Chemoattractive cytokines (chemokines) and immune renal injury

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Introduction

Immune-mediated renal injuries are characterized by glomerular and tubulointerstitial infiltration of neutrophils and monocytes/macrophages [1,2]. These inflammatory leukocytes, which are usually involved in host defence and phagocytosis of exogenous pathogens, contribute to local tissue damage in autoimmune renal disease, due to their generation of inflammatory mediators such as reactive oxygen species, proteolytic enzymes, cytokines, and growth factors [3–5].

One of the significant features of inflammatory leukocytes in affected tissue is accumulation at the localization of injury. Inflammatory cell recruitment into injured areas begins with the binding of blood cells to the vascular endothelium. Cells then migrate according to concentration gradients of chemoattractants into the tissue. The process of adhesion to endothelial cells involves a series of consecutive cellular steps which include the expression of several groups of molecules on the surface of inflammatory leukocytes and endothelial cells, including selectins, integrins, and adhesion molecules [6,7]. The process of cell adhesion on the endothelium is then followed by the transmigration of cells into the site of primary tissue injury. The initiating events of tissue damage in most immune renal injuries is the binding of antibodies to cell surface antigens, matrix, or the basement membranes which, dependent or independent of complement activation, can release early inflammatory cytokines (such as interleukin 1β and TNFα) [2,6,7]. Interleukin 1β and TNFα can induce the expression of adhesion molecules [7], which might initiate cell attachment. Initial immune injury, however, also may lead to the increased formation of chemoattractants [6,8]. In addition to several lipid mediators a group of cytokines has recently been described which in vitro exerts chemoattractant activities on several inflammatory cells and which could be involved in the recruitment of leukocytes in autoimmune disease.

Chemokines

Chemotactic cytokines or chemokines are a group of small cytokines with a molecular weight that ranges from 8 to 10 kDa and which exhibit an amino-acid homology from 20 to 50%. All the chemokines have four cysteine residues in the amino-acid sequence; however, two groups of molecules have been described based on whether the first two cysteine residues are separated by another amino acid (-C-X-C-class) or whether they are directly adjacent (-C-C-class) [9]. The four conserved cysteine amino acids form disulphide bonds and establish the tertiary structure of the molecules. The -C-X-C-class consists of molecules such as interleukin 8, ENA-78, GRO, NAP-2, and MIP-2. To the -C-C-class chemokines belong the monocyte-chemoattractant proteins (MCP) 1, 2, and 3, macrophagic inflammatory proteins 1α and 1β, RANTES (Regulated upon Activation Normal T-cell Expressed and Secreted) and I-309 [9]. The -C-C-family seems to be clustered on the human chromosome 17, the -C-X-C-class of chemokines is clustered on human chromosome 4.

The role of this group of chemokines as inflammatory mediators is very interesting, since they exert a certain degree of specificity on inflammatory leukocytes [9]. For example interleukin 8 is primarily involved in the recruitment of neutrophils whereas the members of the -C-C-class such as MCP-1 or RANTES elicit their effects on mononuclear cells. An important feature of the chemokines is their basic nature, which makes them extremely good heparin-binding polypeptides. This feature could be relevant after cellular secretion in heparin-sulphate-rich extracellular matrix.

Chemokines act by binding to receptors on target cells and induce, under in-vitro conditions, migration in picomolar to nanomolar concentrations. In addition to their chemoattractant capacities, certain chemokines induce inflammatory mediators in leukocytes. MCP-1 stimulates the formation of cytokines and integrins as well as the production of H2O2 in monocytes [10,11]. Interleukin 8 releases lysosomal enzymes, stimulates expression of complement receptors, and increases the formation of leukotriene B4 and superoxide by neutrophils in accordance with the capacity to mobilize these cells [9]. These in-vitro actions, suggest a role for chemokines as potential mediators of inflammatory renal diseases.
Expression of chemokines in the kidney

Chemokines are synthesized by a wide variety of inflammatory cells; however, their production is not limited to these immune cells. They are expressed by a spectrum of non-immune cells of different organs, including the kidney. Non-immune cells might release, upon appropriate stimulation, chemokines which could contribute to the cellular influx of inflammatory cells into the tissue. Chemokine expression has been demonstrated in glomerular endothelial, epithelial, and mesangial cells as well as in renal tubular cells upon stimulation with inflammatory cytokines and other mediators of disease.

In human mesangial cells in culture Abbot and co-workers [12] demonstrated that IL-1β and TNFα increase expression of mRNA and secretion of IL-8 in a dose-dependent fashion. Similarly in mesangial cells, other authors observed an increased expression of IL-8, mRNA, and protein in renal cortical epithelial cells when exposed to IL-1β, TNF or LPS [13]. These investigators also observed expression of IL-8 protein in the cytoplasm of both proximal and distal renal tubular cells in renal biopsy specimens from patients with acute allograft rejection. Thus the human kidney distal tubular cells might be a source of IL-8 which could exert chemoattractant activity.

A possible involvement of IL-8 in renal inflammatory disease is derived from a recent study by Wada et al. [14] who found that urinary excretion of IL-8 was increased in patients with several entities of proliferative glomerulonephritis. The elevated urinary IL-8 levels were associated with immunohistological detection of IL-8 in diseased glomeruli and the appearance of a higher number of leukocytes. Similarly to the data obtained for IL-8, studies in cultured mesangial cells also revealed expression and secretion of C-C chemokines. The most information is available on MCP-1, which can be stimulated by IL-1β, TNFα, interferon γ, LPS, lipoproteins, cyclosporin A, and IgG complexes [15,16]. TNFα and IL-1β also stimulate the expression of RANTES in mouse mesangial cells in culture [17].

To test whether an initial step of immune injury, due to in-situ antibody binding and consecutive complement activation, could in fact lead to alterations in chemokine formation, the expression of MCP-1 was studied in a rat model of proliferative glomerulonephritis. This lesion was induced by intravenous injection of a heterologous antibody directed against a mesangial cell epitope. MCP-1 expression was evaluated by northern blotting and immunohistology 30 min, 24 h, 5 days, and 21 days after antibody-induced injury. Induction of immune injury significantly increased MCP-1 mRNA expression in glomeruli together with increased appearance of MCP-1 protein when assessed by immunohistology [18]. Immunofluorescence studies suggest that MCP-1 is localized in the mesangium. The enhanced MCP-1 expression was paralleled by an increase of intraglomerular monocytes/macrophages. To study the possible role of complement in the expression of MCP-1 in this disease, animals were complement depleted prior to the induction of the lesion. This approach completely prevented the increase in MCP-1 expression, which suggests a role for the complement system in the increase of MCP-1 in this disease. Similar data for MCP-1 expression in glomerulonephritis have been recently reported in a model of nephrotoxic serum nephritis in the rat and in several forms of human proliferative glomerulonephritis [19].

In another animal model of glomerular immune injury, the accelerated model of nephrotoxic serum nephritis, increased expression of RANTES could be demonstrated in glomeruli of diseased animals [20]. RANTES expression was also detected in mononuclear cells, tubular epithelium and vascular endothelium of kidneys with cellular transplant rejection. These findings suggest an involvement of RANTES in the inflammatory response of this lesion [21].

The detection of chemokines in the kidney, is not restricted to inflammatory diseases. Renal chemokine expression is also found in hypertensive disease, puromycin nephropathy, unilateral renal obstruction, and renal ablation models, i.e. situations associated with an inflammatory cell infiltrate in the kidney [22–24].

These studies demonstrate the expression of chemokines in the kidney in association with inflammatory cell influx. Even though these observations might suggest a functional role in these diseases, the ultimate effects have to be demonstrated by further experimental and clinical studies focusing on the pathophysiological role of chemokines in injury.

References

Is there a role for specific anti-TNF strategies in glomerular diseases?

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Introduction

As the mechanisms of glomerular inflammation and the subsequent progression to scarring are unravelled, the role of cytokines becomes ever more apparent. Cytokines are locally active polypeptides, which are secreted by many (if not all) eukaryotic cells. They modulate both infiltrating and intrinsic glomerular cells in renal damage [1]. Amongst the long list of cytokines, tumour necrosis factor α (TNF) is thought to play a prominent role as a mediator in inflammation. In recent years, increasing evidence has turned up to identify TNF as one major culprit in the pathogenesis of glomerular injury [reviewed in 2].

What are the actions of TNF?

TNF has a dazzling variety of pleiotropic actions on renal cells [2–5]. Such actions include synthesis of local effector substances, i.e. cytokines, chemokines, growth factors, and other mediators of inflammation, synthesis of receptors for these substances, of adhesion molecules and of proteins of the major histocompatibility complex (MHC), expression of regulatory factors in coagulation and fibrinolysis, and of extracellular matrix proteins and proteinases (the balance of which determines net mass of extracellular matrix). Apart from altering synthesis of the above compounds, TNF determines net mass of extracellular matrix. Apart from altering synthesis of the above compounds, TNF also has other actions that may play a role in the pathogenesis of glomerular injury, e.g. induction of mesangial cell contraction, translocation of proteinase 3 (the target of antineutrophil cytoplasmic antibodies—ANCA—in vasculitis) from its intragranular location to the cell surface of neutrophils, and expression of the glycolipid verotoxin receptor (involved in the genesis of haemolytic uraemic syndrome) on human endothelial cells. While TNF stimulates the synthesis of many factors in glomerular cells, it may also be cytotoxic and induce apoptosis in glomerular cells, depending on dose and microenvironment [4,5]. As the net result of these diverse actions, TNF appears to favour recruitment of leukocytes, amplification of the inflammatory response, and to regulate cell survival and accumulation of extracellular matrix.

What is the experimental evidence implicating TNF in models of glomerular inflammation?

The evidence linking TNF to glomerular injury in animals is based on (i) demonstration of synthesis of