Chemokines, chemokine receptors and renal disease

Chemokines are proinflammatory cytokines that function in leukocyte chemoattraction and activation. There are two major families of chemokines, termed CXC and CC, according to the presence or absence of an amino acid between a pair of cysteine residues near the NH2 terminal [1, 2]. CXC chemokines (of which interleukin-8 (IL-8) is the prototype) act on neutrophils and nonhemopoietic cells involved in wound healing, whereas CC chemokines have a wider spectrum of action and they are active on monocytes, T and B lymphocytes, natural killer (NK) cells and dendritic cells, and they are, therefore, of great relevance in renal disease [3]. Monocytes and tissue macrophages are rich sources of CC chemokines, usually associated with de novo synthesis. Monocyte chemoattractant protein-1 (MCP-1) and MCP-2 are major products of stimulated monocytes. Lymphocytes are sources of some chemokines, particularly RANTES, macrophage inflammatory protein-1 (MIP-1) and MIP-1β. Endothelial cells, fibroblasts, epithelial cells and other kidney cells also produce CC chemokines after appropriate stimuli. Chemokines act through interaction with seven transmembrane domain G-coupled receptors. So far, nine receptors have been identified for the CC chemokines (CCR1 to -9), and four for the CXC chemokines (CXCR1 to -4). Chemokine receptors show a promiscuous pattern of ligand recognition and are differentially expressed and regulated in leukocytes [1, 2].

The glomerular and interstitial infiltration of leukocytes is a common phenomenon found in most renal diseases, independently of their immune or non-immune origin. MCP-1 and RANTES are the most studied chemokines implicated in renal disease [3]. The importance of MCP-1 and RANTES in anti-GBM nephritis was supported by the reduction of glomerular damage after blockade of those chemokines by specific antibodies and receptor antagonists. However, although both chemokines seem to participate in glomerular inflammation, only MCP-1 was related to the crescentic and fibrogenic process, suggesting that MCP-1 could also be involved in the turnover of matrix proteins [4]. Surprisingly, MCP-1 deficient mice injected with nephrotoxic serum had a marked reduction in tubular, but not in glomerular, injury, suggesting that, at least in this model, MCP-1 promoted nearly exclusively tubular epithelial cell damage [5].

Contrasting with the ample information about chemokines and renal injury, so far, little is known about the expression and distribution of chemokine receptors on different cells in normal and diseased kidneys. In this issue of *Kidney International*, Segerer et al studied, by means of monoclonal antibodies, the distribution of CCR5 (that binds to RANTES, MIP-1 and MIP-1β, but not MCP-1) in 80 biopsies from patients with various glomerulonephritis, acute and chronic interstitial nephritis, and acute and chronic transplant rejection [6]. The most striking finding was that staining for CCR5 was only detected in areas of interstitial infiltrating cells with the same distribution as CD3-positive T cells. Absence or near absence of staining for CCR5 in infiltrating CD-68 positive macrophages, and in intrinsic renal cells, were noted in nearly all the kidney diseases examined. The lack of CCR5 expression by monocytes/macrophages in the glomerulonephritis studied, mainly systemic lupus erythematosus (SLE), was unexplained. However, it could be speculated that other chemokines besides RANTES, such as MCP-1, released by glomerular and tubular cells during renal injury, may be responsible for the recruitment of macrophages. In fact, various CC and CXC chemokines may be released during glomerular damage. In addition, there are at least three monocyte CC chemokine receptors (CCR1, CCR2 and CCR5). One can assume that CCR5-negative infiltrating cells, both at the glomerular and interstitial level, should be positive for other chemokine receptors, most probably CCR2. In this regard, mice deficient in CCR2 have severe reduction in leukocyte adhesion and monocyte extravasation after intraperitoneal thioglycollate injection, indicating that CCR2, after its stimulation by MCP-1, is a major regulator of macrophage trafficking in vivo.

The mechanisms that regulate expression of the chemokine receptors are not well defined, but it is well known that cytokines can modify the density of receptors in a particular cell. Thus, IL-2 increases the CCR1 and CCR2 expression, as well as the chemotactic responsiveness, in T lymphocytes. Lipopolysaccharide down-regulates the expression of CCR2 in cultured monocytes, mostly due to the rapid degradation of CCR2 mRNA. Those cells are unresponsive to MCP-1 (which activates only CCR2), but they remain responsive to MIP 1 (which activates CCR1 and CCR5). An up-regulation of CCR1

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and CCR3, as well as induction of chemotaxis to CC chemokines, was elicited by interferon-\(\gamma\) (IFN-\(\gamma\)) in human neutrophils. By contrast, IFN-\(\gamma\), an inducer of MCP-1 and MCP-3 in mononuclear phagocytes, selectively inhibits expression of the MCP-1 receptor CCR2 in monocytes [7]. These results are consistent with an emerging paradigm of divergent regulation of chemokine production and receptor expression in monocytes by several agents. The inhibition of CCR2 expression may serve as a means of retaining mononuclear cells at inflammation site, and as a feedback mechanism in the regulation of cell recruitment from the blood. Low density lipoprotein has also been identified as a positive regulator of CCR2 expression [8], and this could be one of the mechanisms contributing to monocyte recruitment to the vessel wall in chronic inflammation and atherogenesis. In this regard, a decrease in vascular lesions and in the accumulation of monocytes was observed in hyperlipidemic CCR2 or MCP-1 knockout mice.

Another intriguing observation of Segerer et al was the absence of CCR5 detection on intrinsic renal cells, including glomerular, tubular and vascular structures. In general, chemokine receptors are expressed, besides in different types of leukocytes, in nonhematopoietic cells, including neurons, astrocytes, fibroblasts, epithelial cells and endothelial cells. The lack of detection of CCR5 on resident renal cells in processes as diverse as those studied by Segerer et al are in agreement with the data of Eitner et al [9]. Using a riboprobe with specificity for CCR5 mRNA, these latter authors were unable to demonstrate constitutive expression of CCR5 in intrinsic renal cells of normal human kidneys and those of patients with chronic tubulointerstitial injury. By contrast, CCR1, CCR2, CCR3 and CCR5 were detected in RNA isolated from normal mouse kidneys by quantitative RT-PCR, and up-regulated in animals with anti-GBM nephritis (cf. [6]). In the rat, CCR2 and CCR5 were also detected in spleen, lung, kidney, thymus and macrophages, whereas CCR5 was detected in brain. Induction of experimental allergic encephalomyelitis was accompanied by increased levels of CCR2, CCR5, CXCR4 and CX3CR1 mRNAs in the lumbar spinal cords of animals displaying clinical signs of the disease. Unfortunately, the techniques employed in these two animal studies could not completely distinguish infiltrating from resident cells. Interestingly, CCR5 has been detected on lymphocytic cells, macrophages, and microglia in actively demyelinating multiple sclerosis brain lesions [10]. The above data indicate that different parenchymal cells express chemokine receptors that can be regulated both in vitro and in vivo. The absence of CCR5 expression in human renal cells and its presence in cells of the central nervous system suggest that the existence of some chemokine receptors could be organ dependent.

Additional studies, focusing on the expression (gene and protein) of other chemokine receptors in normal and diseased kidneys, as well as a better understanding of their respective roles, are necessary for further insight into the complicated network involving leukocyte attraction in immune and non-immune renal diseases. This could provide new molecular targets for therapeutic intervention in kidney diseases.

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