Mini Review

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[1, 2].

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)[3-6]. 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[4, 7]. These observations suggested that cytokines and chemokines may play unique roles in the pathogenesis of renal ischemia-reperfusion injury at particular time points. For examples, 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[8-10]. 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[11]. 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[12-17]. 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[3, 18, 19]. 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)[20].

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[4, 8, 19]. 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 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[21, 22]. Insulin-like growth factor-1 and hepatocyte growth factor have also been reported to have beneficial effects in ischemia-reperfusion in-

Table 1

Receptor	Clinical phase	Compound	Indication	Status
CCR1	II	BX471	MS, psoriasis, endometriosi	No efficacy, trials halted
	II	MLN 3701, ML	RA, MS	MLN 3897, no efficacy in RA
	II	CP 481,715	RA	No efficacy, trials halted
	I	CCX354	RA	Ongoing
CCR2	II	MLN 1202‡	ATHE, MS, RA	No efficacy in RA, ongoing in ATHE and MS
	I	INCB8696	MS, lupus	Ongoing
	I	CCX140	MS, restenosis	Ongoing
	II	MK-0812	RA, MS	No efficacy
	II	PF-4136309	Pain	Ongoing
CCR3	II	TPI ASM8‡	Asthma	Ongoing
	I	776994	Asthma, allergic rhinitis	No longer reported
	I	DPC-168	Asthma	No longer reported
CCR4	I	KW-0761‡	Oncology	Ongoing
CCR5	Approved	Maraviroc	HIV	Approved
	II	Maraviroc	RA	Ongoing
	II	Vicriviroc	HIV	Ongoing
	III	Aplaviroc	HIV	Toxicity, development uncertain
	II	INCB9471	HIV	Ongoing
	I	Pro 140‡	HIV	Ongoing
CCR9	III	CCX-282	IBD, Crohn's disease	Ongoing
CXCR1/CXCR2	II	SCH 527123	COPD	Ongoing
	II	Reparixin	Reperfusion injury	Ongoing
CXCR2	I	SB 656933	COPD, cystic fibrosis	Ongoing
CXCR3	II	T-487/AMG-48	Psoriasis	No efficacy, trial halted
CXCR4	III	Plerixafor	Multiple myloma, NHL	Ongoing

*All programmes are non-peptide in approach except where indicated otherwise with‡.

Data were obtained from the Investigational Drugs Database from Thomson Reuters. ATHE, Atherosclerosis; COPD, chronic obstructive pulmonary disease; IBD, irritable bowel syndrome; MS, multiple sclerosis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

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jury[16, 23, 24]. 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[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.

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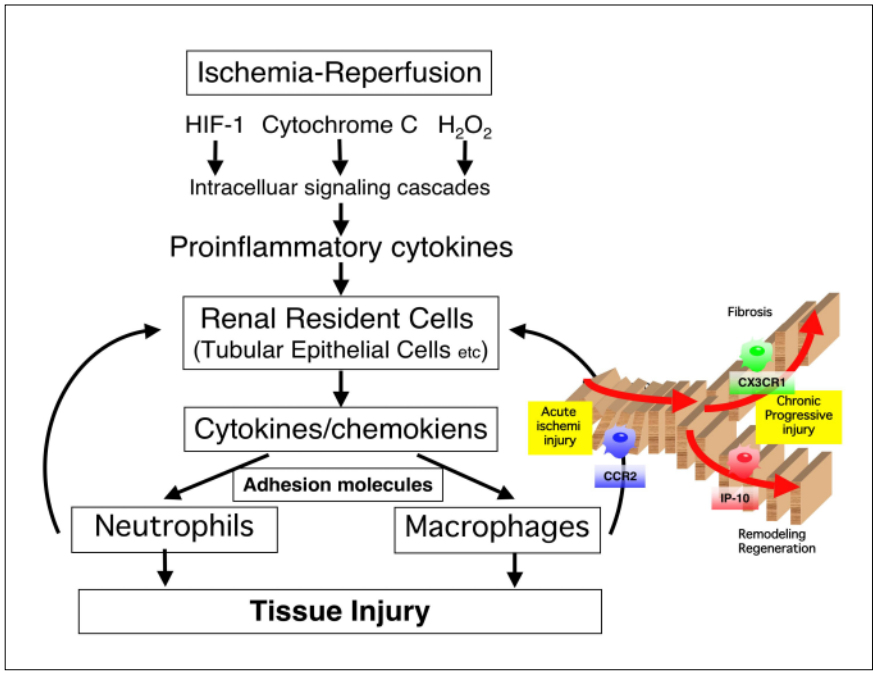

Fig. 1 Hypothetical schema of inflammatory cascades in ischemic kidney injury

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.

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