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REVIEW ARTICLE

Chemokine/chemokine receptor-mediated inflammation regulates pathologic changes from acute kidney injury to chronic kidney disease

Kengo Furuichi · Shuichi Kaneko · Takashi Wada

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Abstract Ischemia–reperfusion injury is a main cause of acute kidney injury. Tubular necrosis and interstitial inflammatory cell infiltration are characteristic pathologic changes of acute kidney injury. The main necrotic area should be repaired with new tubular epithelial cells after the injury. On the other hand, some parts of the injured kidney progress to interstitial fibrosis, a characteristic pathologic change in chronic kidney disease. We hypothesized that interstitial infiltrating leukocytes, that are attracted and activated by chemokines, are key mediators in the pathogenesis of tubular necrosis, regeneration of the necrotic area, or interstitial fibrosis. A large number of chemokines were upregulated after ischemic injury, and chemokine receptor-expressing inflammatory cells were attracted by these chemokines. Genetic or molecular modulating experiments in the mouse model have begun to reveal the key participants and their specific roles at the levels of inflammation, regeneration, and fibrosis. Among these chemokines/chemokine receptors, our data indicated CCR2-mediated macrophage infiltration mainly affected tubular necrosis after ischemic acute kidney injury, interferon-gamma-inducible protein (IP)-10-producing macrophages participate in regeneration of tubular epithelial cells, and CX3CR1-mediated macrophages and platelet infiltration and aggregation play roles in interstitial fibrosis in chronic kidney disease. These chemokines and chemokine receptors on infiltrating inflammatory cells would be novel clinical markers or targets for therapeutic intervention.

Keywords Acute kidney injury · Chemokine · Ischemia–reperfusion · Tubular necrosis · Regeneration · Fibrosis

Introduction

Ischemia–reperfusion injury (IR) is one of main clinical causes of acute kidney injury. Ischemia–reperfusion is unavoidable during renal transplantation, and is also commonly observed in renal artery stenosis, and shock state occurring for a variety of reasons. From the viewpoint of pathogenesis of ischemic acute kidney injury, tubular necrosis and interstitial inflammatory cell infiltration are characteristic pathologic changes. Moreover, the necrotic area is repaired by new tubular epithelial cells several days after the injury. On the other hand, some parts of the injured kidney progress to interstitial fibrosis, a characteristic pathologic change of chronic kidney disease (Fig. 1). Inflammatory mechanisms resulting from ischemic acute kidney injury and leading to chronic kidney disease have not yet been fully defined but may provide opportunities for developing novel therapeutic approaches [1–3]. As well

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K. Furuichi (✉)
Division of Blood Purification, Kanazawa University Hospital,
13-1 Takara-machi, Kanazawa 920-8641, Japan
e-mail: kfuruichi@m-kanazawa.jp

S. Kaneko
Department of Disease Control and Homeostasis,
Kanazawa University Graduate School of Medical Science,
13-1 Takara-machi, Kanazawa 920-8641, Japan

T. Wada
Department of Laboratory Medicine,
Kanazawa University Graduate School of Medical Science,
13-1 Takara-machi, Kanazawa 920-8641, Japan

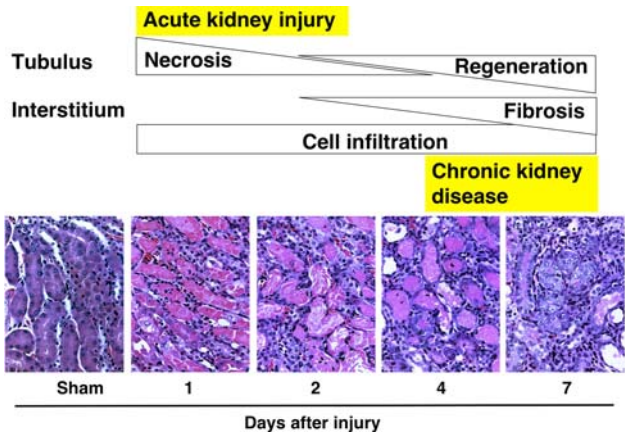

Fig. 1 Natural course of ischemia–reperfusion injury. In acute kidney injury after ischemia, tubular necrosis and interstitial inflammatory cell infiltration are observed in the early phase of injury. The necrotic area is repaired by new tubular epithelial cells. Interstitial fibrosis, a characteristic pathologic change of chronic kidney disease, progresses several days after the injury

as therapeutic targets, to understand the precise mechanisms of progression to acute kidney injury with necrosis, regeneration of necrotic tubular epithelial cells or chronic kidney disease with interstitial fibrosis are important for developing new diagnostic markers. This review focuses on the contribution of inflammation regulated by cytokines and chemokines as a key modulator in renal ischemia–reperfusion injury.

Tubular necrosis

Induction of chemokines after renal ischemia–reperfusion injury

Inflammatory cell infiltration in ischemic acute kidney injury might be one of key responses in the progression of tissue destruction and regeneration of the injured kidney. At least three mechanisms of action induce inflammatory responses:

- The first is adenosine triphosphate (ATP) depression. Oxygen deprivation due to ischemia induces early ATP depletion. ATP depletion stops ATP-dependent transport pumps, resulting in mitochondrial swelling. Mitochondrial swelling results in outer membrane rupture, with release of mitochondrial intermembrane proteins. Caspase 1 or interleukin-1 converting enzyme (ICE) enzymatically cleaves interleukin (IL)-1β. IL-1β is an exponent pro-inflammatory cytokine, and can induce chemokines, for example keratinocyte-induced chemoattractant (KC), macrophage inflammatory protein (MIP)-1α, or RANTES, from renal tubular epithelial cells [4].
- A second species mediating ischemia-induced inflammation in the kidney is hypoxia inducible factor-1 (HIF-1). Three isoforms of HIF have been identified, HIF-1, HIF-2, and HIF-3. HIF-1 and HIF-2 are structurally and functionally similar. However, HIF-3 may be a negative regulator of hypoxia-inducible genes expressed by HIF-1 and HIF-2 [5]. HIF-1 is unstable under normoxic conditions but is stable and works under hypoxic conditions [6, 7]. Many genes encoded for cytokines and growth factors are induced by HIF-1 activation [8, 9].
- The third molecular switch linking ischemia to inflammation involves oxygen-derived free radicals. In particular, hydrogen peroxide, which is a source of oxygen-derived free radicals after IR injury, has been reported to induce TNF-α production by activating p38 mitogen-activated protein kinase (MAPK) [10].

These mechanisms combine to induce inflammation after ischemia–reperfusion, and subsequent mechanisms augment the inflammation and tubular necrosis.

Intracellular signaling pathways linking ischemic injury to chemokine production

A variety of intracellular signaling factors, for example nuclear factor (NF)-κB and activating protein (AP)-1, are necessary for CXCL8/interleukin (IL)-8, CCL2/monocyte chemoattractant protein (MCP)-1, or CCL5/regulated upon activation normal T cells expressed and secreted (RANTES) [11–13]. Activation of NF-κB and AP-1 requires phosphorylation of p38 MAPK. Consistent with this, we found that pharmacological inhibition of p38 MAPK significantly reduced inflammatory cytokine and chemokine production and prevented tubular necrosis in a mouse model of renal IR injury [4]. In the same way, NF-κB decoy oligodeoxynucleotide treatment attenuated tubular necrosis with reduction of CCL2/MCP-1 expression in a rat model of renal IR injury [14]. Thus, these intracellular signaling factors may be good targets for therapeutic intervention in renal IR injury. However, further studies will be needed to clarify the importance and significance of each intracellular signaling cascade on cytokine and chemokine expression in renal IR injury.

Pro-inflammatory cytokines augment inflammation after renal ischemia–reperfusion injury

Renal parenchymal cells, for example tubular epithelial cells, mesangial cells, and endothelial cells, have the potential to produce various kinds of chemokine (e.g. CCL2/MCP-1, CCL5/RANTES, CXCL8/IL-8, CXCL1/growth-regulated oncogene (GRO), CXCL10/interferon-gamma

inducible protein (IP)-10, CXCL2/3/MIP-2, etc.) in response to stimulation with pro-inflammatory cytokines such as IL-1β, TNF-α, and interferon (IFN)-γ, immune complexes, and growth factors, including platelet-derived growth factor and basic fibroblast growth factor [15]. Midkine also enhances migration of inflammatory cells on ischemic injury of the kidney, and may induce chemokine production and ischemic tissue damage [16, 17]. Among chemokine/cytokine-producing cells in the kidney, the tubular epithelial cells seem to be the most sensitive to hypoxic conditions; moreover, tubular cell-derived cytokines/chemokines are thought to augment inflammatory processes in renal ischemia–reperfusion injury.

Chemokine expression in the injured kidney

Chemokines are able to activate many different cell types, including leukocytes and renal parenchymal cells. They have been divided into four subfamilies—CXC, CC, C, and CX3C—according to the number and spacing of conserved cysteine residues in their sequences.

A large number of chemokines and chemokine receptors are expressed after ischemia–reperfusion injury. The CXC chemokines, for example KC and CXCL2/3/MIP-2 in the mouse and CXCL8/IL-8 in man, rabbit, and other mammals, are upregulated in tubular epithelial cells after ischemic injury; this results in marked neutrophil infiltration [18–22]. CXCR2, a receptor for KC and CXCL2/3MIP-2 and CXCL8/IL-8, is one therapeutic target for neutrophil infiltration in a mouse model of renal IR injury [20, 23–25]. However, neutrophil-depletion studies with anti-neutrophil antibodies in mouse models have not provided evidence of an important role of neutrophils in IR [26]. CC chemokines are also upregulated after ischemic injury, with marked monocyte/macrophage infiltration. In contrast with neutrophil depletion, macrophage depletion with clodronate in vivo has furnished evidence of a major role in IR pathogenesis of monocytes/macrophages, which accumulate in the late phase post-injury [27]. Expression of the monocyte-targeted CC chemokine CCL2/MCP-1 is induced in ischemic kidney [28]. Both genetic deletion and pharmacological blockade of CCR2, the specific receptor for CCL2/MCP-1, have been reported to significantly reduce monocyte infiltration and tubular necrosis after ischemic injury [4, 29, 30]. Immunohistological studies indicate that the main resident cell producing CCL2/MCP-1 in the kidney after ischemic injury is located in the distal tubule [31]. Macrophages are also a major source of CCL2/MCP-1, and of the inflammatory cytokines TNF-α, IL-1, and IL-6 [32]. Therefore, these MCP-1/CCR2 positive-feedback loops augment inflammatory reaction after ischemia–reperfusion injury and might participate in progression of tubular necrosis.

Regeneration

Acute kidney injury with tubular necrosis usually recovers after the injury. During the recovery phase, necrotic tubular cell debris is removed and the denuded area is restored by new tubular cells [33]. Although tubular cell regeneration is undoubtedly required for recovery of renal function, the precise mechanisms and factors regulating tubular cell proliferation are poorly understood [34]. From the viewpoint of sources of regenerating tubular cells, several kinds of stem cell have been speculated upon. Bone marrow-derived stem cells or intra-renal mesenchymal stem cells might participate in the regeneration [35], but residual tubular epithelial cells aggressively proliferate to cover the area of the defect. Tubular epithelial cells may produce growth factors (FGF, TGF-α, EGF-like growth factor, IL-2, osteopontin, etc.) at regenerative wound margins associated with leukocyte infiltration [36–38]. It is likely that inflammatory infiltrating leukocytes secrete cytokines and chemokines that may regulate growth-factor production by resident renal cells. Concurrent with growth factor production, regenerative changes of cell proliferation associated with leukocyte infiltration have been detected at wound margins. However, excessive cell proliferation should be harmful for perfect recovery of the injured kidney. Therefore, as well as cell proliferation, inhibitory mechanisms of cell proliferation might be necessary for perfect regeneration. On this topic we reported that IP-10 had an inhibitory effect on tubular cell proliferation in vivo and in vitro. The interstitial infiltrated F4/80-positive cells were main source of IP-10 [39]. Further studies are needed to investigate whether regeneration from tubular necrosis is a very important part of recovery of the injured kidney.

Interstitial fibrosis after renal ischemia–reperfusion injury

The main parts of ischemic acute kidney injury regenerate and recover renal function. However, some parts progress to interstitial fibrosis, which is one of the characteristic changes in chronic kidney disease and an important poor prognostic factor. It is well known that the fibroblast is a key fibrogenic cell, but we recently reported the importance of circulating connective tissue cell progenitors, fibrocytes, to interstitial fibrosis [40]. In parallel with fibrogenic cells, humoral factors are also important in the progression of kidney fibrosis. Transforming growth factor (TGF)-β and platelet-derived growth factor (PDGF) are well-characterized factors that promote fibrosis in many diseases and organs, including the kidney [41, 42]. As well as tubular epithelial cells and fibroblasts, infiltrating inflammatory cells are rich sources of these factors and,

potentially, other fibrogenic mediators [43]. We revealed that CX3CL1/fractalkine and its unique receptor CX3CR1 are both upregulated after ischemic injury and participate in the pathogenesis of renal fibrosis. The mechanism involves selective effects in the outer medulla, including accumulation of macrophages and platelets, and expression of the macrophage and platelet-derived fibrogenic protein platelet-derived growth factor-B [44].

Anti-inflammatory treatment approaches in renal ischemia–reperfusion injury

Prognosis of acute kidney injury has not changed in the past two decades. New approaches to the disease are necessary for prevention of poor prognosis. We showed the inflammatory reaction might be a key aspect of progression of the disease. Although vasoactive agents such as dopamine, atrial natriuretic peptide, and diuretics are clinically useful for acute kidney injury after renal IR injury, these agents do not directly affect inflammation. Several experimental therapeutic approaches, for example leukocyte depletion, and anti-cytokine, anti-chemokine, and anti-adhesion molecule therapies, have been tested with the objective of controlling renal inflammation after IR injury.

Inhibition of caspase activation is one target for therapeutic treatment of ischemic acute kidney injury. Treatment with the caspase inhibitor Z–Val–Ala–Asp(OMe)-CH_2F effectively diminishes apoptosis, chemokine expression, and neutrophil infiltration after renal ischemia–reperfusion [22].

Intracellular signaling molecules are also therapeutic targets for ischemic acute kidney injury. Inhibitors of NF-κB reduce CCL2/MCP-1 mRNA expression and prevent tissue destruction in ischemic acute kidney injury [28]. We targeted p38 MAPK, a key factor regulating inflammatory chemokine expression, for treatment of ischemic renal injury. An inhibitor of p38MAPK was effective in significantly reducing chemokine expression and in attenuating leukocyte infiltration and tissue destruction [4].

Chemokines and chemokine receptors themselves are potentially important targets of anti-inflammatory therapy. We previously reported that neutralizing anti-IL-8 antibodies or anti-MCP-1 antibodies prevents experimental glomerulonephritis [45, 46]. Moreover, specific inhibitors of chemokine receptors, for example vMIP-II, APO-RANTES or Met-RANTES, 7ND MCP-1, TAK-779, or propagermanium, have been developed and tested successfully in various animal models, including experimental renal IR injury [29, 30, 47–51]. Furthermore, we revealed that neutralizing anti-CX3CR1 antibodies prevents interstitial fibrosis with diminishing macrophage infiltration [44]. These reports are encouraging, and add support to consideration of inflammatory chemokine receptors as targets for IR injury in the clinic.

Conclusion

Interstitial infiltrating leukocytes are key mediators in the pathogenesis of acute kidney injury with tubular necrosis, in the regeneration of necrotic tubular epithelial cells, and in chronic kidney disease with interstitial fibrosis. Various kinds of inflammatory infiltrating cell are mediated by cytokines and chemokines. Many chemokines are upregulated after ischemic injury, and chemokine receptor-expressing inflammatory cells are attracted by these chemokines. Genetic or molecular-modulating experiments in the mouse model have begun to reveal the key players and their specific roles at the levels of inflammation, regeneration, and fibrosis. Among these chemokines/chemokine receptors, our data indicated CCR2-mediated macrophage infiltration mainly affected tubular necrosis after ischemic acute kidney injury, IP-10-producing macrophages participate in the regeneration of tubular epithelial cells, and CX3CR1-mediated macrophages and platelets participate in interstitial fibrosis in chronic kidney disease (Fig. 2). Other major challenges will be to expand these approaches and to translate emerging results for use in human diseases in which renal IR injury occurs, with the objectives of identifying novel clinical markers or targets for therapeutic intervention.

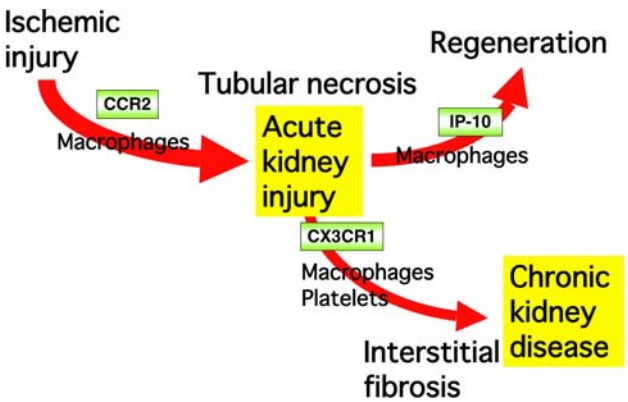

Fig. 2 Chemokine cascades in ischemia–reperfusion injury pathologic change of tubular necrosis after ischemic acute kidney injury are mainly mediated by the action of CCR2 on macrophages. Regeneration of tubular epithelial cells in the late phase of the injury was mediated by IP-10-producing macrophages. Moreover, chronic interstitial fibrosis was mediated by the action of CX3CR1 on macrophages and platelets. Characteristic chemokines/chemokine receptors participate in particular pathologic changes at specific time points

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