[Frontiers in Bioscience 14, 1807-1814, January 1, 2009]

The role of chemokines in acute renal allograft rejection and chronic allograft injury

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1. ABSTRACT

Short and long term outcome of renal transplantation are determined by acute and chronic rejection processes. In acute transplant rejection, expression of chemokines occurs in different renal compartments where it is triggered through various stimuli e.g. brain death, ischemia, reperfusion, and HLA-mismatch. The induction of chemokine expression precedes the process of organ recovery and extends well into the late course of clinical allograft injury. Chemokines function mainly as chemoattractants for leukocytes, monocytes, neutrophils, and other effector cells from the blood to sites of infection or damage. Chemokines are also important in angiogenesis and fibrosis and can have anti-inflammatory functions. The study of chemokine biology in transplantation has broadened the understanding of acute and chronic transplant dysfunction. Data suggest that relatively few chemokine receptors play central roles in these developments, and chemokine blockade, either non-selective or specific, has shown promising results in experimental transplantation and is currently being investigated in human trials.

2. INTRODUCTION

Early acute rejection and late kidney allograft loss remain two major problems in kidney transplantation. The major causes of renal transplant loss are accounted for by death with a functioning graft and loss of the allograft from chronic renal dysfunction. Up to 30 percent of patients awaiting renal transplantation had a previous failed kidney allograft (1-3). Chronic kidney allograft dysfunction is represented by a smoldering immune process with interstitial fibrosis, tubular atrophy, widespread arterial intimal fibrosis, transplant glomerulopathy and global glomerulosclerosis (4). These specific set of findings led to the elimination of the non-specific term “chronic allograft nephropathy or 'CAN” (5). Acute and chronic allograft injury is frequently accompanied by leukocyte infiltration, inflammatory cell injury and eventually fibrosis; therefore, it is not surprising that the chemokine system is important in these events. Chemokines are members of a large family of chemotactic cytokines and act as directional signals for inflammatory cell subsets (Table 1). In order to direct mononuclear cells to the specific site of inflammation, expression of specific chemotactic cytokines at the site of injury along with expression of corresponding receptors on

Table 1. Ligands and leukocyte specificities for human chemokine receptors

Chemokine	Receptor	Target cells
CCL2/MCP-1	CCR1, CCR2	Monocytes, DC, T cells, B cells, PMNs
CCL5/RANTES	CCR1, CCR5	Monocytes, T cells, B cells
CCL11/Eotaxin	CCR3	Eosinophils, Basophils, T cells
CCL19,CCL21	CCR7	T cells, mature DC
CXCL8/IL-8	CXCR1, CXCR2	PMNs, Monocytes
CXCL10/IP-10	CXCR3	T cells, B cells
CXCL13/BCA-1	CXCR5	B cells
CX3CL1/fractalkine	CX3CR1	Monocytes, T cells, NK cells

a well defined subset of mononuclear cells are of crucial importance. With these mediators in effect, highly specific responses initiate and perpetuate distinct patterns of transplant injury. This review will summarize the contribution of chemokines to different forms of acute and chronic kidney allograft injury and the data on anti-chemokine strategies. The importance of chemokines in ischemia-reperfusion injury is discussed separately in this edition.

3. CHARACTERIZATION OF THE ROLE OF CHEMOKINES IN ALLOGRAFT DYSFUNCTION USING ANIMAL MODELS

Different strategies using animal models have been employed to identify which chemokine/chemokine receptor interactions underlie important aspects of allograft dysfunction. These include the application of ligand or receptor knockout mice, gene transfer, blocking antibodies, functional antagonists and small molecule antagonists developed for select receptors (6-8). Due to the paucity of data on murine renal transplantation, vascularized murine cardiac transplantation is often used as a surrogate for the technically challenging experimental renal transplantation. It is important to note that in mice, complete MHC mismatched kidney and liver allografts may be spontaneously accepted, whereas cardiac, skin, and islet allografts in the same strain combinations are rapidly rejected (9-11). The exact reason for this dichotomy in murine response outcomes remains to be determined. Mice with deletions of single chemokines (CCL5/RANTES, CCL3/MIP-1α) or chemokine receptors CCR1, CCR5, CXCR3 and CX(3)CR have been studied (7). Within the CXC chemokine network, CXCR3 deletion reduced the lymphocytic infiltrate, and thus prolonged graft survival in allogeneic murine cardiac transplantation. Mice deficient for CXCR3 were described as highly resistant to acute allograft rejection when treated with a transient, low dose of cyclosporine (12). Probably due to the redundant chemokine system, isolated recipient deletions of either CCL5/RANTES or CCL3/MIP-1α had no effect on survival of heterotopic cardiac allografts (13). Deletions of the gene either for CCR1 or CCR5, however, translated into significantly longer transplant survival of 13 days and 23 days versus 7-8 days in control animals (7, 13). The beneficial effect of CCR5 deletion has not been supported by subsequent studies. In fact, antibody-mediated rejection of cardiac allografts in CCR5-deficient mice was reported (14). However, cardiac allografts transplanted in the absence of CCR5 were found to be better preserved with less vasculopathy (15). This was found to be true for acute cardiac rejection as well as for long-term carotid-artery transplants (15). CCR5 appears to play a role in transplant-associated arteriosclerosis that may involve metalloproteinase mediated vessel wall remodeling. CCR5 knock-out animals disparate in MHC class II show reduced damage in transplanted hearts and treatment with low dose cyclosporine augmented the effects of a targeted deletion of CCR5 (13, 15). One study evaluated chemokine blockade in both, murine kidney and heart transplantation (16). The application of CCL19-IgG fusion protein markedly prolonged allograft survival of both organs. The mechanisms involved the disruption of CCR7-mediated recirculation of dendritic cells consequently impairing T-cell priming. Interestingly, the effects on cardiac allograft survival of CCL19-IgG was better than if CCR7 deficient mice were transplanted (17). Of note, intragraft gene analysis of tolerant animals revealed that tolerance can be induced and maintained in the presence of prominent pro-inflammatory gene expression *in vivo* and might even contribute to tolerance induced by costimulation blockade. Among a set of 66 genes that was induced in rejecting cardiac allografts and in tolerant grafts were CXCL9/Mig, CXCL10/IP-10, CCL2/MCP-1, CCL5/RANTES, and their receptors CCR1, CCR5, and CXCR3 (18).

3.1. Pharmacological anti-chemokine strategies

In light of such ample expression of chemokines and their receptors, pharmacologic interventions are not only helpful to identify the key chemokines involved in the pathogenesis of a disease (e.g. acute rejection) but can also test possible treatment strategies. Met-RANTES in a rat model of acute allograft rejection with subtherapeutic cyclosporine reduced monocytic cellular infiltrates, vascular, and tubulointerstitial injury (19). In a rat model of chronic rejection, the application of Met-RANTES resulted in less lymphocytic infiltrate, less TNF-α and CCL5/RANTES expression, reduced urinary protein excretion and significantly ameliorated glomerulosclerosis, interstitial fibrosis, tubular atrophy, intimal proliferation of graft arteries. However, renal function, i.e. creatinine clearance was not influenced by this intervention (20). Since then, more specific targeting of chemokine receptors is possible through small molecule inhibitors. Presently, inhibitors for CCR1, CCR2 and CCR5 are available and have been studied with their effect on renal transplantation survival. BX471, a specific CCR1 antagonist, improved the function of experimental renal transplants in rabbits (21). Urea and creatinine levels were significantly lower with BX471 treatment and renal transplant survival moderately increased from 12±1.7. days (controls) to 16±2.1. days (BX471) (21). Kidneys from rabbits receiving placebo exhibited extensive infarction of the transplanted kidney which was prevented by BX471 and cyclosporine (21). Both antifibrotic and antiinflammatory effects have been associated with a blockade of CCR1 in the chronic renal allograft model where F344 kidneys were transplanted into to Lewis rats (22). While a reduced inflammatory cell infiltrate in the allograft mediated by BX471 may explain in part the ameliorated kidney fibrosis, additional direct

antifibrotic activities were also identified. Treatment with the CCR1 antagonist prevented the development and progression of glomerular and tubulointerstitial fibrosis. This effect was associated with a decrease in the expression of TGF-β and extracellular matrix proteins. BX471 treatment was found to inhibit secretion of the proinflammatory matrix protein biglycan by CCL5/RANTES stimulated macrophages (22). The small-molecule CCR5 and CXCR3 inhibitor, TAK-779, has been shown to confer protective effects in experimental heart and islet transplantation (23, 24). This mode of chemokine blockade resulted in less inflammatory cellular infiltration, i.e. reduced numbers of CD4, CD8 and CD11c cells (23). Interestingly, in this setting reduced allograft vasculopathy was reported -- an observation that extends the protective effects of chemokine blockade well beyond acute cellular rejection (23). It is important to note that only few animal models are truly sufficient to address chronic allograft injury.

4. CHEMOKINE BIOLOGY IN ACUTE AND CHRONIC HUMAN TRANSPLANT REJECTION

Immune-related injury manifests itself in three temporal phases: early innate immune driven alloantigen-independent injury, acquired immune driven alloantigen-dependent injury, and chronic injury.

4.1. Antigen-independent injury

As with many complex pathogenic processes, the genetic background of each patient (donor and recipient) is likely to contribute to the risk for graft injury after transplantation. Although relatively limited in scope, several studies have reported associations between specific genetic polymorphisms in the donor and/or recipient with posttransplant outcomes, supporting this contention (25, 26). The majority of kidneys used for deceased donor transplantation are recovered from brain-dead donors. Cerebral injury causes hormonal alterations in the donor that, compounded with the unavoidable ischemia–reperfusion injury associated with harvest and transport of the organ, augment the subsequent anti-donor immunity leading to negative long-term consequences on graft function. While the mechanisms are not entirely elucidated, possible mediators include ischemia–reperfusion induced activation of the complement cascade, signaling via Toll-like receptors (TLRs), and release of chemokines and cytokines by the organ cells with an associated upregulation of HLA molecules (27). The importance of these factors is reflected in better outcomes of organs from living donors where ischemia–reperfusion injury is limited (28). Immediately following transplantation, early inflammatory mediators, including endothelial cell-produced chemokines, infiltrating neutrophils and natural killer (NK) cells, are attracted to the healing graft site, where they can cause organ damage and predispose the organ to subsequent alloimmune injury (29). Compared with living organ donor controls, the kidneys recovered after brain death, exhibited increased chemokine (CCL2/MCP-1, CCL5/RANTES) expression as well as interstitial leukocyte invasion (30, 31).

4.2. Antigen-dependent injury

4.2.1. Acute transplant rejection

Both, CC and CXC chemokines have been extensively studied in human kidney transplantation. Early work investigated the expression of the CC-chemokine CCL5/RANTES in the peritubular compartment of human renal allografts with acute rejection (32). An upregulation of CC-chemokine (CCL2/MCP-1, CCL5/RANTES, CCL3/MIP-1α and CCL4/MIP-1ß) expression and their corresponding receptors (CCR1, CCR2, and CCR5) was confirmed on infiltrating cells during acute human allograft rejection (33-37). In addition to CC chemokines, CXC-chemokine expression was also altered in acute transplant rejection and the expression of CXCL10/IP-10 and its corresponding receptor (CXCR3) was increased within the kidney transplant (34, 37-39). These molecules are potentially useful as markers of rejection, and in support of this, levels of CXCL9/Mig, CXCL10/IP-10 and CXCL11/ITAC mRNA and protein were significantly elevated in the urine of renal transplant patients with acute rejection (40, 41). In addition, urine and serum CXCL8/IL-8 concentrations in human transplant recipients with acute rejection were found to be elevated (42).

Of note, pretransplant serum levels of CXCL10/IP-10 correlated with decreased one and five year kidney graft survival. The quartile of renal transplant recipients with the highest serum CXCL10/IP-10 concentration was found to have significantly worse five year graft survival of 78% versus 98% in the lowest quartile (43).

4.2.2. Chronic transplant rejection

Compared to acute rejection, fewer data on the differential chemokine expression in chronic injury are available. In human chronic renal allograft injury, increased CCR1, CCR2, CCR5 and CCL2/MCP-1, CCL5/RANTES, CXCL12/SDF-1 expression was detected on infiltrating cells in biopsy samples (33, 36, 44, 45). CCR1 mRNA expression was not only increased in renal allograft injury, but also correlated with the expression of the corresponding chemokine ligands and serum creatinine (33). Overall, the expression levels were usually lower compared with the levels observed in acute rejection but might suggest their involvement in tissue regeneration and could impact the development of CAN. Akalin *et al.* studied 17 biopsies from 16 allograft recipients with CAN (46). In this study, six biopsies from five patients showed transplant glomerulopathy (TGP), in addition to CAN. No intraglomerular T-cell staining was seen in CAN alone, whereas all TGP samples showed intraglomerular T-cell infiltration and selective chemokine and chemokine receptor expression by intra- and periglomerular mononuclear cells. All TGP cases showed intraglomerular CXCR3+ CD3+ T cells, and concomitant labeling for the CXCR3 ligands, CXCL9/Mig and CXCL10/IP-10. This data argues for the importance of ongoing immune activation in the development of TGP and suggests that different pathologic mechanisms underlie TGP versus CAN.

Based on these observations, the next step in testing the hypothesis of the relevant contribution of chemokine networks to allograft injury are models of selectively altered chemokine expression. This is currently achieved by either studying humans with mutations in their chemokine regulation (Section 5) or by antagonism of selected chemokine receptors, where some data in non-human primate kidney transplant model are available (Section 6).

5. EFFECT OF GENETIC VARIABILITY IN THE CHEMOKINE SYSTEM IN CLINICAL TRANSPLANTATION

There has been an abundance of publications studying the effect of genetic variability in chemokine and chemokine receptor genes on outcomes in organ transplantation (26). Carriers of the variant alleles in some of the candidate genes described above have undergone renal transplantation and can be considered human models to address the question of chemokine overexpression or in some cases deletion. CCL2/MCP-1 expression is known to vary depending on a mutation within the promoter. Carriers of the "G-allele" can be considered high-CCL2/MCP-1 expressors as they exhibit increased CCL2/MCP-1 after stimulation of PBMC with cytokines, also when PBMCs were derived from patients under standard immunosuppressive therapy (47). When allograft function was correlated with the recipient's genotype, the CCL2/MCP-1 high-expressor genotype was associated with significantly shorter median graft survival of 67±14 versus 95±4 months among 232 recipients of first renal transplants (47). Interestingly, this effect was organ specific, since this variant had no influence on the outcome in liver transplant recipients (48). The chemokine CCL5/RANTES has three functional SNPs that were associated with a higher rate of recurrent rejections in a study of 261 kidney transplant recipients (49).

As CCL5/RANTES / CCR5 signalling has integral importance for the early recruitment of mononuclear cells to the graft and a functional deletion of CCR5 has been reported. CCR5 is unique as it is the only chemokine receptor where a beneficial effect of a lack of CCR5 on long term human renal engraftment has been established (50). Only 1.5. % of Caucasian renal transplant recipients are completely devoid of CCR5, the clinical course of 21 such patients was evaluable when a cohort of 1222 renal transplant patients was studied. Individuals lacking CCR5 exhibited a significantly lower risk for graft loss with only one of 21 patients without CCR5 having lost graft function compared to 14.5.% of the control group (50). Of note, patients without CCR5 were not protected from acute rejection episodes and advanced analysis of these biopsy specimens exhibited a strong CXCR3 expression on infiltrating cells (51). Possibly, the lack of CCR5 activation also influences macrophage invasion of the graft and anti-donor antibody production, two mechanisms well known to cause accelerated transplant fibrosis (52).

6. PHARMACOLOGICAL ANTI-CHEMOKINE STRATEGIES IN NON-HUMAN PRIMATE AND CLINICAL KIDNEY TRANSPLANTATION

6.1. Non-human primate

Currently there are no studies published that directly intervened with the chemokine system in clinical transplantation. However, in clinically relevant, nonhuman primate models, data on specific CCR5 blockage is available. CCR5 was expressed in 45% of graft-infiltrating macrophages and in 15% of T cells, and the influx of T cells was significantly inhibited in with Merck's compound 167 (CMPD 167)-treated animals. However, anti-CCR5 monotherapy only marginally prolonged allograft survival. In contrast, relative to cyclosporine A monotherapy, CMPD 167 with cyclosporine A delayed alloantibody production, suppressed cardiac allograft vasculopathy, and tended to further prolong graft survival (52). These findings suggest that other chemokines and receptors can mediate graft infiltration in primates despite successful CCR5 blockade. But CCR5 blockade even with low dose conventional immunosuppression is unlikely to prevent acute allograft rejection in humans.

CXCR3 chemokine signalling has been blocked experimentally in non-human primate kidney transplantation, but no peer reviewed data are currently available. Of note, results suggest that blockade of CXCL10/IP-10 via CXCR3 contributes to renal fibrosis, possibly by upregulation of TGF-β1, concomitant downregulation of hepatocyte growth factor (53).

Unfortunately, some of the results obtained in small animal models have not been supported by studies in non-human primates, and the extent of the importance of chemokine receptor blockage in allograft damage still remains to be firmly established.

6.2. Clinical data

Various mechanisms are available to at least indirectly modulate chemokine mediated signalling. Unlike specific receptor blockers, the effect on chemokine signalling was discovered on further analysis and include anti-cytokine strategies using TNFα, IL-6 and IL-15 antibodies (54). Blocking the effects of cytokines might inhibit chemokine mediated cell recruitment. To date, there are no data available on these drugs in preventing alloimmune response and chronic allograft nephropathy. Agents to target adhesion molecules such as VLA4 (very late antigen-4) (Antegren/Natalizumab), LFA (lymphocyte function-associated antigen)-3/IgG1 fusion (Amevive/Alefacept), or anti-LFA-1 (Efalizumab/Raptiva) are clinically available. Until recently, the sphingosine 1-phosphatase receptor-1 antagonist FTY720 appeared as a promising novel tool in clinical transplantation but despite a clinical efficacy comparable to MMF, future trials were halted in renal transplant recipients. FTY720 acts through stimulation of the sphingosine-1 phosphatase receptor on mononuclear cells, render cells unresponsive to chemotactic signals, and causing them to accumulate in lymphatic organs leading to peripheral lymphopenia (55).

Interestingly, FTY720 affected CCR5 expression on CD4+ and CD8+ cells (56).

It is important to note that despite significant homologies of cDNA sequences between different species, considerable distinctions exist and chemokine antagonists developed for the human system commonly have different pharmacological properties in other species (57). Until now, only limited experience is available with chemokine receptor antagonists in humans. As chemokines are involved in a wide variety of different diseases, some of the knowledge reported below is not derived from clinical transplantation but from trials in other diseases. So far, the most successful approach to block chemokine and chemokine receptor interaction is by means of specific receptor antagonists. Although G protein-coupled receptors (GPCRs) are the most 'druggable' receptor class chemokines, they turned out to be the most difficult GPCRs to identify antagonists for. Most chemokine receptors bind several ligands, so a small molecule that blocks the binding site for one ligand will not necessarily inhibit other ligands. Several compounds are currently being tested in preclinical and in clinical trials (http://www.iddb3.com). No peer reviewed data are available of any human trials using these compounds in kidney transplantation. Data obtained in small animal models provided a rationale for the use of therapeutic agents to block CCR5, CXCR3, CXCR4. As CCR5 serves as a co-receptor for HIV infection, clinical trails focused on HIV-positive patients and oral CCR5 antagonists are currently available. The complete absence of functional CCR5 seems to be well tolerated in humans, suggesting that CCR5 function is well compensated or redundant; however, CCR5-deficient mice have been recently shown to be susceptible to West Nile virus (58). As described earlier, data in a nonhuman primate renal allograft model did not show biological important effects in preventing allograft rejection (52). Combined kidney/nonmyeloablative bone marrow transplant is able to achieve donor allograft acceptance without chronic immunosuppressive therapy (59). Compounds that inhibit the binding of CXCL12/SDF-1 to its receptor CXCR4 are available. CXCR4 is expressed on CD34+ hematopoetic progenitor cells and inhibition of the CXCR4-SDF1 axis releases CD34+ cells from the bone marrow into the circulation, which can then be collected by apheresis. One interesting approach is the use of CXCR4 antagonism to mobilize hematopoetic progenitor cells and transfuse these cells prior to or at the time of kidney transplantation to induce mixed allogeneic chimerism and possibly achieve transplantation tolerance.

6.3. Potential side effects of chemokine antagonism

The ultimate goal of transplantation is to induce immunologic tolerance to the graft without chronic immunosuppression such that there is a specific absence of a detrimental immune response directed at the transplanted organ, but the host's immune system is intact (can respond normally to immune stimuli). Studies in animal models have suggested that tolerance to an allograft can be achieved under certain conditions. The role of chemokines and their receptors in promoting the recruitment of activated T cells to inflammatory sites and blocking these effects is one proposed mechanism of delaying allograft rejection in experimental models. Recent data shed light on the role of chemokines in migration of regulatory T (Treg) cells. Previous reports demonstrated that lymph node occupancy by T cells was critical for the establishment of tolerance (60, 61). Interfering with normal T-cell homing by anti-CD62L mAb, CD62L deficiency, CCL19/CCL21 deficiency (*plt* mice), CCR2 deficiency, or CCR4 deficiency all prevented tolerization (62). These data indicate that targeting some chemokine receptors may render tolerizing strategies ineffective. The results of a study indicated a striking antibody deposition in the cardiac allografts of CCR5-deficient mice (14), suggesting that CCR5 deficiency may in fact promote antibody responses and allograft rejection. In addition, blockade of CXCL10/IP-10 via CXCR3 can contribute to renal fibrosis, possibly by upregulation of TGF-β1, concomitant with downregulation of hepatocyte growth factor (53). There is considerable interest in the potential use of chemokine receptor antagonists to inhibit allograft rejection in clinical transplantation. Preclinical data, however, stress the importance on the timing and duration of these therapies.

7. CONCLUSION

Chemokines and their receptors have been shown to be upregulated in the transplanted organ, and this process is triggered by brain death, ischemia-reperfusion injury, infections and MHC disparity. The degree and regional expression of chemokines and their receptors modulate acute as well as chronic allograft injury. Although early studies from animals and humans with genetically defined variants suggested a benefit of chemokine blockade, the highly promiscuous and redundant chemokine network is much harder to manipulate than initial experiments led us to believe.

8. ACKNOWLEDGEMENTS

B.S. is supported by Satellite Research and National Institutes of Health research grant KO8 AI 071038-01. We wish to thank Drs. Enver Akalin and Susan Lerner for critical review of the manuscript.

9. REFERENCES

1. Chapman, J. R., P. J. O'Connell & B. J. Nankivell: Chronic renal allograft dysfunction. *J Am Soc Nephrol*, 16, 3015-26 (2005)

2. Matas, A. J., A. Humar, K. J. Gillingham, W. D. Payne, R. W. Gruessner, R. Kandaswamy, D. L. Dunn, J. S. Najarian & D. E. Sutherland: Five preventable causes of kidney graft loss in the 1990s: a single-center analysis. *Kidney Int*, 62, 704-14 (2002)

3. Halloran, P. F., A. J. Langone, J. H. Helderman & B. Kaplan: Assessing long-term nephron loss: is it time to kick the CAN grading system? *Am J Transplant*, 4, 1729-30 (2004)

4. Joosten, S. A., Y. W. Sijpkens, C. van Kooten & L. C. Paul: Chronic renal allograft rejection: pathophysiologic considerations. *Kidney Int*, 68, 1-13 (2005)

5. Solez, K., R. B. Colvin, L. C. Racusen, B. Sis, P. F. Halloran, P. E. Birk, P. M. Campbell, M. Cascalho, A. B. Collins, A. J. Demetris, C. B. Drachenberg, I. W. Gibson, P. C. Grimm, M. Haas, E. Lerut, H. Liapis, R. B. Mannon, P. B. Marcus, M. Mengel, M. J. Mihatsch, B. J. Nankivell, V. Nickeleit, J. C. Papadimitriou, J. L. Platt, P. Randhawa, I. Roberts, L. Salinas-Madriga, D. R. Salomon, D. Seron, M. Sheaff & J. J. Weening: Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). *Am J Transplant*, 7, 518-26 (2007)

6. Nelson, P. J. & A. M. Krensky: Chemokines, chemokine receptors, and allograft rejection. *Immunity*, 14, 377-86. (2001)

7. Hancock, W. W., L. Wang, Q. Ye, R. Han & I. Lee: Chemokines and their receptors as markers of allograft rejection and targets for immunosuppression. *Curr Opin Immunol*, 15, 479-86 (2003)

8. Segerer, S. & P. J. Nelson: Chemokines in renal diseases. *ScientificWorldJournal*, 5, 835-44 (2005)

9. Bickerstaff, A. A., J. J. Wang, R. P. Pelletier & C. G. Orosz: Murine renal allografts: spontaneous acceptance is associated with regulated T cell-mediated immunity. *J Immunol*, 167, 4821-7 (2001)

10. Russell, P. S., C. M. Chase, R. B. Colvin & J. M. Plate: Kidney transplants in mice. An analysis of the immune status of mice bearing long-term, H-2 incompatible transplants. *J Exp Med*, 147, 1449-68 (1978)

11. Zhang, Z., L. Zhu, D. Quan, B. Garcia, N. Ozcay, J. Duff, C. Stiller, A. Lazarovits, D. Grant & R. Zhong: Pattern of liver, kidney, heart, and intestine allograft rejection in different mouse strain combinations. *Transplantation*, 62, 1267-72 (1996)

12. Hancock, W. W., B. Lu, W. Gao, V. Csizmadia, K. Faia, J. A. King, S. T. Smiley, M. Ling, N. P. Gerard & C. Gerard: Requirement of the chemokine receptor CXCR3 for acute allograft rejection. *J Exp Med*, 192, 1515-20 (2000)

13. Gao, W., K. L. Faia, V. Csizmadia, S. T. Smiley, D. Soler, J. A. King, T. M. Danoff & W. W. Hancock: Beneficial effects of targeting CCR5 in allograft recipients. *Transplantation*, 72, 1199-205 (2001)

14. Nozaki, T., H. Amano, A. Bickerstaff, C. G. Orosz, A. C. Novick, K. Tanabe & R. L. Fairchild: Antibody-Mediated Rejection of Cardiac Allografts in CCR5-Deficient Recipients. *J Immunol*, 179, 5238-45 (2007)

15. Luckow, B., J. Joergensen, S. Chilla, J. P. Li, A. Henger, E. Kiss, G. Wieczorek, L. Roth, N. Hartmann, R. Hoffmann, M. Kretzler, P. J. Nelson, G. Perez de Lema, H. Maier, W. Wurst, R. Balling, K. Pfeffer, H. J. Grone, D. Schlondorff & H. G. Zerwes: Reduced intragraft mRNA expression of matrix metalloproteinases Mmp3, Mmp12, Mmp13 and Adam8, and diminished transplant arteriosclerosis in Ccr5-deficient mice. *Eur J Immunol*, 34, 2568-78 (2004)

16. Ziegler, E., F. Gueler, S. Rong, M. Mengel, O. Witzke, A. Kribben, H. Haller, U. Kunzendorf & S. Krautwald: CCL19-IgG prevents allograft rejection by impairment of immune cell trafficking. *J Am Soc Nephrol*, 17, 2521-32 (2006)

17. Beckmann, J. H., S. Yan, H. Luhrs, B. Heid, S. Skubich, R. Forster & M. W. Hoffmann: Prolongation of allograft survival in ccr7-deficient mice. *Transplantation*, 77, 1809-14 (2004)

18. Matsui, Y., A. Saiura, Y. Sugawara, M. Sata, K. Naruse, H. Yagita, T. Kohro, C. Mataki, A. Izumi, T. Yamaguchi, T. Minami, T. Sakihama, S. Ihara, H. Aburatani, T. Hamakubo, T. Kodama & M. Makuuchi: Identification of gene expression profile in tolerizing murine cardiac allograft by costimulatory blockade. *Physiol Genomics*, 15, 199-208 (2003)

19. Grone, H. J., C. Weber, K. S. Weber, E. F. Grone, T. Rabelink, C. M. Klier, T. N. Wells, A. E. Proudfood, D. Schlondorff & P. J. Nelson: Met-RANTES reduces vascular and tubular damage during acute renal transplant rejection: blocking monocyte arrest and recruitment. *Faseb J*, 13, 1371-83 (1999)

20. Song, E., H. Zou, Y. Yao, A. Proudfoot, B. Antus, S. Liu, L. Jens & U. Heemann: Early application of Met-RANTES ameliorates chronic allograft nephropathy. *Kidney Int*, 61, 676-85 (2002)

21. Horuk, R., S. Shurey, H. P. Ng, K. May, J. G. Bauman, I. Islam, A. Ghannam, B. Buckman, G. P. Wei, W. Xu, M. Liang, M. Rosser, L. Dunning, J. Hesselgesser, R. M. Snider, M. M. Morrissey, H. D. Perez & C. Green: CCR1-specific non-peptide antagonist: efficacy in a rabbit allograft rejection model. *Immunol Lett*, 76, 193-201 (2001)

22. Bedke, J., E. Kiss, L. Schaefer, C. L. Behnes, M. Bonrouhi, N. Gretz, R. Horuk, M. Diedrichs-Moehring, G. Wildner, P. J. Nelson & H. J. Grone: Beneficial effects of CCR1 blockade on the progression of chronic renal allograft damage. *Am J Transplant*, 7, 527-37 (2007)

23. Akashi, S., M. Sho, H. Kashizuka, K. Hamada, N. Ikeda, Y. Kuzumoto, Y. Tsurui, T. Nomi, T. Mizuno, H. Kanehiro, M. Hisanaga, S. Ko & Y. Nakajima: A novel small-molecule compound targeting CCR5 and CXCR3 prevents acute and chronic allograft rejection. *Transplantation*, 80, 378-84 (2005)

24. Schroppel, B., N. Zhang, P. Chen, W. Zang, D. Chen, K. L. Hudkins, W. A. Kuziel, R. Sung, J. S. Bromberg & B. Murphy: Differential expression of chemokines and

chemokine receptors in murine isl*et al*lografts: the role of CCR2 and CCR5 signaling pathways. *J Am Soc Nephrol*, 15, 1853-61 (2004)

25. Brown, K. M., E. Kondeatis, R. W. Vaughan, S. P. Kon, C. K. Farmer, J. D. Taylor, X. He, A. Johnston, C. Horsfield, B. J. Janssen, P. Gros, W. Zhou, S. H. Sacks & N. S. Sheerin: Influence of donor C3 allotype on late renal-transplantation outcome. *N Engl J Med*, 354, 2014-23 (2006)

26. Marder, B., B. Schroppel & B. Murphy: Genetic variability and transplantation. Curr Opin Urol, 13, 81-9 (2003)

27. Pratschke, J., S. G. Tullius & P. Neuhaus: Brain death associated ischemia/reperfusion injury. *Ann Transplant*, 9, 78-80 (2004)

28. Terasaki, P. I., J. M. Cecka, D. W. Gjertson & S. Takemoto: High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med*, 333, 333-6 (1995)

29. El-Sawy, T., M. Miura & R. Fairchild: Early T cell response to allografts occurring prior to alloantigen priming up-regulates innate-mediated inflammation and graft necrosis. *Am J Pathol*, 165, 147-57 (2004)

30. Nijboer, W. N., T. A. Schuurs, J. A. van der Hoeven, S. Fekken, J. Wiersema-Buist, H. G. Leuvenink, S. Hofker, J. J. Homan van der Heide, W. J. van Son & R. J. Ploeg: Effect of brain death on gene expression and tissue activation in human donor kidneys. *Transplantation*, 78, 978-86 (2004)

31. Gomez del Moral, M., B. Aviles, I. K. Colberger, Y. Campos-Martin, J. Suela, J. Alvarez, M. J. Perez-Contin, A. Sanchez-Fructuoso, A. Barrientos & E. Martinez-Naves: Expression of adhesion molecules and RANTES in kidney transplant from nonheart-beating donors. *Transpl Int*, 18, 333-40 (2005)

32. Pattison, J., P. J. Nelson, P. Huie, I. von Leuttichau, G. Farshid, R. K. Sibley & A. M. Krensky: RANTES chemokine expression in cell-mediated transplant rejection of the kidney. *Lancet*, 343, 209-11 (1994)

33. Mayer, V., K. L. Hudkins, F. Heller, H. Schmid, M. Kretzler, U. Brandt, H. J. Anders, H. Regele, P. J. Nelson, C. E. Alpers, D. Schlondorff & S. Segerer: Expression of the chemokine receptor CCR1 in human renal allografts. *Nephrol Dial Transplant*, 22, 1720-9 (2007)

34. Segerer, S., Y. Cui, F. Eitner, T. Goodpaster, K. L. Hudkins, M. Mack, J. P. Cartron, Y. Colin, D. Schlondorff & C. E. Alpers: Expression of chemokines and chemokine receptors during human renal transplant rejection. *Am J Kidney Dis*, 37, 518-31 (2001)

35. Inston, N. G. & P. Cockwell: The evolving role of chemokines and their receptors in acute allograft rejection. *Nephrol Dial Transplant*, 17, 1374-9 (2002)

36. Ruster, M., H. Sperschneider, R. Funfstuck, G. Stein & H. J. Grone: Differential expression of beta-chemokines MCP-1 and RANTES and their receptors CCR1, CCR2, CCR5 in acute rejection and chronic allograft nephropathy of human renal allografts. *Clin Nephrol*, 61, 30-9 (2004)

37. Panzer, U., R. R. Reinking, O. M. Steinmetz, G. Zahner, U. Sudbeck, S. Fehr, B. Pfalzer, A. Schneider, F. Thaiss, M. Mack, S. Conrad, H. Huland, U. Helmchen & R. A. Stahl: CXCR3 and CCR5 positive T-cell recruitment in acute human renal allograft rejection. *Transplantation*, 78, 1341-50 (2004)

38. Segerer, S., G. A. Bohmig, M. Exner, D. Kerjaschki, H. Regele & D. Schlondorff: Role of CXCR3 in cellular but not humoral renal allograft rejection. *Transpl Int*, 18, 676-80 (2005)

39. Hoffmann, U., S. Segerer, P. Rummele, B. Kruger, M. Pietrzyk, F. Hofstadter, B. Banas & B. K. Kramer: Expression of the chemokine receptor CXCR3 in human renal allografts--a prospective study. *Nephrol Dial Transplant*, 21, 1373-81 (2006)

40. Tatapudi, R. R., T. Muthukumar, D. Dadhania, R. Ding, B. Li, V. K. Sharma, E. Lozada-Pastorio, N. Seetharamu, C. Hartono, D. Serur, S. V. Seshan, S. Kapur, W. W. Hancock & M. Suthanthiran: Noninvasive detection of renal allograft inflammation by measurements of mRNA for IP-10 and CXCR3 in urine. *Kidney Int*, 65, 2390-7 (2004)

41. Hu, H., B. D. Aizenstein, A. Puchalski, J. A. Burmania, M. M. Hamawy & S. J. Knechtle: Elevation of CXCR3-binding chemokines in urine indicates acute renal-allograft dysfunction. *Am J Transplant*, 4, 432-7 (2004)

42. Moutabarrik, A., I. Nakanishi, H. Kameoka, S. Takahara, Y. Kokado, M. Ishibashi & T. Sonoda: Interleukin-8 serum and urine concentrations after kidney transplantation. *Transpl Int*, 7 Suppl 1, S539-41 (1994)

43. Rotondi, M., A. Rosati, A. Buonamano, L. Lasagni, E. Lazzeri, F. Pradella, V. Fossombroni, C. Cirami, F. Liotta, G. La Villa, M. Serio, E. Bertoni, M. Salvadori & P. Romagnani: High pretransplant serum levels of CXCL10/IP-10 are related to increased risk of renal allograft failure. *Am J Transplant*, 4, 1466-74 (2004)

44. Segerer, S., K. M. Mac, H. Regele, D. Kerjaschki & D. Schlondorff: Expression of the C-C chemokine receptor 5 in human kidney diseases. *Kidney Int*, 56, 52-64 (1999)

45. Hoffmann, U., B. Banas, B. Kruger, M. Banas, T. Bergler, C. Boger, M. Kammerl, A. Obed, P. Rummele, S. Segerer, G. A. Riegger & B. K. Kramer: SDF-1 expression is elevated in chronic human renal allograft rejection. *Clin Transplant*, 20, 712-8 (2006)

46. Akalin, E., S. Dikman, B. Murphy, J. S. Bromberg & W. W. Hancock: Glomerular infiltration by CXCR3+ ICOS+ activated T cells in chronic allograft nephropathy

with transplant glomerulopathy. *Am J Transplant*, 3, 1116-20 (2003)

47. Kruger, B., B. Schroppel, R. Ashkan, B. Marder, C. Zulke, B. Murphy, B. K. Kramer & M. Fischereder: A Monocyte chemoattractant protein-1 (MCP-1) polymorphism and outcome after renal transplantation. J Am Soc Nephrol, 13, 2585-9 (2002)

48. Schröppel, B., M. Fischereder, M. Lin, B. Marder, T. Schiano, B. K. Krämer & B. Murphy: Analysis of gene polymorphisms in the regulatory region of MCP-1, RANTES, and CCR5 in liver transplant recipients. *J Clin Immunol*, 22, 381-5 (2002)

49. Krüger, B., C. A. Böger, A. Obed, S. Farkas, U. Hoffmann, B. Banas, M. Fischereder & B. K. Krämer: RANTES/CCL5 polymorphisms as a risk factor for recurrent acute rejection. *Clin Transplant*, 21, 385-90 (2007)

50. Fischereder, M., B. Luckow, B. Hocher, R. P. Wuthrich, U. Rothenpieler, H. Schneeberger, U. Panzer, R. A. Stahl, I. A. Hauser, K. Budde, H. Neumayer, B. K. Kramer, W. Land & D. Schlondorff: CC chemokine receptor 5 and renal-transplant survival. *Lancet*, 357, 1758-61 (2001)

51. Steinmetz, O. M., M. Fischereder, M. Weiss, U. Helmchen, R. A. Stahl & U. Panzer: Acute cellular allograft rejection in homozygous CCR5 Delta32 patients after renal transplantation. *Transplantation*, 84, 559-61 (2007)

52. Schroder, C., R. N. Pierson, 3rd, B. N. Nguyen, D. W. Kawka, L. B. Peterson, G. Wu, T. Zhang, M. S. Springer, S. J. Siciliano, S. Iliff, J. M. Ayala, M. Lu, J. S. Mudgett, K. Lyons, S. G. Mills, G. G. Miller, Singer, II, A. M. Azimzadeh & J. A. DeMartino: CCR5 blockade modulates inflammation and alloimmunity in primates. *J Immunol*, 179, 2289-99 (2007)

53. Nakaya, I., T. Wada, K. Furuichi, N. Sakai, K. Kitagawa, H. Yokoyama, Y. Ishida, T. Kondo, T. Sugaya, H. Kawachi, F. Shimizu, S. Narumi, M. Haino, C. Gerard, K. Matsushima & S. Kaneko: Blockade of IP-10/CXCR3 promotes progressive renal fibrosis. *Nephron Exp Nephrol*, 107, e12-21 (2007)

54. Godessart, N.: Chemokine receptors: attractive targets for drug discovery. *Ann N Y Acad Sci*, 1051, 647-57 (2005)

55. Brinkmann, V., J. G. Cyster & T. Hla: FTY720: sphingosine 1-phosphate receptor-1 in the control of lymphocyte egress and endothelial barrier function. *Am J Transplant*, 4, 1019-25 (2004)

56. Bohler, T., J. Waiser, M. Schuetz, H. H. Neumayer & K. Budde: FTY720 exerts differential effects on CD4+ and CD8+ T-lymphocyte subpopulations expressing chemokine and adhesion receptors. *Nephrol Dial Transplant*, 19, 702-13 (2004)

57. Mestas, J. & C. C. Hughes: Of mice and not men: differences between mouse and human immunology. *J Immunol*, 172, 2731-8 (2004)

58. Lim, J. K., W. G. Glass, D. H. McDermott & P. M. Murphy: CCR5: no longer a "good for nothing" gene--chemokine control of West Nile virus infection. *Trends Immunol*, 27, 308-12 (2006)

59. Buhler, L. H., T. R. Spitzer, M. Sykes, D. H. Sachs, F. L. Delmonico, N. Tolkoff-Rubin, S. L. Saidman, R. Sackstein, S. McAfee, B. Dey, C. Colby & A. B. Cosimi: Induction of kidney allograft tolerance after transient lymphohematopoietic chimerism in patients with multiple myeloma and end-stage renal disease. *Transplantation*, 74, 1405-9 (2002)

60. Bai, Y., J. Liu, Y. Wang, S. Honig, L. Qin, P. Boros & J. S. Bromberg: L-selectin-dependent lymphoid occupancy is required to induce alloantigen-specific tolerance. *J Immunol*, 168, 1579-89 (2002)

61. Ochando, J. C., A. C. Yopp, Y. Yang, A. Garin, Y. Li, P. Boros, J. Llodra, Y. Ding, S. A. Lira, N. R. Krieger & J. S. Bromberg: Lymph node occupancy is required for the peripheral development of alloantigen-specific Foxp3+ regulatory T cells. *J Immunol*, 174, 6993-7005 (2005)

62. Lee, I., L. Wang, A. D. Wells, M. E. Dorf, E. Ozkaynak & W. W. Hancock: Recruitment of Foxp3+ T regulatory cells mediating allograft tolerance depends on the CCR4 chemokine receptor. *J Exp Med*, 201, 1037-44 (2005)

Key Words: Chemokines, Chemokine Receptor, Renal Transplantation, Rejection, Allograft Injury, Transplant Glomerulopathy, Chemokine Antagonist, Review

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