The Role of CXCL12 in Kidney Diseases: A Friend or Foe?

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Abstract
Background: Chemokines are a family of proteins mainly mediating the homing and migration of various cells. The CXC chemokine CXCL12 is a member of low-weight-molecular chemokines. In the kidney, CXCL12 is pivotal for renal development and exerts a modulatory effect in kidney diseases under different etiologic settings by binding with CXC chemokine receptor 4 (CXCR4) or CXC chemokine receptor 7 (CXCR7). Besides, CXCL12 also exerts homeostasis influence in diverse physical conditions and various pathological situations. Thus, we conclude the complicated relationship between CXCL12 and kidney diseases in this review. Summary: In renal development, CXCL12 contributes a lot to nephrogenesis and the formation of renal vasculature via correlating with CXCR4. CXCL12 also plays an essential role in renal recovery from acute kidney injury. However, the CXCL12/CXCR4 axis plays a dual regulatory role in the initiation and development of diabetic kidney disease as well as chronic allogeneic nephropathy after kidney transplants through dialectical consideration. Additionally, the CXCL12/CXCR4 link is considered as a new risk factor for lupus nephritis and renal cell carcinoma. Key Messages: Plenty of studies have presented the influence of CXCL12 and the relation with corresponding receptors in diverse biological and pathological statuses. Simultaneously, some drugs and antagonists targeting CXCL12/CXCR4 axis effectively treat various kidney diseases. However, more researches are needed to explore thorough influence and mechanisms, providing more cues for clinical treatments.

Introduction
CXCL12 was initially described in 1994 as pre-B cell growth-stimulating factor and was then named as stromal cell-derived factor-1 (SDF-1) in 1996 due to its continuous expression in bone marrow stromal cells [1, 2]. According to differential mRNA splicing, CXCL12 was identified as 6 different splice variants including CXCL12α to φ in humans while 3 variants (CXCL12α to γ) were confirmed in mice [3, 4]. As a member of chemokines, CXCL12 usually fulfills biological and pathological func-
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The Role of CXCL12 in Nephrogenesis

It is well known that CXCL12 plays a pivotal role in angiogenesis and organogenesis [8]. When the sight is focused on renal development, the CXCL12/CXCR4 axis also contributes a lot. Takabatake et al. [11] detected that adjacent parts of the podocytes also expressed CXCL12 in addition to stromal cells during glomerular development. As for CXCR4, it is consistently presented in the nephrogenic zone during embryogenesis. Precisely, Gröne et al. [10] exhibited that CXCR4 was strongly expressed in the ureteric bud and pretubular aggregates at the early embryonic stage while its expression diverted to cap mesenchyme instead of ureteric buds at a later stage. Notably, Tachibana et al. [12] found that mice lacking CXCL12 or CXCR4 easily underwent perinatal death. Moreover, CXCL12-secreting cells always surround CXCR4-positive cells in the nephrogenic zone, indicating stromal cells and podocytes mediate signaling transduction in the developing nephrons to promote nephrogenesis [11].

When it comes to mature glomeruli, CXCL12 is expressed in stromal cells as well as podocytes while CXCR4 is expressed in most ECs [11, 13]. Thus, CXCL12 generated by podocytes and stromal cells may regulate survival signals or cell proliferation by interacting with CXCR4 on glomerular endothelial stalks. However, the precise mechanisms underlying the CXCL12/CXCR4 axis accelerating glomerular loop formation remain unclear. Takabatake et al. [11] revealed that both p44/42 mitogen-activated protein kinase (MAPK) and Akt pathways were activated in human umbilical vein ECs stimulated with recombinant CXCL12. Additionally, CXCL12 produced by podocytes could increase the level of CXCR4 in glomerular ECs. At the same time, Romoli et al. [14] observed that some interlobular arteries and afferent arterioles expressed simultaneously both CXCL12 and CXCR4, which supported that the CXCL12/CXCR4 axis improved angiogenic process via an autocrine pathway.

In conclusion, CXCL12 contributes a lot to nephrogenesis by binding with CXCR4, especially in the development of renal vasculature. However, the precise molecular mechanisms have not yet been fully understood, more efforts are needed to explore the underlying mechanisms.

The Interplay between CXCL12 and Kidney Diseases

CXCL12 and Acute Kidney Injury

AKI is defined as a sharp decline of renal function during a short period under different pathological settings. It is thought to be an independent risk parameter accounting for morbidity and mortality of hospitalized patients, especially patients in the intensive care unit [15]. There have been significant efforts to explore the cause of AKI, in which ischemia-reperfusion injury (IRI) is believed to be a critical issue [16, 17]. Thereupon, IRI-induced defects in renal vascular integrity significantly affect renal regeneration. In addition, renal tubule is also sensitive to ischemic stress, ultimately leading to tubular necrosis. Moreover, inflammation infiltration is also a key pathophysiologic process during AKI. There is a consensus that
CXCL12 plays an essential role in the renal recovery from AKI as we delineate in the following section (shown in Fig. 1).

The renal capillary network repair requires the involvement of diverse cells. Among them, the differentiation of bone marrow-derived cells (BMCs) including EPCs and HSCs into vascular ECs and smooth muscle cells is essential for this process [18]. Tögel et al. [19] observed that CXCL12 showed an elevated level in the kidney after IRI-induced AKI along with decreased expression in the bone marrow, thus resulting in the reversal gradient between bone marrow and kidney. Then BMCs with increasing CXCR4 were modulated into the circulation and migrated to the injury kidney attracted by CXCL12-labeled cells. Subsequently, CXCL12 may participate in BMCs differentiation into ECs by enhancing vessel endothelial growth factor (VEGF) expression [20]. Of note, both CXCL12 and VEGF could be regulated by hypoxia-inducible factor-1α (HIF-1α) induced by various pathological settings, such as mechanical disorders, ischemic injury, hypoxia, and DNA damage. Besides, HIF-1α also improved CXCR4 generation, which accelerated vessel reconstitution by increasing VEGF and endothelial nitric oxide synthase (eNOS) secretion [21].

Moreover, Ge et al. [22] focused on the role of side population (SP) cells in renal injury repair. SP cells harboring stem cell-like characteristics exist in diverse tissues, including kidney. Present studies manifested the marked upregulation of CXCL12 and CXCR4 in SP cells.
upon IRI. Additionally, CXCL12 increased ABCG2 expression in SP cells simulated with IRI through Shh-Gli1 signaling [22]. Meanwhile, CXCL12/CXCR4 improved SP cells chemotaxis and paracrine actions. Furthermore, blocking CXCR4 with the corresponding antagonists counteracted SP cell-initiated renal recovery. Overall, the CXCL12/CXCR4 axis may participate in SP cells-mediated renoprotection in IRI-induced AKI via Shh/Gli1-ABCG2 pathway.

Taking the characteristics of CXCR4 as a member of GPCRs into account, CXCL12 may activate transcription factors to regulate renal cell proliferation, apoptosis and ultimately promote angiogenesis by inducing intracellular downstream cascades, such as intracellular ras, phosphatidylinositol 3-kinase (PI3K), Janus kinase/signal transducer and activators of transcription (JNK/STAT) signaling [23].

It has been well described that dipeptidyl peptidase (DPP)-4 inhibitors serve as antidiabetic drugs [24, 25]. Recently, Kamel et al. [21] identified the renoprotective effect of DPP-4 inhibitor saxagliptin in IRI-induced AKI. In IRI rats, saxagliptin sustained CXCL12 expression as well as upregulated the level of CXCR4 to trigger angiogenesis via the modulation and homing of EPCs [21]. Additionally, saxagliptin also stimulated kidney injury molecule-1 (Kim-1)/STAT-3/HIF-1α/VEGF pathway, accompanied by levels of GLP-1/cAMP [21]. Accordingly, saxagliptin-mediated upregulation of CXCL12/CXCR4 axis may be an outcome of Kim-1/STAT-3/HIF-1α/VEGF pathway coupling with the enhanced expressions of GLP-1/cAMP.

In addition to vascular integrity, renal tubular injury reconstitution also needs more attentions, which depends to a large extent on BMCs homing to the kidney and harboring a phenotype of tubular epithelia. In healthy human kidneys, Lotan et al. [26] discovered that strong immunoreactivity of anti-CXCL12 antibodies could be detected in renal tubular cells. In a model of AKI, renal epithelial cells secreted CXCL12 in response to hypoxia, while hepatocyte growth factor (HGF) was produced in renal interstitium [18]. Both CXCL12 and HGF are essential for migration of BMCs to injured tubules as well as differentiation to the renal tubular epithelia cells (TECs). Neutralizing HGF in AKI mice resulted in renal hypoxia and CXCL12 upregulation, inhibiting tubular cell proliferation and BMCs recruitment [27]. On the other hand, CXCL12 mediated MAPK/Erk kinase pathway by interacting with upregulated CXCR4 to enhance the proliferation of renal epithelial cells, as well as PI3K/Akt signaling [28].

Furthermore, it is worthy to explore whether CXCL12 participates in recruiting inflammatory cells during AKI initiation and progression due to the CXCR4 presence on the surface of various inflammation cells. Actually, little is known about the role of CXCL12 in AKI-associated inflammation infiltration. Stokman et al. [28] reported that CXCL12 antisense administration amplified an intrarenal inflammatory reaction during IRI, different from nonkidney inflammation infiltration including LPS-induced lung injury. It was possible that the increased number of apoptotic TECs improved the demand for neutrophils to migrate to the kidney to clear injured cells [28]. However, Tögel et al. [19] found that T-cell repulsion was induced when the concentration of renal CXCL12 after IRI reached the concentration detected in the bone marrow, thereby exerting an anti-inflammatory effect. Even more to the point, Wan et al. [23] suggested that renal CXCL12 accumulated in response to IRI and was significantly upregulated upon macrophage depletion, indicating that the initial inflammatory response for kidney injury likely determined CXCL12 activation in turn.

Taken together, CXCL12/CXCR4 axis contributes to AKI regeneration by promoting angiogenesis and tubular cell proliferation via various mechanisms. Moreover, the interaction between CXCL12 and inflammatory response including neutrophils infiltration, T-cell depletion, and macrophage initiation is also involved in AKI.

**CXCL12 and Diabetic Kidney Disease**

As a well-known complication of diabetes, DKD has been one of the most common causes of end-stage kidney disease. There have been lots of investigations to explore the mechanisms of DKD, podocyte injury, and mesangial expansion are thought to be significant events [29, 30]. CXCL12 plays an essential regulatory role in the initiation and development of DKD, however, whether it is beneficial or harmful requires dialectical consideration as we sketch in the following part (shown in Fig. 2) [31, 32].

A growing body of data suggests that CXCL12 exerts a renoprotective effect in DKD by binding with CXCR4. The CXCL12/CXCR4 axis maintains the glomerular structure by promoting renal podocyte survival, reducing mesangial expansion and tubular epithelial cell death [31, 33]. Takashima et al. [31] reported that CXCR4 antagonists resulted in podocyte disorder by inhibiting CXCL12/CXCR4 interaction in DKD mice. Besides, CXCR4 blockade also promoted hyperglycemia-stimulated renal TEC death by increasing the level of Bcl-2-related death promoter (BAD) and preventing Akt phosphorylation [33]. Moreover, Zhang et al. [34] reported that CXCL12/
CXCR4 correlation inhibited fibronectin expression and extracellular matrix accumulation through PI3K/Akt signaling in high glucose-induced mesangial cells.

Siddiqi et al. [33] elucidated that CXCL12 expression was enhanced accompanied by the upregulation of matrix metalloproteinase-9 (MMP-9) in both DKD patients and diabetic rats. Due to the effect of cleaving CXCL12, MMP-9 contributed to reducing the phosphorylation of CXCR4 and eliminating the phosphorylation of downstream Akt in turn [35]. Thus, MMP-9-mediated CXCL12/CXCR4 inactivation depresses its renal protection in DKD.

Dipeptidyl peptidase-4 (DPP-4) is another cleavage enzyme of CXCL12 [36], its inhibitors can further increase the expression of CXCL12 in glomerular and medullary tissues [31]. Fujita et al. [37] treated patients in the early DKD stage with DPP-4 inhibitors based on angiotensin II type 1 receptor blockade, they found that the therapy prevented DKD progression along with renal oxidative stress and proteinuria reduction by activating the CXCL12-cAMP pathway. Therefore, DPP-4 inhibitors can sustain glomerular podocytes via the antioxidant and antifibrotic effects of CXCL12 [31].

Nowadays, a series of investigations report that blocking the CXCL12/CXCR4 axis exerts a therapeutic effect in DKD clinical treatment [32, 38]. The CXCL12/CXCR4 axis is not only beneficial to renal regeneration, but it is also indeed related to DKD progression. Sayyed et al. [38] observed that CXCL12 produced mainly by podocytes potentiated proteinuria and glomerulosclerosis in type 2 diabetic db/db mice. Subsequently, they found that temporarily blocking CXCL12 could effectively prevent the
CXCL12 and Lupus Nephritis

Inflammatory infiltration and autoantibodies deposits are cardinal to the pathogenesis of systemic lupus erythematosus-mediated organ perturbation, specifically lupus nephritis [41]. Although CXCL12 is defined as a homeostasis chemokine, several investigations showed that CXCL12 might be a risk factor for the progression of lupus nephritis (shown in see online suppl. Fig. 1; see www.karger.com/doi/10.1159/000514913 for all online suppl. material) [42–44].

Antibody-secreting cells (ASCs), including plasma-blasts and memory plasma cells, are essential for lupus nephritis. In NZB/W mice, Balabanian et al. [43] confirmed that the upregulation of CXCL12 depended largely on podocytes in glomeruli. Simultaneously, CXCR4-positive ASCs were attracted to the kidney, leading to autoantibodies deposits. In addition to ASCs, other lymphocytes, including T cells, peritoneal B1a (PerB1a) lymphocytes, were also activated and modulated to renal tissues via CXCL12/CXCR4 axis [43]. Furthermore, Badr et al. [44] proposed that B cells involved in lupus nephritis presented a marked upregulation in responsiveness to CXCL12 via PI3K/AKT, NF-κB, and ERK signaling excessive activation. Meanwhile, the correlation between CXCR4 and CXCL12 also triggered MAPK and JAK/STAT signaling, ultimately initiating aberrant cellular issues [41]. Interestingly, CXCR4 enhancement in podocytes is consistent and even strengthened by CXCL12. Then the CXCL12/CXCR4 axis may activate NADPH-oxidase via an autocrine pathway, thereupon resulting in reactive oxygen stress accumulation, consequently attacking the glomeruli of NZB/W mice [43].

In contrast, both CXCL12 neutralization and CXCR4 antagonists can restore renal function and attenuate lupus nephritis damage. Balabanian et al. [43] illustrated that CXCL12 neutralization prevented proteinuria and death in NZB/W mice along with decreased numbers of PerB1a lymphocytes as well as suppression of T lymphocytes activation. Additionally, Cheng et al. [45] elucidated that long-term CXCR4 blocker treatment downregulated the level of autoantibodies uncoupling with inhibition of the inflammatory process in lupus nephritis. Thus, the CXCL12/CXCR4 axis results in lupus nephritis progression via ACSs-mediated autoantibodies deposits as well as T cell and PerB1a lymphocytes infiltration in diverse signaling pathways.

CXCL12 and Kidney Transplantation

Kidney transplantation is the effective treatment for ESRD patients. However, kidney transplant recipients are
CXCL12 and Renal Cell Carcinoma

Clear cell RCC (cc-RCC) is the most common subtype of RCC, mainly characterized by the inactivation of the von Hippel-Lindau (VHL). VHL can induce various target proteins degradation, including HIF-1α, a key transcription factor for CXCL12 gene expression in RCC [59]. Struckmann et al. [60] demonstrated that VHL dysfunction led to the accumulation of HIF-1α coupled with increased expressions of CXCL12/CXCR4 in cc-RCC, ultimately leading to the imbalance of cell growth and angiogenesis (shown in online suppl. Fig. 3).

Both Wu et al. [61] and Wang et al.’s [62] teams showed that CXCL12 was one of the central potential target genes and biomarkers of cc-RCC, contributing to deciphering the molecular mechanisms of cc-RCC occurrence as well as being used as a diagnostic biomarker and therapeutic target for cc-RCC. The genetic polymorphisms of CXCL12/CXCR4 are related to the increased sensitivity of Chinese to RCC, indicating a new risk factor for RCC in the Chinese population [63].
Gahan et al. [64] and Schrader et al. [65] indicated that compared with normal kidney tissues, the expressions of CXCL12, CXCR4, and CXCR7 in RCC tissues were upregulated. Simultaneously, Wang et al. [66] and Wehler et al.’s. [67] teams proved that the elevations were associated with poor overall survival and relapse-free survival of RCC. Rasti et al. [68] also discovered that the expression of CXCR4 was positively correlated with the grade, stage, and microvascular invasion of RCC. Moreover, in the view of Tang et al. [69], the expression of CXCR4 was relatively stronger in RCC patients with lower Fuhrman grade.

As known, RCC has the characteristic of organ-specific metastasis. The CXCL12/CXCR4 axis also provides RCC with a strong ability to regulate cell cycle and inhibit apoptosis, as well as invade the tissue barrier and migrate to other organs [59, 60, 70]. Interestingly, Wang et al. [66] detected that the level of CXCL12 in surrounding tissues was higher than that in RCC tissues, suggesting that a possible metastasis channel was constructed between cancer tissues and surrounding normal tissues and organs via the concentration gradient of CXCL12. Besides, they also showed that the expression of CXCR4 in metastatic foci of RCC was higher than that of RCC in situ. At the same time, CXCR4 was mainly localized in cytoplasm and nucleus in metastatic RCC instead of the cell membrane in primary RCC, indicating that metastatic ability of RCC was related to the high expression and nuclear localization of CXCR4 [71, 72].

Furthermore, Jones et al. [73] raised that the CXCL12/CXCR4 axis was also involved in triggering the adhesion of RCC cells to vascular ECs and subendothelial matrix, contributing to RCC metastasis. Notably, CXCR4 expressed by RCC cells mediates the chemical inducement of CXCL12 secreted by the target organs [74], CXCL12 induces internalization of surface CXCR4 in turn [75]. Besides, the study constructed by Gassenmaier et al. [76] proved that CXCR4 could also predict the survival time of nonmetastatic RCC patients. Gahan et al. [64] also established a prospective study reporting that CXCL12+CXCR7+ had approximately 80% accuracy in predicting cc-RCC metastasis.

In addition, Pan et al. [59] found that the treatment of specific anti-CXCL12 antibody significantly reduced the transfer of RCC to target organs in the in situ RCC model. Wang et al. [74] also targeted CXCR4 to inhibit the metastatic process of RCC, leading to RCC cell apoptosis. It can be seen that the regulation of CXCR4/CXCL12/CXCR7 biological axis may be a potential therapeutic target for RCC. As a result, CXCL12/CXCR4 axis leads to RCC poor survival by promoting tumor growth and metastasis via various mechanisms, which provides a promising target regarding RCC treatment.

**Conclusion**

CXCL12 belongs to a large family of small protein chemokines and its interplay with receptors including CXCR4 and CXCR7 is involved in various biological and pathological situations. In the kidney, the CXCL12/CXCR4 interaction advances renal development, especially vasculature formation. Notably, CXCL12 plays a dual role in renal diseases of different etiologic settings. CXCL12/CXCR4 axis mediates BMCS activation and homing to the defected kidney, which results in renal regeneration or accelerates disease advancement. The data aforementioned above have postulated that DPP-4 inhibitors and CXCL12 neutralization may be promising therapeutic ideas through sustaining and dampening CXCL12 expression, respectively. However, no clinical trials have been carried out to identify the role of CXCL12 in renal diseases. The underlying molecular mechanisms about the interaction between CXCL12 and kidney injury also lack thorough investigations. Accordingly, current data and conclusions may provide some clues for renal disease treatments and novel drug exploitation. Simultaneously, we still need to pay more efforts to explore the nature of CXCL12 in renal diseases via numerous fundamental and clinical studies.

**Conflict of Interest Statement**

The authors have no conflicts of interest to disclose and the results in this paper have not been published previously.

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**Author Contributions**

Chun Zhang conceptualized the review. Anni Song and Anni Jiang wrote a draft of the review and equally contributed to this paper. Chun Zhang, Wei Xiong, and Anni Song revised the paper. The figures were drawn by Anni Song and Anni Jiang. Chun Zhang performed the final edits.
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