Chemokines, Chemokine Receptors, and Renal Disease: From Basic Science To Pathophysiologic and Therapeutic Studies

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Abstract. Leukocyte trafficking from peripheral blood into affected tissues is an essential component of the inflammatory reaction to virtually all forms of injury and is an important factor in the development of many kidney diseases. Advances in the past few years have highlighted the central role of a family of chemotactic cytokines called chemokines in this process. Chemokines help to control the selective migration and activation of inflammatory cells into injured renal tissue. Chemokines and their receptors are expressed by intrinsic renal cells as well as by infiltrating cells during renal inflammation. This study summarizes the in vitro and in vivo data on chemokines and chemokine receptors in renal diseases with a special focus on potential therapeutic effects on inflammatory processes.

“In the injured glomerulus increased capillary permeability is associated, as in other examples of inflammation, with a so-called increased stickiness of the endothelial cells. Circulating polymorphonuclear neutrophils adhere to these sticky walls and thus accumulate in the glomerulus” (1). This observation by Jones in the early 1950s describes a fundamental premise of this review. Namely, what makes the endothelium “sticky” at a specific site of the vasculature to a specific subset of inflammatory cells and then controls their subsequent transmigration and entry into renal tissue? Developments over the past 10 years have highlighted the roles of specific adhesion molecules and chemokines in this process (2–6).

Chemokines are a family of chemotactic cytokines that were first identified on the basis of their ability to induce the migration of different cell types, particularly those of lymphoid origin (7–9). A wealth of data has demonstrated that chemokines working in concert with selectins and integrins act as directional signals to sort and direct effector leukocyte migration (4,10,11). In addition, chemokines have also been shown to activate leukocytes, influence hematopoiesis, and modulate angiogenesis (12–14).

The receptors for chemokines are expressed in a cell type-specific manner and are restricted primarily to subsets of leukocytes (15). The discovery that some chemokine receptors act as coreceptors for HIV entry into target cells has accelerated research in this field (16–22). Advances over the past few years have included the discovery of new chemokines, receptors, and antagonists, and a greater appreciation for the diverse biologic functions displayed by this cytokine family (15,23–25). Several recent reviews have dealt with the basic biology and the roles of chemokines in various disease processes (2–4,9,15,26–28). This review will focus on the biology of the chemokine and chemokine receptor families in the context of renal diseases.

Chemokines: Classification and Mechanisms of Action

The Chemokine Superfamily Is Comprised of Four Members

More than 40 chemokines and 17 chemokine receptors have been described to date, with additional candidates currently under investigation (Tables 1 and 2) (3,4,15,27,29). Chemokines are characterized by a series of shared structural determinants including conserved cysteine residues that form disulfide bonds in the chemokine tertiary structure (29,30). The chemokines were initially subdivided into two branches based on the position of these cysteine residues (9,15,27). In the CXC chemokine family, the first two cysteine residues in the primary amino acid sequence are separated by a single amino acid (X represents any intervening amino acid residue). In the CC subfamily, the cysteine residues lie next to each other. Although most of the chemokines belong to one of these two classes, two additional branches of the chemokine superfamily each containing a single member have been described in recent years (31,32). The C chemokine lymphotactin lacks both the first and third cysteine in the “4 cysteine motif,” but shares homology at its carboxyl end with the CC chemokines (32). Fractalkine has three intervening amino acids between the first two cysteine residues (31). This CX3C chemokine is tethered directly to the cell membrane via a long mucin stalk and has recently been shown to combine the function of a chemokine and an adhesion molecule (33).
Some CXC chemokines display an additional structural designation, namely, the amino acid motif E-L-R-CXC (glutamic acid-leucine-arginine-cysteine-X-cysteine) just proximal to their first two cysteine residues. The E-L-R-CXC chemokines act primarily as neutrophil chemoattractants (30). In contrast, the CXC chemokines that lack the E-L-R motif bind different CXC receptors and are active on lymphocytes (9,30).

Chemokines are involved in more than the control of cell migration. Melanoma growth stimulating activity/growth-related oncogene-α (GRO-α) was originally identified as an autocrine growth factor for malignant melanoma cells (30,34). Interferon-inducible protein-10 (IP-10) has been shown to induce the proliferation of mesangial cells (35). Interleukin-8 (IL-8) can cause release of granules and respiratory burst in neutrophils (12). Regulated upon activation, normal T cell expressed and secreted (RANTES) can induce eosinophil and basophil degranulation, respiratory burst in eosinophils (36), and has been shown to augment T cell proliferation (37). Platelet factor 4 (PF4) inhibits megakaryopoiesis (38) and can be bactericidal (39). In addition, some chemokines are involved in hematopoiesis (13,40–42). A novel role for some classes of chemokines and their receptors as anti-inflammatory mediators has recently been suggested (43). The CXC chemokines IL-8, epithelial cell-derived neutrophil attractant 78 (ENA-78), and GRO-α,β,γ, which contain the E-L-R-CXC motif, have been shown to act as angiogenic agents (44), while PF4, IP-10, monokine induced by interferon-γ (MIG), and stromal cell-derived factor-1 (SDF-1), which lack this motif, can act as angiostatic factors (14). During embryogenesis, wound healing, chronic inflammation, and tumor growth, the expression of chemokines may help to determine the microvascularization within the tissue.

**Regulation of Chemokine Expression**

Chemokines are regulated at transcriptional, posttranscriptional, translational, and posttranslational levels (2). Many, but not all, of the proinflammatory chemokines are induced by IL-1β or tumor necrosis factor-α (TNF-α). Some CXC chemokines (MIG, IP-10) were initially identified on the basis of their specific upregulation by interferon-γ (IFN-γ) (45). Other chemokines, especially those that play a role in normal leukocyte trafficking, appear to be constitutively expressed (SDF-1, B cell attracting chemokine-1, thymus-expressed chemokine, secondary lymphoid tissue chemokine, EB1I ligand chemokine, hemofiltrate CC chemokine-1, liver and activation-regulated chemokine) (28).

Some of the best-studied proinflammatory chemokines (e.g., IL-8, RANTES, monocyte chemoattractant protein-1 [MCP-1]) are controlled at the transcriptional level by the transcription factors nuclear factor-κB (NF-κB), CAAT enhancer binding protein, and activator protein-1 (21,46,47). Their activation requires a complex cascade of steps including phosphorylation by multiple kinases and phosphatases, degradation of transcriptional inhibitors, translocation of transcription factors from cytoplasm to nucleus, etc. (4). These signaling pathways can be different for each stimulus and transcription factor and are further complicated by “cross-talk” between the various path-
Table 2. DARC, CXC, CX3C, and C chemokine receptors, their tissue distribution, and ligands

<table>
<thead>
<tr>
<th>Chemokine</th>
<th>IL-8</th>
<th>IL-8</th>
<th>I-TAC</th>
<th>SDF-1α</th>
<th>BCA-1</th>
<th>Lymphotactin</th>
<th>Fractalkine</th>
<th>CC, CXC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemokine receptor</td>
<td>GCP-2</td>
<td>GRO-α</td>
<td>IP-10</td>
<td>SDF-1β (const. expr.)</td>
<td>(const. expr.)</td>
<td>chemokines (RANTES, MCP-1, GRO-α, IL-8, NAP-2, PF4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptor expressing cell type</td>
<td>Neutrophil</td>
<td>Neutrophil</td>
<td>B cell</td>
<td>T cell (naive)</td>
<td>T cell</td>
<td>T cell</td>
<td>T cell</td>
<td>Natural killer cell</td>
</tr>
<tr>
<td></td>
<td>(immature)</td>
<td></td>
<td></td>
<td>Dendritic cell (mature)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

DARC, Duffy antigen receptor for chemokines; IL, interleukin; GCP, granulocyte chemotactic protein; GRO, growth-related oncogene; ENA-78, epithelial cell-derived neutrophil attractant 78; NAP-2, neutrophil-activating peptide-2; LIX, lipopolysaccharide-induced CXC chemokine; I-TAC, interferon-inducible T cell alpha chemoattractant; IP-10, interferon-inducible protein 10; MIG, monokine induced by interferon-γ; SDF, stromal cell-derived factor; const. expr., constitutive expression; BCA-1, B cell-attracting chemokine 1; PF4, platelet factor 4. Other abbreviations as in Table 1.

Selective Expression of Chemokine Receptors
Contributes to Cell Specificity of Chemokine Action

The biologic actions of chemokines (Table 3) are mediated through a family of G protein-coupled receptors with seven transmembrane domains (4,25,55,56). The nomenclature used to describe these receptors is based on the class of chemokine ligands that interact with the receptor (i.e., C, CC, CXC, and CX3C receptors) (27). Many chemokines bind to several different receptors (Tables 1 and 2) (57). The differential expression of the receptors by distinct leukocyte subsets is an important component of the specificity of chemokine action (27,58). The complexity and apparent redundancy of the system is thought to provide a high degree of effectiveness and flexibility in vivo (57).

Binding of a chemokine to its receptor activates a signal transduction cascade leading to activation of phospholipase Cα1 and α2, and the production of inositol (1,4,5)-trisphosphate and diacylglycerol (2,4). In addition, a rapid and transient increase in intracellular calcium, and the activation of protein kinase C are observed (59–61). A variety of kinases may be involved in signal transduction, including serine/threonine kinases (e.g., members of the mitogen-activated protein kinase cascade) as well as tyrosine protein kinases (59). The various stimulatory and inhibitory pathways involved in these activation cascades are providing insight into the design of potential pharmacologic agents.

The Duffy Antigen Receptor for Chemokines

The Duffy antigen receptor for chemokines (DARC) is a “promiscuous” receptor-like structure that binds the CXC family proteins IL-8 (62,63), GRO (63), PF4 (64), neutrophil activating peptide-2, as well as the CC chemokines MCP-1 (62,63) and RANTES (63). DARC, first identified as the Duffy blood group antigen, is expressed on erythrocytes and endo-
thelial cells of postcapillary venules of the kidney (64–66). DARC mediates Plasmodium vivax entry into red blood cells, and DARC-“negative” individuals (generally of central African lineage) are resistant to this form of malaria but still express DARC on their endothelial cells (67). At present, a function for the erythroid-expressed form of DARC is not known. Chemokine-induced signal transduction through DARC has not been demonstrated, and DARC is not coupled to G proteins. One hypothesis is that DARC may act as a scavenger that helps to clear chemokines from the circulation (62). DARC protein expressed on postcapillary venules may act as a presentation-like structure for chemokines on these surfaces, and hypothetically could contribute to induced leukocyte adhesion and transmigration at these sites.

Chemokines, Chemokine Receptors, and Th1, Th2 Immune Responses

The immune system mounts distinct and selective immune responses to different types of infection or antigenic challenge. These responses have been termed Th1-like and Th2-like after the two classes of T helper cells (Th) involved (68–70). Th1 and Th2 responses appear to represent the extremes of a spectrum of immune responses. Th1 responses are stimulated by pathogens that invade and inhabit cells and result in activation of cytotoxic T lymphocytes and delayed-type hypersensitivity. The Th1 subtype produces cytokines that stimulate strong cellular immune responses (IFN-γ, IL-2, leukotriene A, granulocyte macrophage colony-stimulating factor). The Th2 subtypes produce cytokines that evoke strong antibody responses (IL-3, -4, -5, -6, -10, and -13). In addition, Th2 cytokines can inhibit the inflammatory reactions induced by Th1 cytokines. A third subtype called Th0 secretes cytokines of both types and is believed to give rise to the “polarized” Th1 and Th2 lineages. The recently characterized Th3/T-regulatory-1 T cell subset is thought to downregulate antigen-presenting cells, possibly via transforming growth factor-β (TGF-β) (71).

Table 4. CXC chemokines produced by renal cells

<table>
<thead>
<tr>
<th></th>
<th>IL-8</th>
<th>GRO</th>
<th>CINC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mesangial cells</strong></td>
<td>IL-1β (102, 221, 222)</td>
<td>IL-1β (127)</td>
<td>IL-1β (224)</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone (222)</td>
<td>Dexamethasone (127)</td>
<td>Dexamethasone (224)</td>
</tr>
<tr>
<td></td>
<td>PDTC (218)</td>
<td>IL-1β (225)</td>
<td>LPS (225)</td>
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<tr>
<td></td>
<td>Interferon-γ (225)</td>
<td></td>
<td>Genistin (225)</td>
</tr>
<tr>
<td><strong>Epithelial cells</strong></td>
<td>IL-1α (226)</td>
<td>IFN-γ (226)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-1β (209)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-17 (227)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>TGF-β1 (129)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>TNF-α (209, 226)</td>
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<td></td>
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<tr>
<td></td>
<td>LPS (209)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Porin (228)</td>
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<tr>
<td></td>
<td>CD40 ligand (229)</td>
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<tr>
<td><strong>Endothelial cells</strong></td>
<td>IL-1β (230)</td>
<td></td>
<td>IL-1β (225)</td>
</tr>
<tr>
<td></td>
<td>TNF-α (230)</td>
<td></td>
<td>Genistin (225)</td>
</tr>
<tr>
<td><strong>IP-10</strong></td>
<td>IL-1β (112)</td>
<td>IFN-γ (112, 231)</td>
<td>IL-1β (225)</td>
</tr>
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<td></td>
<td>PDTC (218)</td>
<td>TNF-α (112, 231)</td>
<td>LPS (225)</td>
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<tr>
<td><strong>ENA-78</strong></td>
<td>IL-1β (225)</td>
<td>Genistin (225)</td>
<td></td>
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<td></td>
<td>TNF-α (225)</td>
<td></td>
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</tr>
<tr>
<td><strong>MIP-2</strong></td>
<td>IL-1β (207)</td>
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<td></td>
</tr>
<tr>
<td><strong>Mesangial cells</strong></td>
<td>TNF-α (232)</td>
<td></td>
<td>IL-1β (225)</td>
</tr>
<tr>
<td><strong>Epithelial cells</strong></td>
<td>TNF-α (232)</td>
<td></td>
<td>IL-1β (225)</td>
</tr>
<tr>
<td><strong>Endothelial cells</strong></td>
<td>TNF-α (230)</td>
<td></td>
<td>IL-1β (225)</td>
</tr>
<tr>
<td><strong>Interstitial cells</strong></td>
<td>TNF-α (230)</td>
<td></td>
<td>IL-1β (225)</td>
</tr>
</tbody>
</table>

*+,* upregulation; *−*, inhibition; CINC, cytokine-induced neutrophil chemoattractant; TNF-α tumor necrosis factor-α; PMA, phorbol myristate acetate; Fe-R, Fc receptor; bFGF, basic fibroblast growth factor; PDTC, pyrrolidine dithiocarbamate; LPS, lipopolysaccharide; TGF-β1, transforming growth factor-β1; IFN-γ, interferon-γ. Other abbreviations as in Tables 1 and 2.
### Table 5. CC chemokines produced by renal cells

<table>
<thead>
<tr>
<th></th>
<th>MCP-1</th>
<th>RANTES</th>
<th>MIP-1α</th>
</tr>
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<tbody>
<tr>
<td><strong>Mesangial cells</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IFN-α (224)</td>
<td>Dexamethasone (224,236)</td>
<td>IL-1β (224,236,245)</td>
<td>Dexamethasone (247)</td>
</tr>
<tr>
<td>IFN-γ (53,112,234)</td>
<td>IL-1ra (221)</td>
<td>IFN-α (224)</td>
<td>IFN-γ (114)</td>
</tr>
<tr>
<td>IL-1α (221)</td>
<td>TGF-β1 (240)</td>
<td>IFN-γ (112)</td>
<td>PDTC (247)</td>
</tr>
<tr>
<td>IL-1β (51,102,112,115,224,234–236)</td>
<td>PGE2 (53)</td>
<td>TNF-α (247)</td>
<td>DMTU (247)</td>
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<tr>
<td>IL-6 (236)</td>
<td>DMTU (241)</td>
<td>TNF-α (114,236,245–247)</td>
<td>Hydroxymethoxyacetophenone</td>
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<tr>
<td>TNF-α (53, 102, 106, 114, 221, 234, 236, 237)</td>
<td>TMTU (106)</td>
<td>TFN-β (245)</td>
<td>(247)</td>
</tr>
<tr>
<td>PMA (112,237)</td>
<td>Genistein (52,237)</td>
<td>bFGF (114)</td>
<td>LPS (245)</td>
</tr>
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<td>Phorbol esters (52)</td>
<td>Calphostin C (239)</td>
<td>IgG-IC (247)</td>
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<td>Diacylglycerol (52)</td>
<td>Herbimycin (51, 52, 237)</td>
<td>ROS (247)</td>
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<tr>
<td>bFGF (114)</td>
<td>Tyrophostin (52,237)</td>
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<td>C5a (238)</td>
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<td>Crosslinking of Fc-R (223)</td>
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<td>FCS (112)</td>
<td>dBCAMP (237)</td>
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<td>High glucose (239)</td>
<td>Forskolin (53)</td>
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<td>IgG-IC (53, 105, 106, 191)</td>
<td>PDTC (218)</td>
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<tr>
<td>IgA (218)</td>
<td>NF-κB antisense oligo (51)</td>
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<td>LIF (236)</td>
<td>Antioxidants (54)</td>
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<td>MMSP (241)</td>
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<td>Lovastatin (172)</td>
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<td>NADPH (106)</td>
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<td>ox-LDL (242)</td>
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<td>PDGF-AB (115)</td>
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<td>PDGF-BB (115)</td>
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<td>Serotonin (115)</td>
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<tr>
<td>Shiga toxin (243)</td>
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<td>Superoxide (106, 241)</td>
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<td>Thrombin (244)</td>
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<td>TRAP1–7 (244)</td>
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<td>Cryoglobulins (191)</td>
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<tr>
<td><strong>Epithelial cells</strong></td>
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<td>Dexamethasone (120)</td>
<td>IFN-γ (111)</td>
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<td>TGF-β1 (129)</td>
<td>IL-1α (111,248)</td>
<td>PDTC (119)</td>
</tr>
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<td>IL-17 (227)</td>
<td>Cycloheximide (108, 116, 118)</td>
<td>IL-4 (117)</td>
<td>Cycloheximide (111)</td>
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<td></td>
<td></td>
<td></td>
<td>Sodium salicylate (119)</td>
</tr>
</tbody>
</table>
or Th2-type immune response, because specific chemokine receptor expression has been shown to characterize these T helper cell subtypes (72). Th1 cells appear to preferentially express the chemokine receptors CXCR3 and CCR5, while Th2 cells display CCR4, CCR8, and some CCR3 (28, 72, 73). The chemokine receptors expressed by different populations of T cells may thus dictate to a significant degree the tissue infiltration of Th1 and Th2 cells and the direction of the eventual immune response.

This is an important issue in the interpretation of results obtained from animal models. For example, different inbred mouse strains often demonstrate a more pronounced Th1- or Th2-like response. After an immunologic insult, C57BL/6 mice show a more Th1-like bias compared with Balb/C mice, which show a more Th2-like response (74, 75). This can influence the composition of the cellular infiltrate and subsequently the course of the renal disease model (75).

### Chemokines Control Important Aspects of Acute and Chronic Inflammation

Inflammation is a process involving changes in hemodynamics, vascular reaction of endothelial cells, leukocyte adhesion, activation, and migration (76). The nature of the inflammatory response is dictated by the pathogenic insult. The process of leukocyte trafficking from the peripheral circulation into tissue spaces involves a series of interactions between soluble mediators and surface molecules expressed by the endothelium and leukocyte, as well as subsequent interactions with the extracellular matrix (77). Chemokines mediate events at multiple stages in this process (78, 79). The early events in this process entail the rolling of leukocytes along the microvascular surface through transient interactions between vascular addressins and selectins (80). The addressin/selectin-dependent cell-cell interaction is essential in leukocyte homing and promotes transient surface contact between the rolling leukocyte and the endothelial surface. The endothelium provides a selective interface between the peripheral circulation and extravascular space and ultimately acts as a discriminator of leukocyte infiltration.

During inflammation, the endothelium upregulates chemokine presentation structures (such as specific glucosaminoglycans), selectin ligands (addressins), selectins, and the Ig partners of leukocyte-expressed integrins (11, 81). Thus, inflamed microvascular endothelium increases its capacity to bind chemokines and upregulates the expression of molecules required for the efficient rolling and firm adhesion of leukocytes.

Early in inflammation, as the microvascular endothelium becomes activated, chemokines generated by endothelial cells, subendothelial tissue, or released after platelet activation bind to the “activated” endothelial surface (78, 82). Thus situated chemokines act as directional signals for leukocytes as they roll across the endothelium. A notable exception appears to be fractalkine, which is a membrane-bound chemokine that also enables direct leukocyte adhesion via its receptor CX3CR1 (33). Chemokines can trigger activation of leukocyte-expressed integrins, resulting in the arrest and firm adhesion of leukocytes to the activated endothelial surface. Important adhesion molecule pairs in this process include the selectins (E,
L, and P), the Ig-like molecules intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, and the β2 and β1 integrins (e.g., leukocyte function-associated antigen-1 and very late antigen-4) (80). (Note: The nomenclature of these factors is often confusing as it reflects the manner in which the proteins were first identified rather than their structural characteristics.)

After firm adhesion, leukocytes undergo spreading, diapedesis, extravasation, and migration into interstitial spaces. Although some chemokines are important for the control of leukocyte arrest, other chemokines appear to influence the subsequent events associated with leukocyte emigration. Leukocyte emigration in vivo occurs in a complex background of chemotactic signals where several receptors may be activated simultaneously or successively. Thus, the migrating leukocyte must distinguish among the various chemotactic signals within the three-dimensional environment of the tissue to move both up and down gradients to eventually reach the site of inflammation (21,83).

**Chemokines May Play a Role in the Resolution or Progression of Inflammatory Processes**

As leukocytes reach the site of inflammation and undergo activation, they can produce additional proinflammatory factors resulting in propagation and amplification of the inflammatory response. The accumulation of specific leukocytes at the site of injury normally results in removal of the initiating insult (e.g., phagocytosis of bacteria, immune complexes, apoptotic cells, cell debris, etc.) and tissue repair. Inactivation and removal of inflammatory effector cells once their goal has been accomplished are important to prevent chronic inflammation and progressive tissue destruction. Factors that govern the termination of the inflammatory response are thought to involve the downregulation of chemokine synthesis by local factors (e.g., prostaglandins, TGF-β) or a specific combination of inflammatory mediators leading to local apoptosis of the leukocytes involved (84).

During renal diseases, the infiltration of monocytes/macrophages and T cells into kidneys is thought to play a central role in progressive interstitial fibrosis and the progression of chronic renal failure (85). During this process, a cross-talk between cytokines, vasoactive substances, chemokines, and their respective target cells takes place. This interaction contributes to the outcome, i.e., healing or progression of the renal disorder. Chemokines appear to be integral players in this complex and dynamic process.

**Transgenic and Knockout Mice: Models of Chemokine and Chemokine Receptor Action**

The targeted disruption of chemokine and chemokine receptor genes as well as the expression of chemokines as transgenes has identified important roles for these molecules in specific aspects of the inflammatory response.

The ability of chemokines to direct leukocyte infiltration depends on a low regional expression level. In studies with MCP-1 transgenic mice, the systemic overexpression of a mouse mammary tumor virus long terminal repeat-MCP-1 transgene led to a general paralysis of the response to this chemokine (86). Only the local production as seen in insulin promoter-MCP-1 transgenic mice was shown to be effective in selectively recruiting monocytes (86). Besides persistent MCP-1 expression and insulitis, the macrophage infiltrate did not result in progressive tissue destruction. Therefore, additional costimulatory signals are required for the activation of macrophages.

Knockout mice with a targeted disruption for either MCP-1 or the MCP-1 receptor CCR2 gene show a reduced capacity to recruit monocytes and have suggested a fundamental role for these molecules in the generation of atherosclerotic lesions (87–89). In addition, CCR2(−/−) mice show significant defects in delayed-type hypersensitivity responses and in the production of Th1-type cytokines (89). Mice deficient for CCR5 show an increased humoral response to T cell-dependent antigenic challenge, suggesting a novel role for CCR5 in downmodulating T cell-dependent immune responses (90). Targeted disruption of the eotaxin gene demonstrated that eotaxin enhances the magnitude of early but not late eosinophil recruitment after antigen challenge (91). CXCR4 is broadly expressed by cells of the immune and central nervous system and mediates the migration of resting leukocytes and hematopoietic progenitors in response to its ligand SDF-1 (92). Essentially identical lethal defects were seen in mice deficient for either CXCR4 or SDF-1 (93–95). These include severely reduced B lymphopoiesis, reduced myelopoiesis in bone marrow, defective formation of the large vessels supplying the gastrointestinal tract, as well as cardiac defects and abnormal cerebellar development (93–95). In normal mice, CXCR5 is expressed on mature B cells and a subpopulation of T helper cells. CXCR5 knockout mice lack inguinal lymph nodes and possessed little or no normal Peyer’s patches. Lymphocyte migration into splenic follicles of these mice were significantly impaired (96). Information obtained with chemokine and chemokine receptor knockout in models of renal diseases is discussed in later sections.

**Chemokines, Chemokine Receptors, and Viral Biology**

Given the important roles of chemokines in diverse immune processes, it is not surprising that viruses have exploited chemokine biology through the course of evolution. This phenomenon is emphasized by the large number of chemokine receptors, chemokines, and general inhibitors or modulators of chemokine action that are encoded by different viral genomes (21,60,97–101). One of the most dramatic developments in the viral/chemokine connection is the observation that select chemokine receptors act as coreceptors for HIV entry into target cells (16–20). The chemokine ligands for these receptors can suppress infection by some strains of HIV-1 and may act as important moderators of HIV replication in vivo (21). CCR5 represents the major coreceptor for macrophage-tropic strains of HIV-1, whereas CXCR4 acts as a coreceptor for T cell-tropic strains. CCR5 appears to play a unique role in viral pathogenesis, as individuals homozygous for a nonfunctional allele of CCR5 (CCR5Δ32) are highly protected from HIV-1...
infection (21). These results have opened new avenues of research into the pathogenesis of HIV and have led to the development of new strategies to block viral fusion.

Chemokines, Chemokine Receptors, and the Kidney

All Types of Renal Cells Can Express Chemokines upon Stimulation

Nearly 10 years ago, we and others described the induced expression of chemokines by mesangial cells (Tables 4 and 5). An expanding body of data now strongly suggests that chemokines contribute to inflammatory glomerular as well as tubulointerstitial diseases (2,53,54,102–110). All types of renal cells (i.e., endothelial, mesangial, tubular epithelial, interstitial cells, and podocytes) are able to produce chemokines in a cell- and stimulus-specific manner. Details of the in vitro regulation of various chemokines can be found in Tables 4 and 5 and in several recent reviews (2,3). In general, proinflammatory stimuli such as TNF-α, IL-1β, IFN-γ, and lipopolysaccharide (LPS), especially when used in combination, rapidly (within a few hours) induce MCP-1, IL-8, and IP-10 (53,104,111–113). The induction of RANTES occurs in a more delayed manner (12 to 48 h). IgG and IgA immune complexes can also induce upregulation of MCP-1, RANTES, IL-8, and IP-10 expression by mesangial cells (Tables 4 and 5). Reactive oxygen species are able to upregulate chemokine expression and may represent a common mechanism of injury-induced chemokine generation (106).

Growth factors such as platelet-derived growth factor and basic fibroblast growth factor can induce MCP-1 and RANTES expression by mesangial cells (114,115). This expression may be related to the macrophage influx seen during proliferative responses related to tissue repair, regeneration, and remodeling (114). MCP-1 expression by proximal tubular cells is seen after exposure to hyaluronan, a glucosaminoglycan degradation product of extracellular matrix that accumulates in the interstitium during kidney diseases (116). The interaction of CD40 with its ligand (CD154), together with IL-4 and IL-13, results in MCP-1, RANTES, and IL-8 generation by cultured proximal tubular cells (117), observations that may be relevant for tubulointerstitial inflammatory cell infiltrates in transplant rejection and other forms of interstitial diseases.

The generation of chemokines by proximal tubular cells can be induced by albumin, which is thought to mimic the effects of proteinuria and may be related to the tubulointerstitial damage seen in glomerular disease (118–120). Wang et al. described an increase of MCP-1 mRNA expression in proximal tubular cells in response to delipidated bovine serum albumin (BSA), holotransferrin, and apotransferrin, which was mediated by NF-κB (118,120). Lysine, an inhibitor of protein uptake, reduced the MCP-1 expression (118). Zoja et al. found a dose-dependent increase of RANTES expression by proximal tubular epithelial cells exposed to BSA (119). However, this effect required very high albumin concentrations (i.e., 10 to 30 mg/ml), probably not achieved in proximal tubular fluids. Although the significance of these in vitro effects of albumin on tubular epithelial cell chemokine production for the nephrotic syndrome remains hypothetical, it does suggest that the prolonged proteinuria and proximal tubular epithelial overload of proteins (“nephrosis”) may lead to tubular cell activation and chemokine induction. Furthermore, the role of lipids in the nephrotic syndrome and of lipid droplets in proximal tubules deserves attention in this context, as lipid oxidation may occur and oxidized lipids can stimulate chemokine production (121).

Vasoactive Agents Can Stimulate Chemokine Expression

Vasoactive agents and chemokines may directly interact. Wolf et al. found that angiotensin II via the AT1 receptor could stimulate RANTES production by glomerular endothelial cells (122). Moreover, the infusion of angiotensin II into rats led to an influx of macrophages into the glomerulus, which was attenuated by the administration of an AT2 receptor antagonist (122). The differential regulation of RANTES and MCP-1 could explain the apparent divergent reports from other groups implicating the AT1 rather than the AT2 receptor in “chemokine” stimulation (122–125).

The Production of Proinflammatory Chemokines Is Transitory

Some chemokines appear to be constitutively expressed (i.e., those that control normal leukocyte trafficking). The proinflammatory chemokines appear to be kept under tight regulatory control and are expressed only in response to specific stimuli (Tables 4 and 5). The basal expression of chemokines often seen in cultured renal cells may represent a tissue-culture artifact, as serum and endotoxin (a common contaminant of growth media) are potent stimuli for chemokine induction (112).

It is thought that the expression of proinflammatory chemokines normally follows a self-limited course. Interestingly, different time frames for the expression of various chemokines in response to the same stimulus have been reported (112,126). In general, chemokines that are rapidly induced (e.g., MCP-1) return to “baseline” within a day. Stimulation with a combination of cytokines (e.g., TNF-α, IL-1β, and IFN-γ) often results in a more prolonged expression (114,115). RANTES expression can be slower with an increase seen after 12 to 24 h, but the levels may remain elevated for days (114). The different time courses suggest different signal transduction events used for the individual chemokines.

Inhibition of Chemokine Expression

The expression of inflammatory chemokine genes can be inhibited by glucocorticoids (127,128), cytokines such as TGF-β (129), and prostaglandins (e.g., PGE2) (53). The inhibitory effect of prostaglandin appears to involve modulation of the second messenger cAMP (51–53,130). Because TGF-β and prostaglandins are generated at sites of tissue injury, the net effect on local chemokine generation may depend on the balance between proinflammatory and anti-inflammatory agents. The dual character of TGF-β is again illustrated by the report that this cytokine can inhibit MCP-1 expression by proximal...
<table>
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<td>( \uparrow ) MCP-1 (125,138,139,141,142)\  ( \uparrow ) RANTES (138,139,141)\  ( \uparrow ) IP-10 (141,142)\  ( \Leftrightarrow ) MIP-1(\alpha) (139,142)\  ( \uparrow ) CCR1 (142)\  ( \uparrow ) CCR2 (142)\  ( \uparrow ) CCR5 (142)</td>
<td>MCP-1 antibody (139)\  Met-RANTES (139)\  MCP-1 knockout (140)\  CCR1 knockout (141)\  AT(\alpha) knockout (125)</td>
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<td>Nephrotoxic serum GN in rats</td>
<td>( \uparrow ) MCP-1 (143,144,146–152,156,157,160,250)\  ( \uparrow ) RANTES (145,150,151)\  ( \uparrow ) MIP-1(\alpha) (143,148,149,151)\  ( \uparrow ) MIP-1(\beta) (143,148,150,151)\  ( \uparrow ) MCP-3 (151)\  ( \uparrow ) CINC (148)\  ( \uparrow ) MIP-2 (148,149,250)\  ( \uparrow ) TCA3 (151)\  ( \uparrow ) PF4 (149)\  ( \uparrow ) IP-10 (149)\  ( \uparrow ) Lymphotactin (155)\  ( \uparrow ) Fractalkine (154)\  ( \uparrow ) CX3CR1 (154)\  ( \uparrow ) CCR2 (154)\  ( \uparrow ) CCR5 (154)</td>
<td>MCP-1 antibody (146,156,157)\  MIP-1 antibody (148)\  Lymphotactin antibody (43)\  MIP-2 antibody (153)\  CINC antibody (148)\  CCR5 antibody (43) (154)\  vMIP II (150)\  PDTC (147)\  CD8+ T depletion (143)\  Dexamethasone (149)\  Irradiation (144,148)\  PMN depletion (148)\  Complement depletion (148)\  COX inhibitors (145)\  LPS (250)\  IL-6 receptor antagonist (250)\  IL-1 receptor antagonist (250)\  Soluble IL-1 receptor (250)\  Soluble TNF receptor (250)</td>
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<td>Anti-Thy-1 nephritis in rats</td>
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<td>MCP-1 antibody (160)\  AOP-RANTES (162)\  AT1 receptor antagonists (123)\  Complement depletion (107)\  PGE infusion (161)\  COX inhibitors (145)</td>
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<td>Immune complex GN in rats</td>
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<td>( \Leftrightarrow ) CINC (169)</td>
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<td>Adriamycin nephrosis in rats</td>
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<td>( \uparrow ) MCP-1 (178,179)</td>
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<td>5/6 nephrectomized rats</td>
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<td>AT II injection in rats</td>
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<td>Renal ischemia in rats</td>
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<td>Tubulointerstitial nephritis in rats</td>
<td>( \Leftrightarrow ) MCP-1 (173,174)</td>
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\( a \) GN, glomerulonephritis; vMIP, macrophage inflammatory protein of viral origin; PMN, polymorphonuclear neutrophil; COX, cyclo-oxygenase; NZB/W, New Zealand black/white mice; AOP-RANTES, AOP-RANTES, a partially “blocking” RANTES derivative; HMG-CoA, hydroxymethylglutaryl CoA; ACE, angiotensin-converting enzyme; BSA, bovine serum albumin; NO, nitric oxide; \( \alpha \)-MSH, \( \alpha \)-melanocyte-stimulating hormone. Other abbreviations as in Tables 1, 2, 4, and 5.
tubular cells and at the same time enhanced synthesis of the neutrophil-specific chemokine IL-8 (129).

**Renal Cells May Also be Targets for Chemokines**

Renal cells also express chemokine receptors. Thymus-derived chemotactic agent-4 (TCA4), a mouse chemokine, can bind to mouse mesangial cells and mediate chemotaxis and proliferation (131). The TCA4-specific receptor expressed by mesangial cells has not yet been identified (131,132). In a human mesangial cell line, stimulation with IFN-γ led to induction of functional CCR1 expression (112). The activated mesangial cells were found to migrate in response to RANTES (112). In these experiments, no expression of CCR3, CCR4, CCR5, and CCR8 could be detected (112).

Romagnani et al. demonstrated the expression of CXCR3 both in cultured human mesangial cells and renal biopsies (35). The mesangial cells were shown to flux Ca²⁺, migrate in response to IP-10, and proliferate in response to MIG (35). The overall function of chemokine receptor expression by intrinsic renal cells remains to be defined, but could play a role in mesangial cell migration-proliferation during mesangial repair and could even function as local immune modulator. It is hoped that these questions can be addressed with receptor knockout models.

**Expression of Chemokines and Chemokine Receptors in Experimental Models of Renal Diseases**

Animal models have been helpful in identifying potential roles for chemokines in the initiation and propagation of renal disease. The results of these experiments are sometimes difficult to interpret due to differences in the genetic backgrounds of the animals used. The genetic background can profoundly influence the susceptibility, type of inflammatory infiltrate, and the eventual course of renal disease (133). The importance of adequate backcrossing cannot be overstated because a significant part of experimental findings assigned to the knockout phenotype are often explainable by the different genetic backgrounds used (134,135). The genetic background may also be important because of polymorphisms in the chemokine gene that may influence the expression of the chemokine (136,137).

**Nephrotoxic Serum Nephritis**

Many groups have used the classic model of nephrotoxic serum nephritis (NTS-GN) induced by the injection of antibodies against glomerular basement membranes for the study of chemokine expression and action (138–141). Mice with accelerated NTS-GN show increased expression of RANTES (138,139,141,142), MCP-1 (138–142), IP-10 (141,142), and MCP-3 (140) mRNA, whereas no change was seen in macrophage inflammatory protein-1α (MIP-1α) expression (139).

The biologic action of different chemokines has been studied through the use of neutralizing antibodies and specific chemokine antagonists. Lloyd et al. blocked RANTES-associated events in NTS-GN in CD1 mice (an outbred mouse strain) by the use of the antagonist Met-RANTES. Animals treated with Met-RANTES showed reduced proteinuria, reduced T cell infiltration, and mononuclear cell infiltration. However, glomerular crescent formation was not significantly reduced. Treatment with a neutralizing MCP-1 antibody led to a reduction in proteinuria, infiltrating macrophages, and a striking decrease in crescent formation and collagen production, suggesting that MCP-1, and not RANTES, is involved in crescent formation and early interstitial fibrosis (139). This issue was also examined in MCP-1 knockout mice. Tesch et al. induced NTS-GN in F1 generation littermates of MCP-1 knockout 129SV/J and wild-type C57BL/6 (i.e., a mixed genetic background). The animals developed a glomerular injury consisting of hyalinosis, capillary dilation and thickening, focal segmental sclerosis, and crescents (140). Glomerular hypertrophy or hypercellularity was not present (140). The lack of glomerular chemokine expression in this model is consistent with the lack of glomerular leukocyte infiltration, while the predominant tubular MCP-1 expression was associated with tubulointerstitial cell infiltrate (140). In the MCP-1-deficient F1 generation (129SV/J/XC57BL/6), a reduced macrophage infiltrate adjacent to tubules was seen. The authors suggest that tubular epithelial cells represent the primary source of MCP-1 protein in this model. MCP-1 so positioned could act to recruit peritubular macrophages that could then promote tubular interstitial injury (140). Hisada et al. used the NTS-GN model in mice to evaluate the role of angiotensin II type 1a receptor (AT₁a) by use of AT₁a receptor-deficient mice (AT₁a⁻/⁻) (125). AT₁a⁻/- mice were backcrossed with C57BL/6 for five generations (representing adequate backcrossing) (125). In these animals, a peak of MCP-1 mRNA expression was seen after 6 h. An additional increase in MCP-1 after 14 d, which was stronger in the AT₁a⁺/+ mice than in the AT₁a⁻/- mice, was also seen (125). The higher expression of MCP-1 in wild-type mice was associated with a more severe disease course (125). The authors propose that angiotensin II via the AT₁a receptor mediates the late MCP-1 expression and may play a role in progression of immune-mediated renal injury.

NTS-GN results in induction of CCR1, CCR2, and CCR5 that is associated with the expression of corresponding chemokine mRNA for MCP-1, RANTES in CD1 mice (142). Another recent abstract indicates that mice deficient in CCR1 show more severe renal impairment and proteinuria than the wild-type mice, suggesting a novel immune modulatory role for CCR1 (141).

In Wistar-Kyoto rats, the injection of NTS-GN antibodies leads to crescentic glomerulonephritis in which CD8⁺ T cells are thought to play a major role (143). In this model, an upregulation of MCP-1 (143–152), MIP-1α (143,148,149,151), MIP-1β (143,148,151), RANTES (145,150,151), MCP-3 (151), CINC (148,149), MIP-2 (148,149,153), PF4 (149), TCA3 (151), fractalkine (154), lymphotactin (155), and IP-10 mRNA (149) was detected (Table 6).

A correlation between the expression of neutrophil-attracting chemokines and an early neutrophil influx and the later expression of macrophage-attracting chemokines followed by a macrophage influx was described (148,149). The MCP-1 mRNA was localized to intrinsic glomerular cells after 3 h.
After 24 h, the predominant source of MCP-1 was from infiltrating monocytes/macrophages (156). MCP-1 protein (156) was demonstrated in glomeruli (144,150,152,157), vascular endothelial cells (157), and tubular epithelial cells (157). Expression of RANTES (150), MIP-1α (148), MIP-1β (150), and MIP-2 (153) protein was also demonstrated. Recently, the upregulation of fractalkine mRNA, as well as an induction of the fractalkine receptor (CX₃CR1) mRNA, was described in NTS-GN. Fractalkine protein was localized to glomerular endothelium (154). Antibodies against CX₃CR1 markedly attenuated the crescentic nephritis (154). A neutralizing antibody against MCP-1 decreased macrophage infiltration of the glomeruli and reduced proteinuria (146,156,157). This beneficial effect was shown to persist to day 56 after induction of the disease, with lower proteinuria and blood urea nitrogen seen compared with untreated rats (157).

Neutralizing antibodies against other chemokines have also shown partial “positive” effects. Blocking MIP-1α and MIP-1β resulted in a 60% reduction in proteinuria after 24 h, but the animals did not show a corresponding reduction in leukocyte influx (148). Blocking CINC (the rat homologue of GRO) also resulted in decreased proteinuria and reduced early glomerular cell infiltration by polymorphonuclear neutrophils (148). The combination of anti-CINC and anti-MIP treatment did not show an additive beneficial effect (148). A single injection of an anti-MIP-2 (CX₃C chemokine) antibody resulted in a reduced neutrophil influx and a significant decrease in proteinuria (153).

A natural and broadly acting chemokine receptor antagonist of viral origin, vMIP-II, can block both CC and CXC receptors (99,150). Treatment with vMIP-II decreased infiltration with CD8+ T cells, macrophages and reduced proteinuria to one-third of the control group (150).

Agents that modulate expression of chemokines have beneficial effects on the outcome of the disease. Treatment with dexamethasone can limit glomerular MCP-1 expression, as well as polymorphonuclear neutrophil and monocyte/macrophage infiltration (149). MCP-1 mRNA expression is controlled to a significant extent by the transcription factor NF-κB (147). Treatment of rats with the NF-κB inhibitor pyrrolidine dithiocarbamate led to a decrease in MCP-1 expression, reduced proteinuria, and preserved renal function (147). Treatment of animals with a nonselective cyclo-oxygenase (COX) inhibitor (indomethacin) or selective COX-2 inhibitors (meloxicam, SC 58125) resulted in an upregulation of MCP-1 and RANTES (145). The nonselective COX inhibitor led to a stronger induction of chemokines compared with the group treated with the COX-2 inhibitor. COX products (i.e., prostaglandins) may serve as endogenous chemokine repressors (Table 6) (53,145).

In summary, the animal models of nephrotic serum glomerulonephritis suggest a role for chemokines in the initiation and propagation of this disease. The blockade of select chemokines, or their receptors, can lead to a partial improvement of the disease. Surprisingly, recent abstracts indicate that interference with lymphotactin (43), or the elimination of CCR1 (141), may worsen the disease, suggesting “anti-inflammatory” functions for some chemokines.

**Anti-Thy-1 Nephritis**

In rats the injection of anti-thymocyte antiserum can lead to complement-dependent mesangiolysis followed by monocyte influx and a mesangial proliferative glomerulonephritis (107,158). These lesions heal spontaneously over several weeks. The type of renal disease is dependent on the rat strain used. Wistar and Lewis rats develop a transient influx of macrophages (159). By contrast, F344 rats do not show an influx of macrophages, but have a pronounced proliferative glomerulopathy (159).

MCP-1 (107,123,145,160–162) and RANTES (145,162) are upregulated in this model, and MCP-1 protein localizes to glomeruli (107,159). An important role for MCP-1 in this disease process was suggested in blocking experiments using MCP-1 neutralizing antibodies, which led to a decreased infiltration of monocytes/macrophages after 24 h (160). Treatment with AOP-RANTES (a partially “blocking” RANTES derivative) as described in a recent abstract showed a 60% decrease of glomerular macrophage infiltration and ameliorated collagen type IV deposition (Table 6) (162).

Prostaglandin E (PGE) infusion (161), depletion of complement (107), and AT₁ antagonists have been shown to significantly decrease MCP-1 expression and glomerular macrophage infiltration (123). As seen in the NTS-GN model, COX inhibitors enhance production of MCP-1 and RANTES (Table 6) (145).

**Models of Systemic Lupus Erythematosus**

New Zealand black mice crossed with New Zealand white (NZB/W) mice serve as a model for lupus nephritis. The F1 hybrid develops circulating antibodies to nucleic acid, renal immune deposits, and proteinuria (163). MCP-1 mRNA expression is upregulated during the initial 6 mo of the disease (163). In situ hybridization localized MCP-1 mRNA to intrinsic glomerular cells, infiltrating mononuclear cells, and tubular epithelium (163). At later stages of the disease, MCP-1 expression in tubuli corresponded to an “adjacent” leukocyte infiltration (163). Mice treated with cyclophosphamide showed better survival, lower proteinuria, as well as less severe glomerular and interstitial changes, and reduced MCP-1 expression (163). Bindarit, a novel immunosuppressive drug, was recently tested in this model at different time points and in combination with low-dose steroids (164). Starting at 2 mo of age, bindarit administration significantly reduced expression of MCP-1, proteinuria, renal impairment, and prolonged animal survival (Table 6) (164).

The MRL-Fas<sup>−/−</sup> mouse serves as an additional model of systemic lupus. These animals show an upregulation of RANTES and develop a nephritis with glomerular, perivascular, and interstitial inflammation (165). Tubular epithelial cells, genetically manipulated to express RANTES protein, were injected into kidneys of MRL-Fas<sup>−/−</sup> mice. This led to an interstitial infiltrate composed mainly of CD4<sup>+</sup> T cells and to a lesser extent CD8<sup>+</sup> T cells and macrophages. By contrast, when colony-stimulating factor-1 (CSF-1) was overexpressed in kid-
neys using the same approach, an equal number of CD4+ and CD8+ T infiltrating cells were seen. The authors postulated complementary roles for RANTES and CSF-1 during autoimmune nephritis in MRL-Fas<sup>lpr</sup> mice.

**Immune Complex Glomerulonephritis**

A model of immune complex glomerulonephritis in the rabbit is induced by the administration of BSA in combination with LPS (166). An influx of neutrophils into glomeruli, fusion of foot processes, and proteinuria by day 8 characterize this model (166). IL-8 expression by affected glomeruli was associated with an increased urinary IL-8 excretion (166). Injection of an anti-IL-8 antibody reduced glomerular neutrophil infiltration, prevented fusion of foot processes, and normalized proteinuria (166).

In Wistar rats, an immune complex nephritis was induced by the injection of ovalbumin over a period of several weeks. This resulted in an increase of MCP-1 mRNA expression in the renal cortex (167). Immunohistochemistry showed intense MCP-1 staining in glomerular capillaries, mesangial areas, proximal tubular epithelium, and interstitial mononuclear infiltrates (167). Treatment with an angiotensin-converting enzyme inhibitor reduced MCP-1 expression (167). These data suggest a possible link between renal immune injury, the angiotensin system, and specific chemokines (Table 6) (122,123,125,167).

A recent abstract described increased MCP-1, RANTES, CCR1, CCR2, and CCR5 mRNA during the early phase of apoferritin-induced immune complex nephritis in Balb/c mice (168). This upregulation of chemokines preceded the glomerular infiltration of leukocytes. Chemokine expression and the leukocyte infiltration disappeared after discontinuation of antigen exposure and the initiation of healing (168).

**Puromycin Aminonucleoside Nephrosis**

In rats the injection of puromycin aminonucleoside leads to proteinuria. A marked mononuclear interstitial infiltrate (predominantly macrophages) occurs together with an increase of IP-10, MCP-1, MCP-3, and TCA3 mRNA expression (169–171). Expression of CINC, MIP-2, and MIP-1α was not detected, and RANTES expression was low and did not change (171). A neutralizing MCP-1 antibody reduced interstitial infiltration by macrophages (169).

The hepatic hydroxymethylglutaryl CoA reductase inhibitor lovastatin suppressed MCP-1 expression by mesangial cells (172) and significantly reduced the interstitial influx of macrophages in the puromycin model (170). These findings are of particular interest, because interstitial infiltrates are a prognostic factor for the progression of human disease (85).

**Tubulointerstitial Nephritis**

Immunization of Brown Norway rats with bovine tubular basement membrane induces a severe tubular interstitial nephritis (173). In this model, MCP-1 mRNA expression precedes an influx of mononuclear cells on day 8 but is no longer detectable by day 10 (173). The early increase in CINC and MIP-2 mRNA expression was associated with neutrophil infiltration. A later expression of MCP-1, MIP-1α, and MIP-1β mRNA correlated with a monocyte influx (174). Treatment with a neutralizing MCP-1 antibody or an MCP-1 receptor antagonist reduced macrophage influx (20 and 60%, respectively) (Table 6) (174).

**Other Renal Disease Models**

Interstitial infiltrate and fibrosis in rats can be induced by daily injections of BSA. In a study by Eddy and Giachelli, Lewis rats received intraperitoneal injections of BSA after nephrectomy of the left kidney (175). MCP-1 mRNA expression was significantly elevated after 2 and 3 wk in whole kidney preparations (175). MCP-1 protein was found in glomeruli and occasionally in tubular cells (175). Because a significant macrophage infiltrate is seen in this model before MCP-1 expression, the infiltrate appears to be due to additional chemoattractants (175).

Injection of diethylaminoethyl dextran leads to proteinuria in Lewis rats but without significant cellular infiltration and without immune complex deposition (176). In this model, strong glomerular localization of RANTES was seen, but apparently was insufficient to cause a cell infiltrate (176).

A model of endotoxemia by LPS injection in Wistar rats leads to glomerular RANTES expression and an influx of macrophages (177). Supplementation with l-arginine, a precursor for nitric oxide (NO) synthesis, reduced the RANTES expression. A nonspecific NO synthase inhibitor resulted in increased RANTES expression and a glomerular infiltrate (177). These studies suggest that the NO pathway may be a counter regulator for LPS-induced RANTES expression and macrophage infiltration.

**Chemokine Expression in Unilateral Ureteral Obstruction**

Interstitial macrophage infiltration is a prominent feature of unilateral ureteral obstruction (178). MCP-1 mRNA is induced by tubular cells in the obstructed kidney (178,179). Angiotensin-converting enzyme inhibition and an AT<sub>1</sub> antagonist decreased MCP-1 expression and reduced the macrophage infiltration and fibrosis (178).

**Chemokine Expression in Renal Ischemia**

As early as 1991, Safirstein et al. described the expression of mRNA of the “early response genes” JE (MCP-1) and KC (GRO-α) during renal ischemia (180). The induction of MCP-1/JE can be prevented by treatment with methylprednisolone (128). Furthermore, renal ischemia causes an upregulation of IL-8 that can be inhibited by treatment with α-melanocyte-stimulating hormone, raising the possibility that α-melanocyte-stimulating hormone may act as a counter-regulatory hormone for chemokine induction (181).

Temporary renal pedicle occlusion with simultaneous right nephrectomy resulted in expression of RANTES and MCP-1 after 2 d (182,183). Treatment with bioflavonoids, agents with potential immunosuppressive and renoprotective properties, preserved histologic integrity and renal function, and prevented MCP-1 and RANTES upregulation (183). Blocking the T cell costimulatory molecule B7 by a soluble CTLA4Ig protein
resulted in nearly complete suppression of RANTES and MCP-1 (182). Thus, non-immune-mediated injuries can be potent inductors of chemokines, which appear to play an integral role in tissue injury and repair and the associated leukocyte influx, regardless of the initiating insult.

Renal Transplantation
Rat models of transplantation have allowed a functional analysis of the role of chemokines in acute and chronic renal rejection (81,184,185). In acute renal allograft rejection in the rat, Nagano et al. found that RANTES mRNA was upregulated by 6 h during the initial transplant rejection phase and again after 3 to 6 d (185). The authors speculated that expression of E-selectin and RANTES within the first few hours after engraftment may occur secondary to ischemic injury and could help trigger subsequent immunologic events (185). In addition, they concluded that macrophages and their products may play a larger role in the process than previously appreciated (185).

The functional role of RANTES and its receptors was recently evaluated in rat models of acute renal allograft rejection using the RANTES receptor antagonist Met-RANTES (81). Treatment with Met-RANTES significantly reduced the vascular and tubular damage associated with acute rejection and suppressed mononuclear infiltration (81). Treatment with Met-RANTES and low-dose cyclosporin A markedly attenuated the damage to vessels, tubules, and the interstitial rejection (81). The potential clinical advantage of chemokine antagonists such as Met-RANTES may lie in their early effects on the suppression of cellular infiltration and subsequent graft damage, which may help lower the inclination toward the development of chronic transplant dysfunction.

Chemokines in Human Kidney Diseases
Much has been learned about the relationships between chemokine expression and the progression of human renal disorders. Obviously, biopsy studies can provide only a snapshot of a given stage in the development of a disease. Recent developments suggest that monitoring chemokines in the urine may provide a more dynamic picture of the inflammatory state of the kidney (186–192).

Chemokines and Chemokine Receptors in Glomerular Diseases
The expression of IL-8 and MCP-1 (108,186,188,193) has been reported in IgA nephropathy. IL-8 mRNA was localized to glomeruli (188), and MCP-1 protein was detected in vascular endothelial cells (188), tubular epithelial cells (108,186,188,193), infiltrating mononuclear cells (186,188), and parietal cells of Bowman’s capsule (186). MCP-1 was not seen in glomeruli that did not show proliferative nephropathy (144,194). In mild disease courses, MCP-1 was rarely expressed, whereas severe cases with interstitial infiltrates showed strong expression of MCP-1, which correlated well with monocyte infiltration and interstitial damage (186). Renal function was found to be significantly worse in patients with detectable MCP-1 expression (194). In IgA nephropathy, CCR1, CCR2a, and CCR2b were detected in biopsy tissue by reverse transcription-PCR (194). A strong glomerular expression of CXCR3, primarily by mesangial cells, was found by immunohistochemistry (35). CXCR3 was also found on infiltrating leukocytes, and endothelial and vascular smooth muscle cells (35). On the other hand, CCR5-positive cells are not present in glomeruli, but were a prominent part of the interstitial infiltrate (195). In summary, in IgA nephropathy MCP-1 is expressed by tubulointerstitial cells, and the chemokine receptors CCR2 and CCR5 are found on inflammatory cells. CXCR3 is expressed on intrinsic glomerular cells and may act as a mechanism for glomerular mesangial proliferation (35).

MCP-1 expression has not been found in glomeruli from nonproliferative diseases, such as membranous nephropathy, minimal change disease, thin basement membrane disease, and diabetic nephropathy (144). In contrast to the absence of glomerular chemokine expression in membranous nephropathy, MCP-1 and RANTES were expressed by tubular epithelial cells during proteinuria, and their expression was associated with interstitial cell infiltration and fibrosis (193,196). No CCR5-positive cells were detected within glomeruli during membranous nephropathy, but CCR5-positive mononuclear cells—predominantly CD3-positive T cells—were seen in the interstitium (195). This CCR5-positive T cell infiltrate may be related to the tubulointerstitial damage noted in these biopsies (195).

Chemokines and Chemokine Receptors in Proliferative and Crescentic Glomerulonephritis
Rovin et al. described the distribution of MCP-1 by immunohistochemistry in patients with idiopathic crescentic glomerulonephritis, Wegener’s granulomatosis, and lupus nephritis (144). A focal, granular staining for MCP-1 with a mesangial distribution (and in some crescents) was detected (144). Cockwell et al. studied 20 patients with glomerulonephritis due to different forms of vasculitis by in situ hybridization (197). MCP-1, MIP-1α, and MIP-1β were expressed in some glomeruli at similar levels and in crescents (197). RANTES expression was described in 11% of the glomeruli (197). MCP-1 was not detected in the glomeruli of patients with lupus nephritis (189). By in situ hybridization, patients with lupus nephritis showed MCP-1 expression on endothelial cells, cortical tubules, and infiltrating mononuclear cells in the interstitium (189,197). In patients with cryoglobulinemic glomerulonephritis, a significant upregulation of MCP-1 expression was seen in glomeruli and in areas of tubulointerstitial damage (191). The MCP-1 was localized to tubular cells, parietal cells, and cells of the glomerular tuft, and correlated with glomerular and interstitial macrophage infiltration (191). The expression of MIP-1β and MIP-1α fits with the preliminary observation that crescents contain CCR5-positive cells (198). In crescentic glomerulonephritis, the expression of MIP-1α and MCP-1 was found in tubules, peritubular capillaries, and infiltrating leukocytes. MIP-1α was also present in crescents (199). Cockwell et al. described the distribution of IL-8 mRNA and protein in patients with antineutrophil cytoplasmic antibody-associated glomerulonephritis (200). About 30% of the glomeruli showed IL-8 expression at sites of inflammation. Outside the glomeruli, IL-8 mRNA was detected in interstitial infiltrates and
proximal tubular epithelial cells. IL-8 protein was present in 50% of the glomeruli and was prominent in crescents and parietal cells. Intraglomerular leukocyte accumulation correlated with the IL-8 expression (200).

Chemokines and Chemokine Receptors in Tubulointerstitial Diseases

Biopsy samples from patients with acute interstitial nephritis were studied by in situ hybridization and immunohistochemistry for MCP-1 expression (186). MCP-1 was expressed by tubular as well as infiltrating cells and was detected in parietal cells of Bowman’s capsule but not within the glomerular tuft. Eitner et al. described expression of CCR5 mRNA in interstitial infiltrates (201) that was confirmed by immunohistochemistry, where CCR5-positive cells correlated with the presence of an interstitial T cell infiltrate (195).

Chemokines and Chemokine Receptors during Renal Transplant Rejection

Acute allograft rejection is characterized by a mononuclear cell infiltrate consisting primarily of T cells, macrophages, and occasional eosinophils (202,203). The chemokines IL-8, ENA-78, MCP-1, MIP-1α, MIP-1β, and RANTES have all been implicated in the pathogenesis of acute rejection (204–209). One of the most studied chemokines in this regard is the CC chemokine RANTES (205,210). During cell-mediated rejection, in situ hybridization localized RANTES mRNA to infiltrating cells and tubular epithelium (210). RANTES protein was found on mononuclear cells, tubular epithelium, and the vascular endothelium (205). This expression mirrors the distribution of CCR5-positive leukocytes found in areas of endothelialitis, tubulitis, and interstitial infiltrates during cellular rejection (195). Strehlau and coworkers used reverse transcription-PCR to evaluate gene expression in human renal allograft biopsies and concluded that RANTES and IL-8 expression are sensitive but not specific markers of allograft rejection (211). Grandaliano et al. found an increased amount of MCP-1 in urine during rejection corresponding to elevated renal MCP-1 expression (204). An increased amount of urinary IL-8 was described during acute rejection, which returned to normal levels after successful treatment (206).

DARC Expression in Kidney Disease

A study of children with HIV-associated nephropathy, HIV-associated hemolytic uremic syndrome (HUS), and classic HUS (212) reported DARC mRNA and protein localized to endothelial cells of postcapillary renal venules in normal kidney. The biopsies of the patients showed increased DARC expression on glomerular capillaries, collecting duct epithelial cells, and interstitial inflammatory cells (212). DARC upregulation on peritubular endothelium was described during transplant rejection especially at sites of inflammation in a recent abstract (213). The role of this upregulation of DARC during renal diseases is unknown.

Quantification of Urinary Chemokines as a Measure of Renal Production

Elevated urinary MCP-1 levels occur in proliferative lupus nephritis, IgA nephropathy, proliferative glomerulonephritis associated with endocarditis, membranoproliferative glomerulonephritis, crescentic glomerulonephritis, and in transplant rejection (187–191,199). Only moderately increased amounts of MCP-1 have been measured in membranous nephropathy, focal segmental glomerulosclerosis, and diabetic nephropathy, consistent with moderate glomerular cell infiltration in these diseases (190). Urinary MCP-1 levels correlated with urinary protein excretion and macrophage infiltration of the glomeruli (190). No correlation between serum and urine MCP-1 was seen (187).

High urinary MCP-1 excretion was found in patients with active lupus nephritis compared with healthy control subjects (189,190,192). Urinary MCP-1 levels were reduced by high-dose glucocorticoid therapy and remained low during remission (187,189,192). Elevated urinary excretion of MCP-1 and MIP-1α was also reported in patients with crescentic glomerulonephritis, and treatment reduced excretion of both chemokines (199). Similar results were reported for IL-8, with high levels seen during severe lupus nephritis, and a significant reduction in IL-8 levels was seen after glucocorticoid therapy (187,189).

A correlation between urinary MCP-1 levels, mesangial proliferation, and interstitial infiltrate has been described in IgA nephropathy (186,188). Patients with severe IgA nephropathy showed higher MCP-1 levels compared with patients with mild disease (186). IL-8 levels were only elevated during the acute phase and correlated with glomerular endocapillary proliferation and the degree of hematuria (188).

Other renal diseases that present elevated levels of IL-8 include acute postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, and cryoglobulinemia (187). The urinary IL-8 levels were higher in patients with glomerular leukocyte infiltration than in those without infiltration (187). Children with HUS showed a significant increase in both IL-8 and MCP-1 excretion (214). Thus, urinary excretion of chemokines may reflect the intrarenal inflammatory cell infiltrate and may be of prognostic value as a measure of continued intrarenal inflammation.

A Model for Chemokines in Renal Diseases

The emerging picture of chemokine action allows us to construct models of potential roles for chemokines in various pathophysiologic processes thought to contribute to renal disorders. In this model (Figure 1A), a pathologic insult to the glomerular or tubulointerstitial compartment activates intrinsic renal cells and leads to the local generation of proinflammatory mediators (initiation phase) (Figure 1B). This insult may be immunologic, toxic, ischemic, or mechanical, and may target a specific renal cell type (e.g., endothelial, mesangial, and epithelial or interstitial cell). The expression of select chemokines and chemokine receptors, together with the local release of inflammatory mediators (such as IL-1, TNF-α, IFN-γ, platelet-activating factor, reactive oxygen species, etc.), promotes the
upregulation and activation of selectins and integrins on leukocytes and endothelial cells leading to adhesion, transendothelial migration, and infiltration of specific subsets of leukocytes. T cells, monocytes, and polymorphonuclear leukocytes appear to preferentially adhere to different microvascular compartments in the kidney. For example, T cells are rare in glomeruli but are common in interstitial infiltrates. The specialized endothelia found in the kidney, e.g., glomerular, peritubular, have different characteristics, but at present information on the surface expression of selectin ligands is lacking (215). The role of this endothelial heterogeneity in the kidney for the leukocyte adhesion and infiltration process remains to be elucidated.

An additional consequence of local cell activation may include the induced expression of chemokine receptors such as CCR1 and CXCR3 by mesangial cells, and other renal cell types. The expression of CXCR3 by mesangial cells in concert with local production of the chemokine IP-10 could lead to mesangial cell proliferation (35).

During the “amplification phase,” spillover of proinflammatory factors from affected glomeruli could reach the peritubular capillary circulation, as well as the tubular lumen via ultrafil-

Figure 1. Hypothetical model of the role of chemokines and chemokine receptors during progressive renal diseases. (A) Normal renal tissue. (B) Initiation phase. (C) Amplification phase. (D) Progression phase.
tration, especially in the context of proteinuria with loss of the ultrafiltration barrier. In addition, protein and lipids escaping through damaged glomeruli could “stress” proximal tubular cells. In concert with inflammatory mediators, this could lead to an activation of tubular and interstitial cells and the production of additional chemokines, resulting in interstitial mononuclear cell infiltration. Similarly, the parietal cells of Bowman’s capsule apparent bystander cells in this process could become activated and thus release chemokines into the surrounding interstitium. This sort of event could help explain the accentuated periglomerular infiltrate seen in some renal diseases. The periglomerular infiltrate may play a role in the eventual rupture of Bowman’s capsule, which would open the door for T cells, macrophages, and fibroblasts to invade the urinary space and damage the parietal and visceral epithelial cells. This could be an example of the “point of no return,” in which amplification of a glomerular injury results in irreversible sclerosis. Thus, a cycle initiated through glomerular damage could, in the absence of sufficient counter-regulatory signals, result in downstream tubular-interstitial injury, interstitial inflammation, and fibrosis (progression phase) (Figure 1D).

Of course, renal inflammation does not always end with chronic damage. The events initiated during inflammation normally end in resolution of the disease process. Recent results suggest that some chemokines and their receptors may also assist in downmodulating the inflammatory response, a hypothesis that deserves further investigation.

Conclusions, Future Directions, and Therapeutic Outlook

Current therapies used for the treatment of renal diseases can influence chemokine expression. The production of chemokines by various renal and infiltrating cells can be suppressed by glucocorticoids in vitro (126,216). Glucocorticoids function in part via an inhibition of transcription factor NF-κB (217), and blockade of NF-κB function leads to suppression of chemokine release by renal cells (51,218). Elevated urinary chemokines in human lupus nephritis are decreased by glucocorticoid therapy (187,189,190,192). Glucocorticoid suppression of chemokine expression may be one component of the general beneficial effects of glucocorticoid therapy seen in lupus nephritis.

In animal models, a connection between angiotensin II, chemokine production by renal cells (122), and beneficial effects of angiotensin blockade were described (122,125,145). In addition, PGE has been shown to decrease monocyte-macrophage infiltration (161), whereas NSAID can enhance it (145). Thus, NSAID may enhance renal chemokine production and hence renal inflammation, an additional reason for avoiding their use in patients with renal disease.

Taken together, these studies shed light on therapeutic protocols that may influence the regulation of chemokine/chemokine receptor expression and suggest efficacy for the development of agents that selectively target chemokine biology. In general, receptor-blocking drugs have proven to be very successful therapeutically. The development of chemokine receptor antagonists for the treatment of inflammatory disorders and HIV is a major focus of the pharmaceutical industry. The redundancy of the chemokines, which creates a robust system, could be a drawback for therapeutic interventions (57). Therefore, blockade of multiple chemokine receptors simultaneously might be necessary. This strategy has already been successfully exploited by nature, as viruses can produce broad-spectrum chemokine antagonists, e.g., vMIP-II (150). On the other hand, the redundancy might be of potential benefit for the treatment with antagonists, as this might lead to a reduction of side effects.

Given the large number of chemokines and chemokine receptors, the intricate control of their expression, and their diverse biologic actions, the emerging story reveals a biologic system that is extraordinarily complex. The therapeutic intervention into the system might depend on the underlying disease, the time point, and comedication. Based on experimental models and the immunohistologic findings in human biopsies, blockade of CCR5-positive infiltrating cells might prove to be a promising therapeutic strategy for inflammatory renal diseases including transplant rejection. Clearly, antagonists for chemokines and their receptors have the potential to become additional therapeutic tools in inflammatory disorders, including kidney diseases.

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