Cytokines and chemokines as therapeutic targets for ischemic kidney injury

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Cytokines and chemokines induce the migration, activation, proliferation, and/or differentiation of inflammatory cells and resident cells, and participate in the pathogenesis of some autoimmune diseases. Some of these molecules are effective therapeutic targets. Anti-tumor necrosis factor (TNF)-α and anti-interleukin (IL)-6 therapies are effective in patients with rheumatoid arthritis, and have markedly altered the therapeutic strategies for this disease. In ischemic kidney disease, cytokines and chemokines also play key roles in the progression of tissue destruction or remodeling. Accumulated data regarding ischemic kidney disease suggested that chemokines or chemokine receptors participate in unique pathological changes at particular time points in renal injury. Some molecules involved in these cytokine/chemokine cascades are potential therapeutic targets. In addition to antagonists for single chemokine receptors, promiscuous antagonists for chemokine receptors are currently under investigation. Further studies are needed to develop cytokine- and chemokine-based therapeutic strategies for ischemic kidney injury.


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Introduction
Cytokines and chemokines play important roles in the progression of ischemic kidney injury. Previous reports indicated that cytokines and chemokines participate in unique pathological reactions at particular time points in renal injury. It is important to clarify the mechanisms involved in “cytokine and chemokine cascades” to prevent or modulate the progression of ischemic kidney injury. In this mini review, we first focus on the mechanism of cytokine and chemokine cascades, and then summarize the possible therapeutic approaches.

Cytokine chemokine cascades in ischemic kidney injury
Although the immune system evolved to eliminate pathogenic organisms, the systems also participate in inflammatory diseases, such as rheumatoid arthritis, asthma, diabetes, inflammatory
bowel disease, and multiple sclerosis. Cytokines and chemokines induce the migration, activation, proliferation, or differentiation of inflammatory cells and resident cells, and participate in the pathogenesis of these diseases. Therefore, cytokines and chemokines are potentially important therapeutic targets in various diseases. Anti-tumor necrosis factor (TNF)-α and anti-interleukin (IL)-6 therapies are effective in patients with rheumatoid arthritis, and have altered the therapeutic strategies for this disease. 

In kidney diseases, cytokines and chemokines are produced by activated tubular epithelial cells as well as infiltrating leukocytes. Activated tubular epithelial cells were reported to produce a range of cytokines and chemokines, including TNF-α, IL-1, monocyte chemotactic protein (MCP)-1/chemokine (CC motif) ligand-2 (CCL-2), IL-8/chemokine (CXC motif) ligand-8 (CXCL8), platelet-derived growth factor (PDGF), regulated upon activation normal T-cell expressed, and presumably secreted (RANTES)/CCL5, endothelin-1, and vascular endothelial growth factor (VEGF). All of these factors directly or indirectly participate in the progression of tubulointerstitial inflammation after ischemia-reperfusion injury and induce inflammation through leukocyte infiltration. Various gene-targeting studies in mice have demonstrated the importance of cytokines and chemokines in ischemia-reperfusion injury. We and other groups have reported that cytokines and chemokines contribute to the exacerbation of ischemic kidney injury. These observations suggested that cytokines and chemokines may play unique roles in the pathogenesis of renal ischemia-reperfusion injury at particular time points. For example, CCR2 participates in progression of tubular necrosis at early phase of the ischemic kidney injury, and CX3CR1 in interstitial fibrosis at late phase of the injury. To recognize these cytokine and chemokine cascades in the ischemic kidney injury, it would be important and useful for effective cytokine and chemokine therapy in the diseases.

Renal transplantation is one of the most important clinical settings involving exposure of the kidney to the risk of ischemia-reperfusion injury. Clinical studies have indicated steady improvements in the rate of early function loss of transplanted kidneys. However, the rate of late function loss of transplanted kidneys has remained almost unchanged for three decades in Japan. Early nonspecific ischemia-reperfusion injury was reported to lead to later immunological rejection. Therefore, regulation of inflammatory reactions after ischemia-reperfusion would prevent rejection after transplantation. Data regarding chemokine and chemokine receptor polymorphism in human kidney transplantation, or chemokine expression in animal models suggest that chemokines play critical roles in transplanted kidney destruction. Therefore, cytokines and chemokines play key roles in the pathogenesis of renal injury in transplantation, and may be useful clinical markers and therapeutic targets to prevent rejection after transplantation.

Therapeutic approach for inflammatory process in ischemia-reperfusion

Various animal and clinical studies revealed that cytokines and chemokines induce migration, activation, proliferation, or differentiation of inflammatory cells and resident cells, and participate in the pathogenesis of various diseases, especially those with autoimmune mechanisms. Specific inhibitors of chemokine receptors, such as viral macrophage inflammatory protein (vMIP)-II, APO- or Met-RANTES, 7ND, 9-76MCP-1, TAK-779 or propagermanium, or inhibitors of intracellular signal transporters, have been developed and subjected to trials in various animal models, including experimental renal disease models. Pharmaceutical and biotechnology companies are engaged in research and development efforts to identify safe and effective drugs to treat these diseases. In clinical settings, a number of trials for antagonists of chemokine receptors have been publicly disclosed (Table 1).

In acute renal injury, some vasoactive agents, such as dopamine, atrial natriuretic peptide, and diuretics, are useful under some specific clinical conditions. However, these agents could not prevent the inflammatory processes, and there is no solid evidence for acute kidney injury. We reported that p38 mitogen-activated protein kinase (MAPK), one of the key intracellular signaling molecules for chemokine expression, and MCP-1/CCR2 signal inhibitors, reduced the inflammatory reaction in experimental renal disease models, including ischemia-reperfusion injury. Although there have been a number of reports regarding anti-chemokine/cytokine therapy, further studies are needed to develop these anti-inflammatory agents for clinical use.

On the other hand, the balance of pro- and anti-inflammatory cytokines in inflammatory cascades may be useful as therapeutic targets for ischemia-reperfusion injury. From this viewpoint, some anti-inflammatory cytokines, such as osteopontin and α-melanocyte-stimulating hormone, are therapeutic candidates in ischemia-reperfusion injury. These cytokines have been reported to inhibit inducible nitric oxide synthase production, chemokine production, and adhesion molecule expression. Insulin-like growth factor-1 and hepatocyte growth factor have also been reported to have beneficial effects in ischemia-reperfusion in-
jURY. Therefore, these factors have therapeutic potential in ischemia-reperfusion injury.

Limitations of receptor-specific antagonists and possibility of promiscuous antagonists

Several recent clinical trials with antagonists to single chemokine receptors ended in failure (Table 1). The reasons for these failures were speculated to include complexity and redundancy of chemokines and chemokine receptors. A number of chemokines and chemokine receptors have been identified, and these molecules largely participate in complex immunological networks. Moreover, these molecules and receptors show intricate patterns of redundancy. To overcome these problems, new alternative approaches in which multiple chemokine receptor subtypes are inhibited by the use of promiscuous non-peptide antagonists are currently under development\textsuperscript{20, 25-27}. These approaches are expected to be more successful than those using receptor-specific antagonists, and may provide beneficial effects in various diseases.

Conclusion

Studies in various animal models and clinical data in human cases of ischemic kidney injury revealed that cytokines and chemokines play key roles in the pathogenesis of renal injury. Therefore, cytokines and chemokines are thought to be useful and effective therapeutic targets and/or clinical markers in renal injury. However, several recent clinical trials with antagonists to single chemokine receptor ended in failure. Therefore, new approaches using promiscuous antagonists are currently in development. Further studies are needed for the development of cytokine and chemokine therapy for clinical use in cases of ischemic kidney injury.

References

Various types of ischemic stress in the kidney induce cytokine production, and these cytokines promote the expression of other cytokines and chemokines. In the cascades, each chemokine or chemokine receptor participates in unique pathological changes at particular time points. CCR2 participates in macrophage and neutrophil infiltration and tubular necrosis at early time points, while CX3CR1 participates in interstitial fibrosis at late time points. IP-10/CXCL10 participates in regeneration during the remodeling stage.