Special Issue "Autoinflammation vs Autoimmunity"

Mini Review

Involvement of inflammation in autoinflammation and autoimmune disease

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Various recent studies reveal that many autoinflammatory syndromes result from inflammasome related protein abnormality. Some inflammasomes closely correlate with caspase 1. Caspase 1 is a key molecule for activation of IL-1β, which is responsible for induction and augmentation of inflammation. Inflammatory cytokines, including IL-1β, are necessary for T_H17 differentiation from T_H0 cell. T_H17 cells were recently reported to play major roles in autoantibody production. In this point of view, inflammasome inducing inflammation participates in prominent roles both in autoinflammatory syndromes and autoimmunity. On the other hand, non-immunological ischemic injury deeply correlates with immunological reaction in kidney transplantation. Inflammation would share significant part both in non-immunological tissue destruction and immunological reaction of rejection in kidney transplantation. Inflammatory cytokines, including IL-1β, and chemokines are key regulators in progression of inflammatory reaction in ischemic kidney injury. Our data indicate that specific chemokines or chemokine receptors participate in specific pathologic changes at specific time points in the injury. One of some molecules, which work for these pathological changes would be new therapeutic targets for transplantation.

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Inflammasome in autoinflammation

Various types of autoinflammatory syndromes with hereditary periodic fever without any infection were reported since the end of 1990[1]. Many of them were demonstrated genomic abnormality (Table 1). Mendelian autoinflammatory diseases were reported to be involved in pyrin[2, 3]. Cryopyrin were found to cause the autosomal dominant disorders familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) in 2001[4]. Mutations in the same gene were identified in patients with neonatalonset multisystem inflammatory disease (NOMID) in 2002[5]. Mutations in the p55 TNF receptor led to TNF receptorassociated periodic syndrome (TRAPS) in 1999[6]. Moreover. Recent study revealed that the deficiency of the IL-1 receptor antagonist might one of causes of patients with autoinflammatory syndrome[7].

Parallel with these certification of genetic abnormality, interaction of these molecules was investigated. Inflammasome is an intra cellular molecular complex for inflammation. Inflammasome was shown to activate caspase-1 and promote interleukin-1ß (IL-1ß) maturation[8]. IL-1ß is a well-known player in the process of inflammation and fever. Moreover, hereditary autoinflammatory syndromes are characterized by an increased IL-1ß production that directly triggers the inflammatory cascade in these patients. Therefore, the central role of IL-1ß in pathogenesis of autoinflammatory syndromes was highlighted. Furthermore, inflammasome contains various kinds of protein including NALP family[9]. Those family genes recently reported to be main causes of autoinflammatory syndromes.

As well as IL-1ß production, inflammasome participate in a special type of cell death, pyroptosis[10, 11]. Pyroptosis is a pathway to cell death mediated by the activation of inflammasome with caspase-1, and the inflammatory cytokines, such as IL-1ß. That is pyroptosis features cell lysis with releasing inflammatory cellular contents, and induces inflammation around the dead cell. Therefore, pyroptosis would participate in pathogenesis of autoinflammatory syndromes [12].

Inflammation and autoimmunity

Inflammation, as well as existence of autoantibody, is one of a key feature of autoimmune disease. IL-6 and IL-1ß are pleiotropic and proinflammatory cytokines secreted by macrophages, Dendritic cells, T cells, and tubular epithelial cells, and exerts manifold effects in T cell differentiation. Both of IL-1ß and IL-6 are also important factors for pathogenesis in various autoimmune dis-

Table1. Inflammasome related autoinflammatory syndromes

Familial Mediterranean Fever; ***MEFV*/pyrin,**	**1997**
TNF receptor associated periodic syndrome; ***TNFRSF1A*/TNFRSF1A, TNFR1, p55,**	**1999**
Familial cold autoinflammatory syndrome ***CIAS1* or*NLRP3*/cryopyrin or NLRP3 or NALP3,**	**2001**
Muckle-Wells syndrome ***CIAS1* or*NLRP3*/cryopyrin or NLRP3 or NALP3,**	**2001**
Neonatal-onset multisystem inflammatory disease ***CIAS1* or*NLRP3*/cryopyrin or NLRP3 or NALP3,**	**2002**
Hyperimmunoglobulinemia D with periodic fever syndrome ***MVK*/mevalonate kinase**	**1999**
The deficiency of the IL-1 receptor antagonist ***IL1RN*/IL-1Ra**	**2009**

eases. These cytokines are key molecules for TH17 differentiation from TH0[13]. TH17 cells had reduced Fas ligand production and resistance to Fasinduced apoptosis. The long-lasting apoptosisresistant TH17 cells activate B cells and their immunoglobulin production[14]. TH17 cells may lead to the induction of latent inflammatory TH17 response and hyper-activation of B cells, and may participate in production of autoreactive Abs[14]. TH17 induces autoimmunity in experimental models, and in genetically-predisposed individuals, that may assign TH17 cell lineage as a hallmark for autoimmunity[13] (Table 2). In this point, inflammatory cytokines including IL-1 and IL-6 would be important mediators for induction of autoimmune diseases (Figure 1).

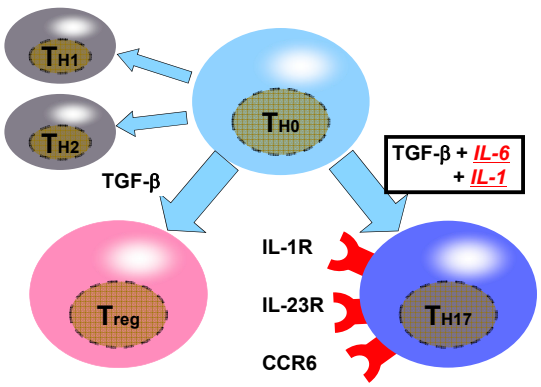

Figure 1 TH17 and inflammatory cytokines

TH0 cells differentiate to various types of T cells. Although TH0 cells differentiate to Treg under condition of TGF-β without inflammatory cytokines, the cells differentiate to TH17 under condition of TGF-β and inflammatory cytokines, IL-1 and IL-6.

Rheumatoid arthritis is a most common autoimmune disease. Recently, proinflammatory cytokines were highlighted as key therapeutic targets for rheumatoid arthritis[15]. It was reported that chronic inflammatory arthropathy resembling rheumatoid arthritis was developed in interleukin 1 receptor antagonist-deficient mice[16]. Moreover, various kinds of cytokines were detected in synovial tissue and fluid[17]. Biological agents targeting to these cytokines were clinically used, and showed high good responsiveness[18]. Using these biological agents, therapeutic strategy of rheumatoid arthritis management has been dramatically changed in the last 10 years. These biological agents apparently inhibit structural destruction and improve physical function and quality of life in RA patients. Although agents target only one molecule, such as TNF-a or IL-6, the agent largely affects their disease activity. These data indicated that one inflammatory molecule would be key regulator in autoimmune disease.

Inflammation and immunological reaction ---Ischemic injury and transplant immunology in kidney---

Total allograft rejection rate in kidney transplantation was apparently prevented year after year by immunosupression therapy. However, the total prevention mainly depends on prevention of acute rejection. Chronic rejection rate is almost similar around 30 years ago. Recent paper reveals that ischemic time is a key factor for allograft rejection in kidney transplantation[19]. These data indicate that non-immunological ischemic injury induces immunological reaction of allograft rejection. In this point of view, the inflammation on ischemic kidney injury is key reaction to understand transplant immunology.

One important point is how inflammatory reaction induces after ischemic injury. At least three ways of reaction induce inflammatory responses after ischemic kidney injury. The first way of the reaction is adenosine triphosphate (ATP) depletion. ATP depletion induces mitochondrial swelling. Injured mitochondria releases activated caspase 1, and activated caspase 1 cleaves IL-1β. IL-1β is an exponent pro-inflammatory cytokine, and can induce chemokines, such as keratinocyte-induced chemoattractant (KC), macrophage inflammatory protein (MIP)-1α or CCL5 / RANTES, from renal tubular epithelial cells[20]. The second way of the reaction that mediates ischemia-induced inflammation in the kidney is hypoxia inducible factor (HIF)-1. HIF-1 is just stable and works under hypoxic condition[21]. Many genes encoded for inflammatory cytokines and growth factors are induced by HIF-1 activation[22]. The third molecular switch linking ischemia to inflammation involves oxygen-derived free radicals. These molecules

also induce TNF-α production by activating p38 mitogen-activated protein kinase (MAPK)[23]. Gathering all these three mechanisms induces inflammation after ischemic kidney injury.

Table2. TH17 related autoimmune diseases

•Multiple sclerosis (MS) and EAE
•Psoriasis-like dermatitis
•Rheumatoid arthritis and Ag-induced Arthritis
•Autoimmune diabetes
•Anti-ANCA-associated vasculitis
•Sjogren's syndrome
•Allergen-induced airway and contact Hypersensitivity
•Autoimmune thyroid diseases
•Thrombocytopenia

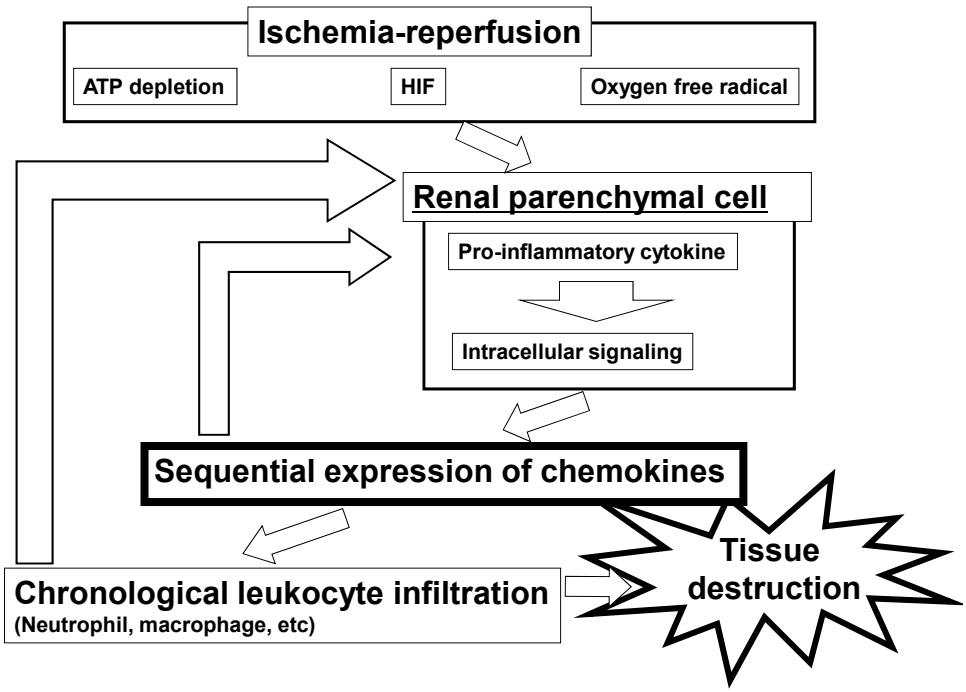

Figure 2. Inflammatory cascades in ischemic kidney injury
At least three ways of reaction induce inflammatory responses after ischemic kidney injury; ATP depletion, HIF-1 induction, and oxygen free radical. Tubular epithelial cell producing pro-inflammatory cytokines augment inflammation after renal ischemic kidney injury.

Pro-inflammatory cytokines augment inflammation after renal ischemic kidney injury. Tubular epithelial cell appears to be the very sensitive to hypoxic conditions, and the cell has potential to produce various kinds of chemokines (e.g. CCL2/MCP-1, CCL5/RANTES, CXCL8/IL-8, CXCL1/growth-regulated oncogene (GRO)). A large number of chemokines and chemokine receptors were expressed on tubular epithelial cells after ischemic kidney injury. The CXC chemokines, such as KC, CXCL2/3MIP-2 and CXCL8/IL-8, are upregulated in tubular epithelial cells after ischemic kidney injury, and this result in marked neutrophil infiltration[24,,25]. Therefore, CXCR2, a receptor for KC, CXCL2/3MIP-2 and CXCL8/IL-8, is one of a key molecule for neutrophil infiltration in a mouse model of ischemic kidney injury[24], and these inflammatory cell infiltration augments inflammatory reaction after ischemic non-immunological injury (Figure 2).

Chemokines are able to activate many different cell types, including leukocytes and renal parenchymal cells. Similarly to CXC chemokine, CC chemokines also upregulated after ischemic injury with marked monocyte/macrophage infiltration. Macrophage depletion with clodronate *in vivo* has supported a major role of monocyte/macrophage in pathogenesis of ischemic kidney injury[26]. Expression of the monocyte-targeted CC chemokine CCL2/MCP-1 is induced in ischemic kidney[27]. Both genetic deletion and pharmacological blockade of CCR2, the specific receptor for CCL2/MCP-1, have been reported to significantly reduce macrophage infiltration and tubular necrosis after ischemic injury[27,28]. Immunohistological studies indicate that the main resident cell producing CCL2/MCP-1 in the kidney after ischemic injury is located in the distal tubule[29]. Macrophages are also a major source for CCL2/MCP-1, and for the inflammatory cytokines TNF-α, IL-1 and IL-6[30]. Therefore, these MCP-1/CCR2 positive feedback loops augment inflammatory reaction after ischemic kidney injury and might participate immunological reaction (Figure 3).

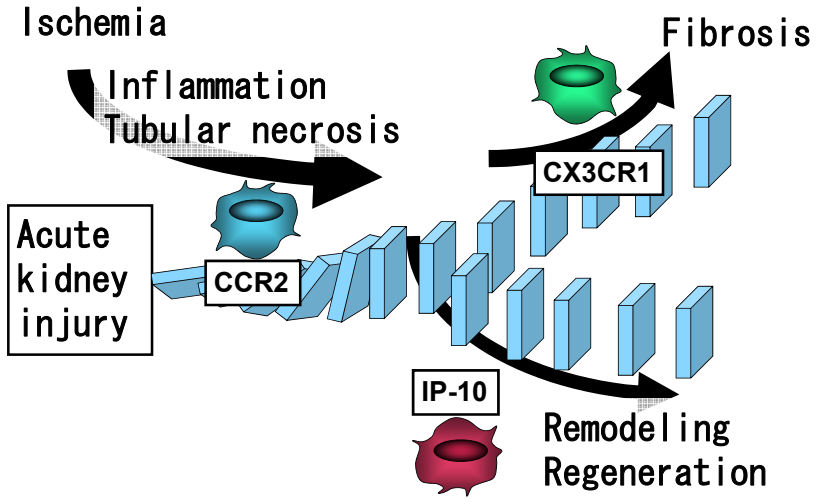

Figure 3 Chemokine cascades in ischemic kidney injury
Specific chemokines or chemokine receptors participate in specific pathologic changes at specific time points. CCR2 participates in macrophage and neutrophil infiltration and tubular necrosis in early time point, CX3CR1 participates in interstitial fibrosis in late time point. IP-10 participates in regeneration in remodeling time point.

As well as CCL2/MCP-1 regulated macrophage infiltration in tubular necrosis, our data indicated that interferon-gamma inducible protein (IP)-10 producing macrophage participate regeneration of tubular epithelial cells, and CX3CR1 mediated macrophage and

platelet infiltration and aggregation play some roles in interstitial fibrosis in chronic kidney disease (Figure 3). All these inflammatory reaction might participate in immunological responses after ischemic kidney injury. Therefore, these chemokines and chemokine receptors on infiltrating inflammatory cells in ischemic injured kidney would be novel therapeutic targets of immunological reaction in kidney transplantation.

Conclusion

Inflammasome related inflammatory reaction would share important parts in pathogenesis of autoinflammatory syndrome, autoimmune diseases, and immunological reaction in transplantation.

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