Introduction

After the recognition of chemotactic cytokines as mediators of inflammation about a decade ago, specific chemokine antagonists are now approaching first clinical trials for non-renal indications [1]. In the field of nephrology, the potential of targeting the chemokine system has also gained much interest. In general, cytokines orchestrate cell–cell communication in order either to maintain tissue homeostasis or to initiate response mechanisms during tissue injury triggered by e.g. trauma, toxicity, immunological insults and infection. Among the cytokines, the chemokines are a distinct group of peptides involved in leukocyte trafficking, which mediate their biological effects through a group of G protein-coupled receptors, the chemokine receptors (CCRs) (reviewed in [2]). In this article we present current paradigms of chemokine biology and indicate future perspectives towards new therapeutic options for the treatment of kidney diseases.

Paradigm no. 1: some chemokines are involved in tissue homeostasis

A subgroup of chemokines within the chemokine family contributes to tissue homeostasis either by supporting the structural and functional integrity or by mediating leukocyte migration for physiological immune surveillance and preservation of tolerance. For example, one of the homeostatic chemokines is CCL21, which binds to CCR7 and is critical for the structural and functional organization of secondary lymphoid tissues (reviewed in [3]). In the healthy kidney, CCL21 is secreted by podocytes and binds to CCR7 on mesangial cells where it appears to contribute to glomerular homeostasis and regeneration [4]. Furthermore, dendritic cells upregulate CCR7 upon stimulation and migrate to regional lymph nodes where the CCR7 ligand CCL21 is expressed at high levels [5]. Depending on the presence or absence of an additional E-L-R-CXC amino-acid motif, chemokines may also promote or inhibit angiogenesis.

Paradigm no. 2: some chemokines mediate compartment-specific leukocyte recruitment in the initiation phase of renal injury

The regulatory role of chemokines for leukocyte recruitment during inflammatory tissue injury has gained most interest over the last decade. In the kidney, all types of renal cells have been shown to produce inflammatory chemokines upon various kinds of injury, including CCL2, CCL3, CCL4, CCL5 or CXCL10 (reviewed in [6]). Local production of these chemokines initiates recruitment of macrophages, natural killer cells and T-cell subsets, which leads to subsequent glomerulonephritis in the glomerular compartment and to interstitial nephritis in the tubulo-interstitium (Figure 1). Secreted chemokines bind to endothelial surfaces or interstitial matrix components and mediate leukocyte migration through their corresponding CCR on the surface of the leukocyte. The specificity of recruiting a particular leukocyte subset is provided by specific surface expression patterns of CCR. For example, neutrophils but not macrophages express CXCR1, which facilitates recruitment upon recognition of the neutrophil attractant chemokine CXCL8.

Glomerular and interstitial leukocyte recruitment is regulated by different chemokines. For example, CCL5 is critical for glomerular macrophage recruitment, as CCL5 blockade reduces glomerular macrophage counts during immune complex glomerulonephritis [7], but CCL5 blockade or lack of the CCL5 receptor CCR5 has no effect on interstitial macrophage and T-cell accumulation after unilateral ureteral obstruction [8]. In contrast, CCR1 is critical for interstitial macrophage and T-cell recruitment during progressive lupus nephritis, but CCR1 blockade does not affect the number of glomerular macrophages in that model [9].
Paradigm no. 3: infiltrating leukocytes contribute to local chemokine production in the amplification phase of nephritis and bias towards resolution or progression of disease

In addition to their role in the initiation of local inflammation, chemokines play a critical role for resolution or progression of inflammatory lesions in either glomerulonephritis or interstitial disease (reviewed in [10]; Table 1). This is facilitated by additional chemokine production by infiltrating leukocytes and continuous chemokine expression by renal cells [11–13]. However, cessation of the initial insult can down-modulate local chemokine production as a premise for disease resolution. For example, proteinuric immune complex glomerulonephritis can be induced in Balb/c mice by daily injection of apoferritin. Glomerular macrophage infiltrates are triggered by local production of CCL2 and CCL5, but discontinuation of antigen exposure stops local chemokine production followed by complete resolution of proteinuria and histopathological changes [14]. In contrast, if local chemokine production by glomerular macrophages is augmented by external stimuli, such as bacterial DNA, mice with apoferritin-induced glomerulonephritis develop severe and irreversible lesions associated with additional glomerular macrophage recruitment [15]. This mechanism may be relevant in acute forms of glomerulonephritis, e.g. IgA nephropathy and post-infectious nephropathy, but may also apply to disease flares of chronic nephropathies, e.g. lupus nephritis.

Paradigm no. 4: non-redundant chemokines or CCR represent therapeutic targets

Similar expression patterns for chemokines and CCRs in different renal disease models led to the assumption of a high degree of redundancy within the chemokine network [16]. However, recent studies with targeted deletions of chemokines or CCRs in mice or chemokine antagonists have disclosed the specific functions of individual chemokines and CCRs for renal inflammation [17]. For example, CCR1 and CCR5 are both expressed on macrophages and T cells, but regulate different stages of the rolling → adhesion (CCR1) → transmigration (CCR1 and CCR5) sequence of the endothelium–leukocyte interaction [18].
with a CCR1 antagonist lowers interstitial leukocyte counts associated with less renal fibrosis after unilateral ureteral obstruction [19] or after induction of focal segmental glomerulosclerosis with adriamycin [20]. Late onset of CCR1 blockade also preserves renal function in progressive lupus nephritis of MRL/lpr mice [9] and improves survival of collagen IVA3-deficient mice with Alport’s disease (unpublished data).

Another target for therapeutic intervention in kidney disease is CCL2. Deletion of the Ccl2 gene dramatically reduced tubulointerstitial injury in mice with nephrotoxic serum nephritis or lupus nephritis of MRL/lpr mice [21,22]. Gene transfer of a truncated human CCL2 protein demonstrated beneficial effects in renal fibrosis after unilateral ureteral obstruction in mice [23], protein-overload disease in rats [24], ischaemic acute renal failure in mice [25] and in MRL/lpr mice with lupus nephritis [26]. Epidemiological studies in renal transplant recipients with mutations in chemokine or CCR genes support the relevance of such renal disease in human kidney disease [27,28]. These data suggest that interstitial fibrosis, the common final pathway of most chronic nephropathies, may be susceptible for therapeutic blockade of selected chemokines or chemokine receptors.

Paradigm no. 5: inflammatory chemokines have additional immunoregulatory functions

Studies with chemokine antagonists or mice with targeted deletions of chemokine genes have generated some unexpected findings in renal disease models. In general, it can be concluded that these findings are related to the additional functions of chemokines in regulating immune responses. For example, CCR2+CD4+CD25+regulatory T cells control the proliferation of antigen-specific or autoreactive T cells [29]. Blockade of CCR2 late during the course of lupus nephritis in MRL/lpr mice may aggravate renal disease through such a mechanism [30]. Another example is therapeutic blockade of CCL5 in apoferritin-induced glomerulonephritis. The two antagonists Met-RANTES and AOP-RANTES aggravated glomerulonephritis despite blocking glomerular macrophage recruitment through agonistic effects on CCR5 on resident macrophages, leading to the release of proinflammatory mediators and impaired uptake of apoptotic cells [7]. The selective inhibition of the CCR5-mediated FAK kinase signalling pathway but not of the JAK/STAT signalling pathway by these antagonists may account for this observation. As another example, mice lacking the Cerl gene had aggravated nephritis after injection of nephrotoxic serum in association with a shift in the Th1/Th2 balance towards a Th1-type response [31]. These data led to the assumption that CCR1 would not be a valuable therapeutic target. However, such effects were never observed in a number of studies with CCR1 antagonists using protocols where the antagonist is given after the disease is already established [8,9,20].

Together, these data indicate that interfering with the chemokine system can modulate disease through additional mechanisms than renal leukocyte recruitment. Furthermore, data from studies with knockout mice may not be able to predict the therapeutic potential of chemokine antagonism, as in the knockout mice the lack of the chemokine or CCR exists since conception, so that the entire immune system may be altered.

Paradigm no. 6: the chemokine network is species specific

Despite significant homologies of cDNA sequences between different species, considerable distinctions exist that may affect the interpretation of data derived from rodent disease models to humans [32]. In fact, chemokine antagonists developed for the human system commonly have different pharmacological properties in other species, obviating their use for interventional experiments [1,33]. Therefore, species specificity of the chemokine or CCR antagonist must be demonstrated before its use in animal disease models.

Conclusion

Chemokines are a group of cytokines that mediate the initiation and progression of renal disease by leukocyte trafficking into the kidney. Furthermore, chemokines facilitate other functions, including physiological leukocyte migration, tissue homeostasis, angiogenesis, dendritic cell migration and modulation of adaptive immune responses. Therapeutic chemokine blockade has to face these multiple roles of chemokines. As the timing of chemokine blockade is critical, knockout mice may not always be useful in predicting the outcome of therapeutic blockade of a specific chemokine. Therefore, chemokine antagonists must be used to predict the outcome of therapeutic antagonism in relevant treatment protocols.

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