of GVHD that donor-derived T cells migrate into GVHD target organs, in which chemokine receptors and their ligands are important molecules involved (33).

The expression of the inflammatory CCR2 on donor-derived $CD8^+$ T cells is relevant for the control of $CD8^+$ T cell migration and development of GVHD in murine bone marrow transplantation models. The recipients of $CCR2^{-/-}$ $CD8^+$ T cells developed less damage of gut and liver than recipients of wild type $CD8^+$ T cells, which correlated with a reduction in overall GVHD morbidity and mortality. Interestingly, the graft-versus-tumor (GVT) effect mediated by $CCR2^{-/-}$ $CD8^+$ T cells was preserved, which suggests that interference with T cell migration by blockade of CCR2 signaling can separate GVHD from GVT activity (34).

These findings implicate that the donor non-T cell compartment is a critical regulator of GVHD, and suggest that CCR2 expression in this cellular compartment may be an important molecular determinant of activation-induced cell death and GVHD pathogenesis.

Skin transplantation

CXCR3, predominantly expressed on memory/activated T cells, is a receptor for both CXCL10 and CXCL9. CXCR3 is highly up-regulated in spleen T cells and allograft from BALB/c recipients by day 7 of receiving skin transplantation, whereas CCR5 expression is moderately increased. It is reported that CXCR3 is a dominant factor directing T cells into mouse skin allograft to induce acute rejection, without interfering with other functions of the T cells. The peptide nucleic acid (PNA) CXCR3 antisense significantly prolongs skin allograft survival by means of blockade of CXCR3 expression directing T cells into skin allograft in mice (35). The present study indicates the therapeutic potential of PNA CXCR3 to prevent acute transplantation rejection.

Chemokine receptors and transplantation tolerance

It is well-documented that certain chemokine receptors and their ligands guide homeostatic recirculation of T cells and others promote recruitment of activated T cells to inflammatory sites. However, little is known about another functions of chemokine receptors, which they maintain unresponsiveness and transplantation tolerance.

Foxp3 expression is specifically up-regulated within allograft of mice displaying donor-specific tolerance, which recruitment of $Foxp3^+$ regulatory T cells to an allograft tissue depends on intragraft up-regulating of CCR4 and its ligand CCL22. This particular tolerance induction could not be achieved in $CCR4^{-/-}$ recipients (36).

On the other hand, CXCR6 is highly expressed on $V\alpha14^+$ NKT cells. Blocking the interaction between CXCR6 and CXCL16 resulted in the failure to maintain graft tolerance and thus induced the acceleration of graft rejection. In a mouse transplant tolerance model, the expression of CXCL16 was up-regulated in the tolerated allograft, and anti-CXCL16 mAb inhibited intragraft accumulation of NKT cells (37). These results prove the unique role of CXCR6 and CXCL16 molecules in the maintenance of cardiac allograft tolerance mediated by NKT cells.

Conclusion

The emigration of leukocytes from the peripheral circulation into an allograft is an essential component of organ transplant rejection. Ischemic damage and surgical trauma start up the stage of leukocyte infiltration and activation, which in turn lead to the recruitment of additional effector leukocytes to the graft. The migration of dendritic cells from the allograft into secondary lymphoid tissue is also of paramount importance to the rejection process (9). The biology of chemokine receptors underlies both leukocyte recruitment and important aspects of the adaptive immune response. It is a model in in Figure 1 that indicates the effects of chemokine receptors and their ligands in organ transplant rejection (5). In addition to their primary role in regulating cell motility, chemokine receptors can also influence cell survival and

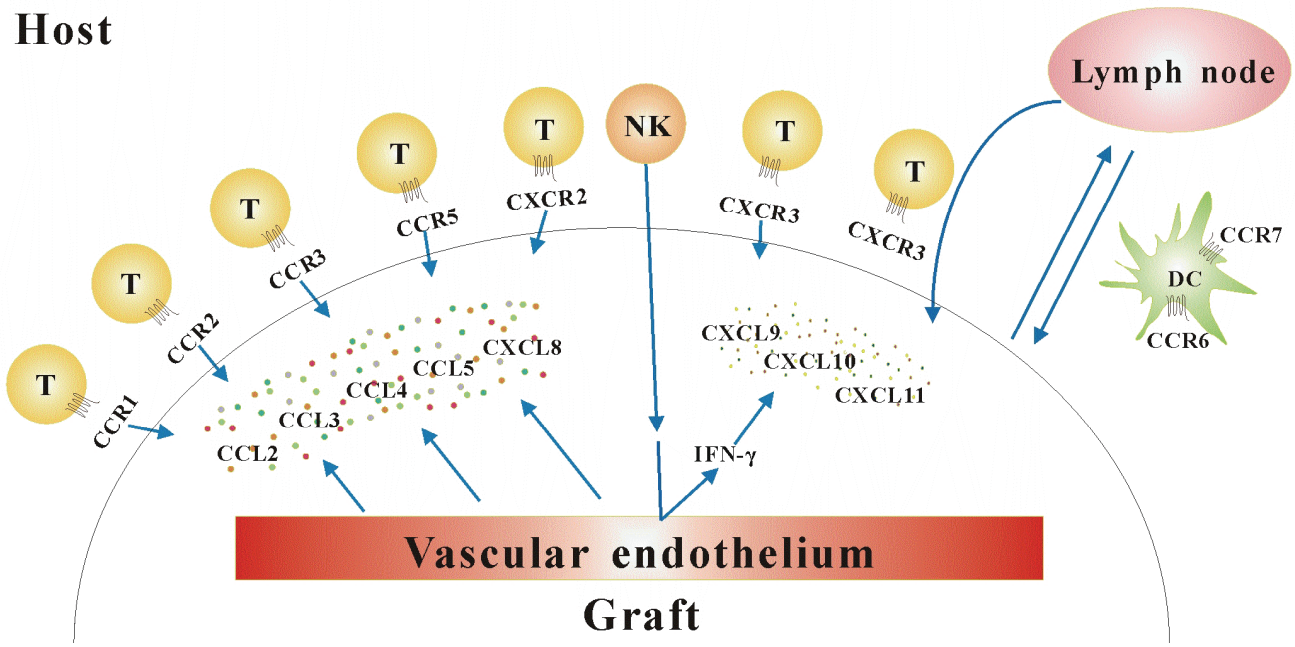

Figure 1. A brief model of the functions of chemokine receptors in organ transplant rejection. Several corresponding ligands are released from the vascular endothelium of allograft in the early stage, and then attract CCR1-, CCR5-, CXCR2-expressing T cells and other types of leukocytes. As a result of MHC mismatch, host NK cells migrate to the vascular endothelium and stimulate to produce IFN-γ. IFN-γ induces to synthesize the CXCR3 ligand, CXCL9, CXCL10 and CXCL11 locally, which lead to recruiting $CXCR3^+$ T cells and plasmacytoid dendritic cells (DC). According to these mechanisms, the acute and chronic rejections take place by host cells invading the graft.

proliferation.

It is crucial for the clinical assessment of many conditions to analyze expression of genes rapidly in small samples of tissue, including allograft transplant rejection. Chemokine receptors have shown to play an essential role in leukocyte recruitment to transplants and in leukocyte localization within graft. Therefore the analysis of chemokine receptor and ligand expression in allograft after transplantation may be a useful early predictor of the onset of rejection. Real-time PCR analysis, which avoids the potential sample contamination during post-PCR manipulations and offers the advantage that several genes can be analyzed from small graft biopsy samples in a shorter period of time, could distinctly distinguish expression of chemokine and chemokine receptor gene from during rejecting allogeneic grafts and in non-rejecting syngeneic grafts. To illustrate, expression of CXCL5 and CCL2 within graft was found by real-time PCR to be independent of T cell infiltration while expression of CCL3, CCL4, CCL5, CXCL9, CXCL10, XCL1 and CCL1 was clearly T cell dependent and increased significantly after transplantation (38).

Table 2. Summary of chemokine receptor expression in transplanted organ/tissue (6, 19, 40)

Organ/tissue	Allograft rejection	Allograft tolerance
Heart	CXCR3, CCR5, CCR3, CCR2, CCR1, CX3CR1	CCR4, CXCR6
Kidney	CCR1, CCR2, CCR5, CXCR3, CXCR2	ND
Islet	CXCR3, CCR5, CCR2, CCR1	ND
Liver	CCR5, CCR6, CXCR3, CXCR4	ND
Bone marrow	CCR2	ND
Skin	CXCR3	ND
Lung	CXCR3, CXCR2, CCR5, CCR2	ND

ND, Not determined.

Although almost every known chemokine receptor and its ligand is expressed at some stage during development of allograft rejection, mechanistic studies indicate that the actual key chemokine receptors are rather few (Table 2). From the Table 2, it can be summarized that CXCR3 and CCR5 are involved in most of the organ/tissue transplant rejection. Antagonists for a number of chemokine receptor have been developed, which promote the possibility of interfering with chemokine function as a therapeutic tool (39). In addition, it is a viable therapeutic strategy to target chemokine intracellular signaling pathways. One of the key signalling targets downstream of a variety of chemokine receptors identified to date is PI3Kγ (phosphoinositide 3-kinase γ), a member of the class I PI3K family (1). Data regarding the chemokine receptor system pathways in ischemia/reperfusion, as well as chronic rejection and tolerance induction following antagonism, provide some new potential entry points for immune monitoring and therapeutic intervention of transplants rejection (25, 41).

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