REVIEW ARTICLE

The role of CXCR3 and its ligands in renal transplant outcome

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ABSTRACT. Chemokines and their corresponding receptors serve as pro-inflammatory and migratory signals for immune cells. CXCR3 and its corresponding ligands, CXCL9, CXCL10 and CXCL11, participate in the induction of immune responses against several foreign antigens. Numerous cells, including macrophages, NK cells and T lymphocytes, express CXCR3 and thus, expression of the receptor and its ligands can induce activity of these important immune cells against foreign antigens, including allogeneic grafts. Several parameters of the immune system participate in the induction and stimulation of powerful immune responses against allogeneic grafts. A thorough understanding of the parameters that regulate these responses can provide insights into new methods for immunotherapy during organ transplantation. The aim of this review is to address the most recent information regarding the roles played by CXCR3 and its corresponding ligands in the outcome of renal transplantation.

Keywords: CXCR3, transplantation, CXCL9, CXCL10, CXCL11

The combined activities of immune cells, including cytotoxic and helper T lymphocytes, NK cells, DCs, and macrophages, play critical roles in the induction and stimulation of immune responses against foreign antigens, especially allogeneic grafts [1, 2]. Previous studies have demonstrated that chemokines, a subtype of cytokines, serve as either recruiter or activator signals for immune cells via interaction with their receptors [3]. CXCR3 is a chemokine receptor that is specific for CXCL9, CXCL10 and CXCL11 [4]. Intracellular signaling by the CXCR3/ligand axis results in the activation of numerous pro-inflammatory transcription factors (described below), and it appears that this axis plays key roles in recruitment and activation of immune cells towards foreign antigens (*figure 1*).

Abbreviation

NK cells	natural killer cells
DCs	dendritic cells
MIG	monokine induced by gamma interferon
I-TAC	interferon-inducible T-cell alpha chemoattractant
MHC	major histocompatibility complex
CXCL	chemokine (C-X-C motif) ligand
MDA5	melanoma differentiation-associated gene 5
GPCRs	G-protein coupled receptors
NF-κB	nuclear factor kappa-light-chain-enhancer
MAPK family	mitogen-activated protein kinase family
Pyk2	protein tyrosine kinase 2
ELR	glutamic acid-leucine-arginine motif

Several disorders lead to serious kidney malfunction. Consequently, kidney transplantation is considered the gold standard for treatment of end-stage kidney disease [5]. However, there are more than one million people worldwide on the kidney transplantation waiting list [6]. However, the high rate of polymorphisms in major histocompatibility complexes (MHCs) makes it difficult to find a suitable donor [6]. Furthermore, although very many allogeneic kidney transplantations are performed worldwide, but some of them will be rejected via recognition of alloantigens by the host immune system [7, 8]. After kidney transplantation, ischemia/reperfusion injury can also occur because of enhanced graft immunogenicity [9]. In response to these challenges, investigators are exploring specific immunotherapies that may help to prevent transplantation rejection and ischemia/reperfusion, mainly because current methods, which rely on immunosuppressive drugs, are associated with several complications such as immunodeficiency [8]. To design an effective immunotherapy, it is important to know the main mechanisms and signaling molecules responsible for the induction and stimulation of the immune system against allogeneic grafts [10]. Because of the the important roles played by CXCR3 and its corresponding ligands in the activation and stimulation of the immune system, the main aim of this review article is to present an overview of the current investigations regarding the roles of these molecules in the pathogenesis of renal rejection.

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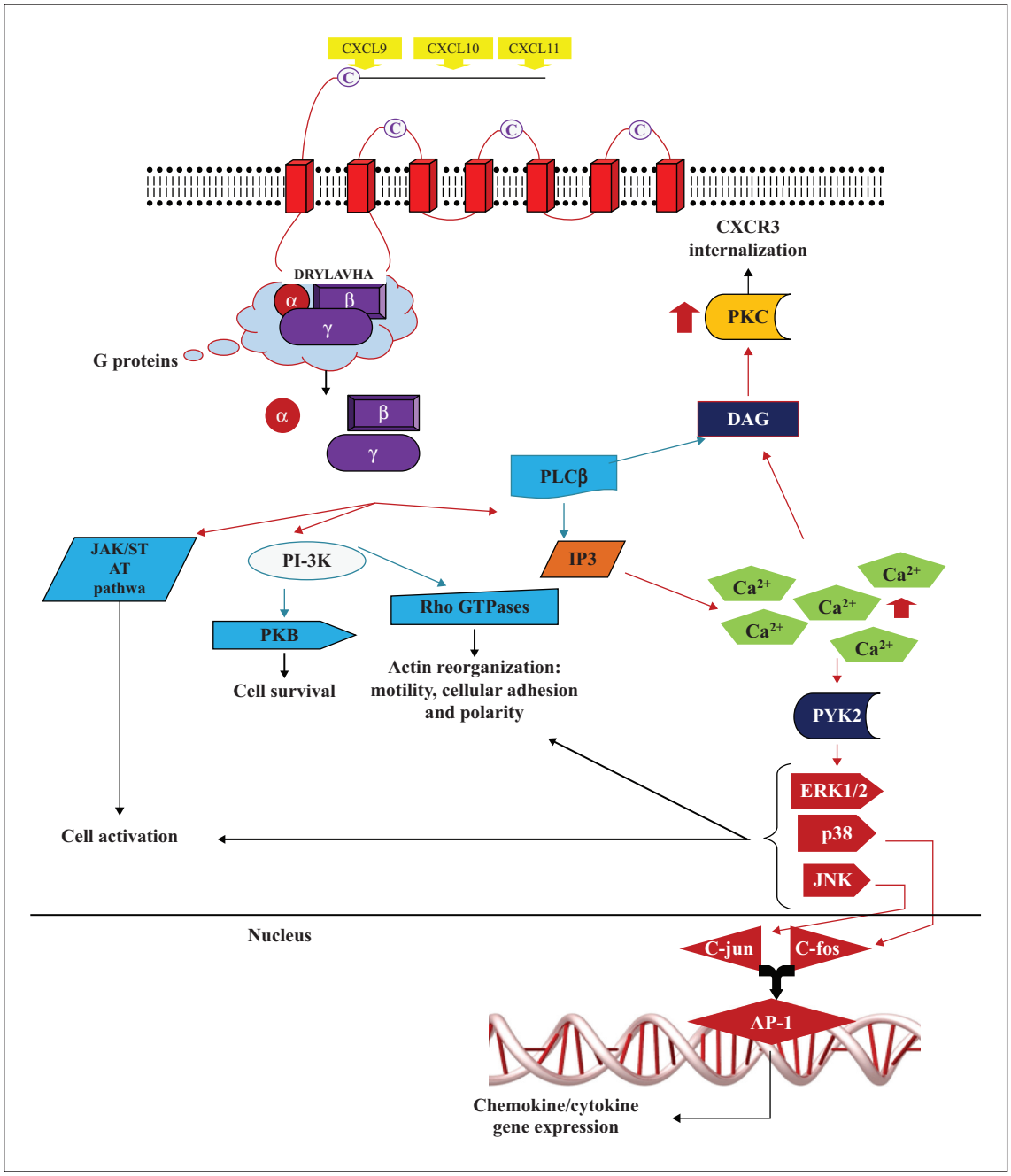

Figure 1

The figure shows the structure of CXCR3 and its intracellular signaling pathways. CXCR3 is a 7 transmembrane domain receptor and interacts with CXCL9, CXCL10 and CXCL11 via its extracellular domain, which results in activation of intracellular signaling pathways via G proteins (α, β and γ chains). Like other chemokines, following CXCR3/ligand interactions and subsequent dissociation from the G protein, the intracellular pathways are activated. Adapted from Zare-Bidaki *et al.* [3].

EVIDENCE

A review of all relevant literature was conducted using medical terms for renal rejection, kidney transplantation, CXCR3, CXCL9, CXCL10 and CXCL11, within the latest date-range up to and including 2015 from international scientific databases including ProQuest, Scopus, Medline, PubMed, Web of Science, Web of Knowledge and Google Scholar. Some advanced search measures such as Boolean operators, Truncations, Controlled Vocabulary (MeSH), limits and field searching were used to achieve more relevant and most recently updated results.

CXCR3, CXCL9, CXCL10 and CXCL11

CXCR3

CXCR3, like other chemokine receptors, is a seven transmembrane-spanning, α-helix architecture protein (Gα protein-coupled CXC receptor) [11]. It is also known as G protein-coupled receptor 9 (GPR9) CD183, CKR-L2, CMKAR3, GPR9, IP10-R and MigR. Its gene is located on Xq13, and contains three exons and two introns [12]. In humans, CXCR3 has three variants (CXCR3A, CXCR3B, and CXCR3alt), which are all considered targets of CXCL4, CXCL4L1, CXCL9, CXCL10 and CXCL11,

as glutamic acid-leucine-arginine motif (ELR)-negative CXC chemokines [13, 14]. CXCR3A and CXCR3B are the receptors for all of the chemokines mentioned, but CXCR3alt is the target of CXCL11 only [15]. CXCR3A has 368 amino acids, while CXCR3B, and CXCR3alt consist of 415 and 267 amino acids, respectively [16]. CXCL9, CXCL10 and CXCL11 are well known as IFN-γ-inducible CXCR3 ligands, while, CXCL4 and its non-allelic variant (CXCL4L1) are best known as platelet-derived CXCR3 ligands [16]. CXCL4, CXCL4L1, CXCL9, CXCL10 and CXCL11 are able to bind to CXCR3A and CXCR3B, as well as proteoglycans, while, CXCL11 shows unique affinity for CXCR3alt and CXCR7 [16]. CXCL11 and CXCL4 can also bind to the Duffy antigen receptor for chemokines (DARC) [17]. Several immune and non-immune cells, including activated T lymphocytes, fibroblasts, epithelial and endothelial cells, dendritic cells, natural killer cells, kidney cells and smooth muscle express either CXCR3A or CXCR3B or a combination of both variants [13, 14]. Interaction between these ELR-negative CXC chemokines and the CXCR3A variant leads to chemotaxis and proliferation of immune cells, while the interaction of the chemokines with the CXCR3B variant results in anti-proliferative and anti-migratory effects [16]. Accordingly, CXCR3A/ligand interactions attract Th1 cells, while blocking the migration of Th2 cells, integrin activation, immune cell cytoskeletal changes and chemotactic migration, which are important phases of the immune responses to allogeneic grafts [18]. The interaction is also able to promote Th1 cell maturation, increase intracellular Ca^{2+} levels, and activate two important intracellular signaling pathways, phosphoinositide 3-kinase and mitogen-activated protein kinase (MAPK) [19]. The details of the signaling pathway are presented in *figure 1*. Negative feedback results in cellular desensitization via phosphorylation of CXCR3 and subsequent receptor internalization [20]. Interestingly, it has been reported that CXCL11 is a more potent inducer of CXCR3 internalization than CXCL9 and CXCL10. CXCL11 is also responsible for CXCR3 internalization following T/endothelial cells contact [21]. Therefore, it may be hypothesized that CXCL9, CXCL10 and CXCL11 lead to different signals via CXCR3. It has been suggested that the three ligands probably make contact with distinct domains of the receptor, which may explain the differing signal transduction responses for each ligand. After internalization, CXCR3 is degraded and new receptors are displayed by *de novo* synthesis [20]. CXCR3 is predominantly expressed on effector/memory T cells, and its ligands are commonly secreted by local cells in inflammatory lesions [22], hence, it can be hypothesized that CXCR3 and its corresponding ligands participate in the recruitment of inflammatory cells during renal rejection.

CXCL9

CXCL9, like CXCL10, CXCL11, CXCL4 and CXCL4L1, is a small cytokine which belongs to the ELR$^-$CXC chemokine family [23]. CXCL9 is also known as MIG, crg-10, CMK, Humig and SCYB9. Its gene is located on 4q21 and consists of 4 exons and 3 introns [12]. As mentioned previously, CXCL9 is a Th1 cell and NK cell chemoattractant and its expression is induced by IFN-γ [18]. Its structure and functions are closely related to other CXCR3 ligands such as CXCL10 and CXCL11 [24]. Interestingly, in humans, the CXCL10 and CXCL11 genes are located near the gene for CXCL9 on chromosome 4 [12].

CXCL10

CXCL10 is another CXCR3 ligand which is also known as IP-10, C7, mob-1, IFI10, INP10, crg-2, SCYB10 and gIP-10 [12]. Its gene, like CXCL9, is located on 4q21 and consists of 4 exons and 3 introns [12]. The CXCL10 structure has been evaluated by NMR spectroscopy [25], which has helped identify CXCR3/CXCL10 interactions that involve a hydrophobic cleft formed by the N and 40s-loop and N and 30s-loop regions of CXCL10 [26]. Both regions make hydrophobic clefts that provide the location of the interaction with CXCR3 [26]. This kind of interaction has been reported for other chemokines such as IL-8 [26].

CXCL11

CXCL11, like CXCL9 and CXCL10, is another known ligand for CXCR3. It can also bind to CXCR3alt, proteoglycans and DARC. It is also known as I-TAC, IP-9, IP9, H174, b-R1, SCYB11 and SCYB9B. Its gene is located on 4q21.2 and includes 4 exons and 3 introns [12]. CXCL11 differs from CXCL9 and CXCL10 in both the strength and the quality of its receptor interactions. CXCL11 bind to CXCR3 with higher affinity, so it is a stronger agonist [27]. In addition, CXCL11 has greater conformational flexibility than CXCL9 and CXCL11. In contrast to CXCL10, CXCL11 does not form dimers, even at millimolar concentrations [28].

CXCL4

CXCL4 is another ligand for CXCR3A and B, and also binds to proteoglycans and DARC. It is also known as PF-4 and SCYB4. Its gene is located on 4q12-q21 and includes 4 exons and 3 introns [29]. CXCL4 is produced and saved in alpha-granules of activated platelets and released after activation of platelets [29].

CXCL4L1

Another ligand for CXCR3A and B is CXCL4L1 and also binds to proteoglycans. It is also known as PF4A, CXCL4V1, PF4-ALT and SCYB4V1. Its gene is located on 4q12-q21 and includes 3 exons and 2 introns [30]. CXCL4L1 is produced and saved in alpha-granules of activated platelets and released after activation of platelets [30].

RENAL REJECTION AND THE ROLES OF CXCR3, CXCL9, CXCL10, CXCL11, CXCL4 AND CXCL4L1

As mentioned in previous sections, immune responses to alloantigens of transplanted kidneys are the main reasons for kidney ischemia/reperfusion injury and renal rejection [1, 31]. Previous sections also elucidate the roles played by chemokines in the induction and stimulation of immune responses against foreign antigens including alloantigens [3]. Additionally, it has been mentioned that CXCR3/ligand interactions represent the core mechanism that results in migration and activation of the main immune cells involved in transplantation rejection; T and

Table 1
The significant findings regarding the roles played by CXCR3 and its ligands in renal transplantation, dysfunction and normal function.

Model study	Results	References
Pathological roles played by CXCR3 and its ligands during renal transplantation		
Human	CXCL10 and CXCL11 result in migration of activated CXCR3-positive T cells to the allograft and induction of acute renal rejection	[33]
Human	CXCR3 mediates renal allograft rejection via cellular but not humoral immunities	[34]
Human	CXCR3 is up-regulated on peripheral $CD4^+$ T cells during allograft rejection and prior to clinical symptoms	[35]
Human	Expression of CXCR3 ligands is associated with $CD3^+$ T cell infiltration of the allografts	[36]
Human	$CXCR3^+$-activated T cells infiltrated the glomerulus in chronic allograft nephropathy with transplant glomerulopathy	[37]
Human	The number of $CXCR3^+$ T cells were significantly increased at the site of injury during renal rejection	[38]
Human	Urine levels of CXCL9, 10 and 11 have a positive association with acute renal-allograft dysfunction	[39]
Human	CXCR3 is up-regulated in urine during acute rejection	[40]
Human	CXCL9 and CXCL10 are up-regulated in urine during renal rejection	[41]
Human	Elevated urine CXCL9 and CXCL10 after transplantation increased the risk of allograft renal rejection	[22]
Human	Elevated urine CXCL10 before kidney transplantation increased the risk of allograft renal rejection	[31, 42-45]
Human	CXCL9 and CXCL10, but not CXCL4, levels are higher in subclinical tubulitis than subclinical borderline tubulitis/normal tubular histology	[46]
Human	Urine levels of CXCL9, CXCL10 and CXCL11 are increased during renal rejection	[45, 47]
Rat	CXCR3-blocking leads to suppression of macrophages infiltration in acute renal allograft rejection	[48]
Mouse	CXCL10 induces immune cell migration and inhibits proliferation of tubular cells following renal ischemia-reperfusion injury	[49]
CXCR3 and its ligands have roles in kidney diseases other than renal rejection		
Human	Upregulation of CXCR3 is associated with renal dysfunction during lupus nephritis	[4]
Human	Urine levels of CXCL9 are increased in nephropathic type 2 diabetic patients	[51]
Rat	CXCL10 induces the migration of macrophages into kidney, which is associated with aggravated puromycin aminonucleoside nephrosis	[52]
Positive roles of CXCR3 and its ligand for renal survival		
Human	Infiltration of CXCR3-positive T regulatory cells into the allograft transplanted kidney is associated with appropriate allograft renal function	[54]
Mouse	Infiltration of T regulatory CXCR3-bearing cells into the kidney is associated with recovery of renal function	[55]
Mouse	CXCL10/CXCR3 blockade led to promotion of progressive renal fibrosis via up-regulation of TGF-β	[56]

NK cells, as well as macrophages. Furthermore, renal tubular epithelial cells are able to produce and secret CXCL9, CXCL10 and CXCL11 in response to IFN-γ [32]. Considering the roles of these cytokines, it is not surprising that CXCR3/ligand interactions are significant participants in renal rejection (*table 1*). For instance, in a prospective, biopsy-controlled study by Panzer *et al.*, it was demonstrated that acute renal rejection is mediated by local expression of CXCL10 and CXCL11, which results in migration of activated CXCR3-positive T cells to the allograft [33]. Interestingly, not only was the expression of CXCL10 (5.2 fold) and CXCL11 (7.2 fold) increased in the transplanted kidney, the number of CXCR3 positive T cells was also elevated during kidney rejection [33]. Segerer and colleagues evaluated the mechanisms of the renal rejection mediated by CXCR3 [34]. They used C4d deposits and infiltration of CXCR3-bearing cells as a marker of humoral and cellular rejection, respectively [34]. Their investigations showed that CXCR3 mediates renal allograft rejection via cellular, but not humoral immunities [34]. Another study showed that expression of CXCR3 on peripheral $CD4^+$ T cells is up-regulated during allograft rejection and prior to clinical symptoms [35]. Interestingly, the study showed that following transplantation, expression of CXCR3 remains elevated for more than two weeks [35]. There are several studies that confirm the roles played by CXCR3 and its corresponding ligands in the infiltration, and activation, of immune cells, especially T cells, into the allograft kidney, and the induction of renal rejection [36, 37]. Hoffmann *et al.* reported that the number of CD4-positive T helper and CD8-positive T cytotoxic cells, which express CXCR3, were significantly increased at the site of injury during renal rejection [38]. In parallel with these studies, Hu *et al.* reported that increases in urine CXCR3-binding chemokines, including CXCL9, 10 and 11, can be considered as markers of acute renal-allograft dysfunction [39]. Interestingly, they demonstrated that urine evaluation of the chemokines can be used for monitoring the response to anti-rejection therapies. Their results demonstrated that the test is more sensitive and predictive than evaluation of serum creatinine [39]. Tatapudi *et al.* also revealed that mRNA levels for IP-10 and CXCR3 are up-regulated in urine, and so they can be considered as markers of the intra-graft cellular traffic

which cause acute rejection [40]. These results were also confirmed by Jackson and colleagues [41] who reported that increased urinary levels of CXCL9 and CXCL10 are markers of renal allograft rejection [41]. An elevated ratio of urinary CXCL10:creatinine is also associated with rejection in renal transplantation. Interestingly, not only is post-transplantation increased expression of CXCL9 and CXCL10 [22] associated with increased risk of renal allograft rejection, increased serum levels of CXCL10 before kidney transplantation is also associated [31, 42-45]. A study by Schaub and colleagues showed higher urinary levels of CXCL9 and CXCL10 in subclinical tubulitis than in subclinical borderline tubulitis/normal tubular histology, while urinary levels of CXCL4 did not differ among the groups [46]. There are also numerous studies which confirmed the presence of CXCL9, CXCL10 and CXCL11 in the urine during renal rejection [45, 47]. All the investigations mentioned were performed in humans, but two studies using animal models confirmed the results. Accordingly, a study on rats reported that blocking CXCR3 leads to the suppression of macrophage infiltration in acute renal allograft rejection [48]. Additionally, the study revealed that following CXCR3 blockage, serum levels of activated macrophage-associated cytokines, such as IFN-γ, were also decreased and graft survival was prolonged [48]. Another study on mice demonstrated that, in addition to the pro-inflammatory effects of CXCL10 by induction of immune cell migration, the chemokine inhibits proliferation of tubular cells following renal ischemia-reperfusion injury in mice [49], which is a marker of renal rejection. It appears that CXCR3 and its ligands have similar functions in small animal models such as mice and rats as those in humans.

According to the results presented by the investigations, it may be concluded that CXCR3 and its corresponding ligands, CXCL9, CXCL10 and CXCL11, play significant roles in the pathogenesis of renal rejection. The roles of CXCL4 and CXCL4L1 are not clear because there has not been enough investigation regarding the roles played by these chemokines during renal transplantation. It appears that the resident immune cells in the transplanted kidney, as well as endothelial cells of the allograft, produce CXCL9, CXCL10 and CXCL11, which results in activation and infiltration of immune cells such as T and NK cells, as well as macrophages, into the allograft via interactions with CXCR3. Additionally, as mentioned previously, pre-transplantation increased expression of the chemokines is associated with a poor prognosis for kidney transplantation. Furthermore, the existence of CXCL9, CXCL10 and CXCL11 in the urine of patients after kidney transplantation can be considered as a sign of renal rejection, which confirms the important roles played by CXCR3 and its ligands in the induction/stimulation of the immune system against alloantigens of the transplanted kidney.

It has also been shown that mesangial cells play critical roles in inflammatory reactions in kidney [50]. Imaizumi *et al.* reported that MDA5, which is an intracellular receptor for microbial RNA, induces the expression of CXCL10 in human mesangial cells [50]. So it may be hypothesized that in addition to alloantigens, microbial infections can also be considered to be inducers of renal rejection through induction of CXCR3-binding chemokines. Based on the current knowledge in the field, it may be hypothesize that the immunotherapies which target CXCR3 and its ligands could represent candidate treatments for inhibiting renal rejection.

The roles of CXCR3 and its ligands in kidney diseases other than renal rejection

In addition to the roles of CXCR3 and its ligands in the pathogenesis of renal rejection, CXCR3 also plays key roles in the induction of renal complications, other than renal rejection, including lupus nephritis [4]. Increased urinary levels of CXCL9 in nephropathic type 2 diabetic patients have been also reported by Higurashi and colleagues [51]. In parallel with the studies in humans, a study in rats revealed that CXCL10 induces the migration of macrophages into kidney, which aggravates puromycin aminonucleoside nephrosis [52]. Thus, it seems that the chemokine network, CXCR3 and its ligands, significantly participates in other inflammatory-based kidney complications.

Positive roles of CXCR3 and its ligand for renal survival

In contrast with the results that considered CXCR3 and its ligands, CXCL9, CXCL10 and CXCL11, as risk factors for kidney transplantation and inflammatory-based kidney diseases, some investigations have shown that the chemokine network can be beneficial in some situations. Previous studies identified that T regulatory lymphocytes significantly participate in survival and normal function of kidneys [53]. Hoerning and colleagues reported the same results. They demonstrated that infiltration of CXCR3 positive T regulatory cells into the kidney allograft is associated with appropriate allograft function [54]. Accordingly, a set of studies involving animal models revealed that T regulatory CXCR3-bearing cells infiltrated the kidney following transplantation. Jun *et al.*, showed that infiltration of mice T regulatory CXCR3-bearing cells into the kidney, 72 h after reperfusion, is either inversely correlated with blood urea nitrogen (BUN) or directly associated with recovery of renal function [55]. In mouse models, CXCL10/CXCR3 blockage also led to promotion of progressive renal fibrosis via up-regulation of TGF-β [56]. Based on these studies, it seems that human and animal models have similar results: hence, it seems that CXCR3 and its ligands play key roles in kidney physiology in mammalians.

The controversial reports regarding the roles of CXCR3 and its ligands during kidney transplantation may be related to the amount of CXCR3 ligand production or the balance between CXCR3A and CXCR3B expression.

It has been demonstrated that IL-2, a cytokine which induces proliferation of T helper/cytotoxic and T regulatory cells [57] either induces immune responses against foreign antigens, via induction of clonal expansion of T helper/cytotoxic cells, or suppression of immune responses, through proliferation of T regulatory cells [58]. Low amounts of IL-2 affect T regulatory cells, while high amounts of IL-2 engage IL-2 receptors on T helper/cytotoxic cells [58]. Accordingly, it may be hypothesized that expression levels of CXCR3 ligands may define the target of the chemokines, so low and high amounts of CXCL9, CXCL10 and CXCL11 may affect T regulatory cells and T helper/cytotoxic cells, respectively. However,

the main mechanisms which results in recruitment of pro-inflammatory cells or T regulatory cells are yet clarified and more research is needed to better understand the mechanisms invoked by CXCR3 and its ligands during renal acceptance or rejection.

CONCLUSION

The key points of the research presented in this review are:
– 1. CXCR3 and its corresponding ligands, CXCL9, CXCL10 and CXCL11, play key roles in the induction of immune responses against allografted kidneys.
– 2. Evaluation of CXCL9, CXCL10 and CXCL11 in urine from kidney transplant patients can be considered for prognostic assessment of acceptance or rejection of the transplant.
– 3. CXCL9, CXCL10 and CXCL11 bind to CXCR3, but their effects may be different. Based on the various functions of CXCR3 variants (CXCR3A and CXCR3B), the controversy may be related to the involvement of the different variants. Additionally, the increased avidity of CXCL11 may lead to different signal transductions. Additionally, based on a study in mice, it has been reported that CXCL9, but not CXCL10, stimulates immune-mediated kidney disease in CXCR3-dependent manner [59]. Thus it seems that a reason for the different effects of CXCR3 ligands on the T helper/cytotoxic or T regulatory cells may be related to the kind of CXCR3 ligands.
– 4. Both T cell sets, T helper/cytotoxic and T regulatory cells, are CXCR3-bearing and hence, can be a target for CXCR3 ligands. It may be hypothesized that the amount of CXCR3 ligands produced during kidney transplantation may determine which target cells infiltrate the transplanted kidney.
– 5. Due to the crucial roles of CXCR3 and its ligands in renal transplantation, it can be hypothesized that blocking CXCR3A or activation of CXCR3B may be considered as new strategies to suppress renal rejection by immune cells. Additionally, based on the fact that T regulatory cells also express CXCR3, it seems that CXCR3 and its ligand can be used for the recruitment of immune cells to inhibit immune responses to alloantigens during renal transplantation. More studies into the roles played by each chemokine in the clearance of the pathology are required so that strategies to block or stimulate appropriate ligands can be used to protect renal transplants against rejection.

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