Monocyte chemoattractant protein-1: does it play a role in diabetic nephropathy?

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Introduction

Both metabolic and haemodynamic pathways impact on the progression of diabetic nephropathy [1,2]. Chronic hyperglycaemia, advanced glycation end (AGE) products, increase of sorbitol, activation of protein kinase C (PKC), glomerular hypertension and genetic susceptibility have been identified as risk factors in the progression of diabetic nephropathy [2]. Moreover, infiltration of the diseased kidneys by inflammatory cells such as monocytes/macrophages (Mφ) is a hallmark of diabetic nephropathy [3,4]. Infiltrated Mφ release lysosomal enzymes, nitrous oxide (NO), reactive oxygen intermediates (ROI) and transforming growth factor (TGF)-β, which play an essential role in renal damage [2,5]. A chemokine, monocyte chemoattractant protein (MCP)-1, also termed monocyte chemotactic and activating factor (MCAF) or CCL2, is secreted by mononuclear cells and various non-leukocytic cells including renal resident cells. In experimental glomerulonephritis models [6–8] and human nephritis [9–11] it is thought to play an important role in the pathogenesis of crescent formation and progressive tubulointerstitial lesions via Mφ recruitment and activation.

In addition to these inflammatory renal diseases, recent studies suggest that MCP-1 is also involved in diabetic nephropathy.

In this editorial comment we focus on (i) MCP-1 and its cognate receptor, CCR2 in human diabetic nephropathy, and (ii) in vitro and in vivo studies of the role of MCP-1/CCR2 in the pathogenesis of diabetic nephropathy. The findings suggest interventions targeting the MCP-1/CCR2 systems as potential strategies to treat diabetic nephropathy.

MCP-1/CCR2 in human diabetic nephropathy

Up-regulation of locally produced MCP-1 may be involved in advanced tubulointerstitial lesions in diabetic patients with nephrotic syndrome through Mφ recruitment and activation [4,12]. This idea is based on the findings that: (i) urinary MCP-1 levels were significantly elevated in patients with diabetic nephrotic syndrome and advanced tubulointerstitial lesions (tubular atrophy, fibrosis, arteriolosclerosis); (ii) urinary levels of MCP-1 were correlated with CD68-positive Mφ in the interstitium; (iii) MCP-1-positive cells were detected in advanced tubulointerstitial lesions of diabetic nephropathy by both immunohistochemical and in situ hybridization analyses; (iv) urinary MCP-1 excretion was correlated with the number of MCP-1-positive cells in the interstitium of renal biopsy specimens; and (v) patients with minimal change nephrotic syndrome showed lower levels of urinary MCP-1, suggesting that massive proteinuria by itself does not necessarily increase urinary MCP-1 levels. We previously reported that MCP-1 plays a pivotal role in the genesis of progressive tubulointerstitial damage and promotes renal dysfunction in crescentic glomerulonephritis, human lupus nephritis and IgA nephropathy as well as in an experimental glomerulonephritis model [13]. Collectively, these findings suggest that up-regulation of MCP-1 may be a common regulatory pathway involved in the progressive diabetic nephropathy as well as in inflammatory renal diseases.

Urinary levels of MCP-1 increased progressively in diabetic patients with advancing glomerular lesions, although MCP-1 was not detected in diseased glomeruli and no correlation was found between the number of CD68-positive cells in glomeruli and urinary levels of MCP-1. These results might be explained by the close association between glomerular and tubulointerstitial lesions in diabetic nephropathy. MCP-1 may also have an indirect impact on glomerular lesions via the progression of arteriolosclerosis (nephrosclerosis).

In contrast to MCP-1, little is known about the role of CCR2 in human diabetic nephropathy. CCR2-positive cells are present in diseased kidneys with diabetic nephropathy (T. Wada, H. Yokoyama, K. Matsushima and K. Kobayashi, unpublished...
In vitro and in vivo expression of MCP-1/CCR2 in diabetic conditions

It is likely that the pathogenesis of diabetic nephropathy involves an interaction of metabolic and haemodynamic factors [5]. Hyperglycaemia is followed by Mφ recruitment that contributes to the molecular and structural events leading to glomerulosclerosis [15,16]. A high glucose concentration in the culture medium stimulates the expression of MCP-1 in human mesangial cells, and high glucose rapidly activates nuclear factor-κB (NF-κB) in mesangial cells through PKC and reactive oxygen species [17,18]. In addition, AGE have been implicated in the pathogenesis of diabetic nephropathy. Supporting this notion, AGE directly induces MCP-1 in human mesangial cells [19]. Interestingly, Pugliese et al. [20] demonstrated an acceleration of diabetic glomerulopathy in galectin-3/AGE receptor 3 knockout mice, suggesting that the galectin-3-regulated AGE receptor pathway is operating in vivo and protects against AGE-induced tissue injury, in contrast to RAGE which aggravates injury. Moreover, relevant metabolic factors include increased formation of polyols, oxidant stress and activation of PKC in addition to glucose-dependent pathways such as advanced glycation [5,21]. Indeed, oxidatively modified lipoproteins found in diabetic plasma stimulate MCP-1 gene expression in endothelial cells [22].

Glomerular filtration of growth factors, such as recombinant human TGF-β and recombinant human hepatocyte growth factor (HGF), increased MCP-1, regulated upon activation, normal T cell expressed and secreted (RANTES, CCL5) in the interstitium [23]. These apical signals might be translated into basolateral events that are recognized by cells in the interstitium. In turn, they stimulate interstitial myofibroblasts via Mφ and lead to accumulation of extracellular matrix proteins and progressive interstitial fibrosis [23]. Concomitantly, MCP-1 mediates collagen deposition in experimental glomerulonephritis by TGF-β [24]. Thus far, TGF-β has been thought to be a key factor in the progression of glomerular and tubulointerstitial lesions [25]. Therefore, once glomerular TGF-β is activated by various stimuli, MCP-1 may be up-regulated at least in the interstitium. MCP-1 may then recruit T cells and Mφ into the kidneys, thereby perpetuating progressive diabetic nephropathy. Angiotensin II-dependent pathways leading to MCP-1 up-regulation have been shown to play an important role in the genesis of glomerular and tubulointerstitial damage [26]. Kato et al. [27] demonstrated that glomerular Mφ recruitment in streptozotocin-treated rats is largely determined by angiotensin-stimulated MCP-1 expression [27]. They concluded that activation of the renin-angiotensin system is an important determinant of local MCP-1 expression, either directly or indirectly through glomerular haemodynamic effects. These findings implicate Mφ recruitment and activation in the pathogenesis of early diabetic glomerular injury. Alternatively, massive proteinuria might induce tubular epithelial cells to activate lysosome and antigen presentation followed by the activation of helper T cells in the interstitium [28]. However, at least concerning human MCP-1, proteinuria itself did not increase urinary levels of MCP-1. Taken together, once endothelial cells, tubular epithelial cells and interstitial infiltrates have been activated by some metabolic and/or haemodynamic process, these cells produce MCP-1, which may be involved in the progression of advanced diabetic nephropathy. In experimental models of diabetic nephropathy, MCP-1 is expressed in the glomeruli [27], although in humans MCP-1-positive cells are detected mainly in the interstitium. The apparent discrepancy between these findings could be explained as follows: (i) activated renal interstitial cells might be more prone to produce MCP-1 than glomerular cells; (ii) the findings may be an artifact due to the detection limits of immunohistochemical analysis; and (iii) there might be differences between human diabetic renal diseases.
and experimental animal models. Further studies will be required to clarify the roles of MΦ via MCP-1/CCR2 in the pathogenesis of progressive glomerular and interstitial lesions in diabetic nephropathy.

**Anti-MCP-1/CCR2 treatments: novel therapeutic intervention for diabetic nephropathy?**

Few reports have focused on MCP-1/CCR2 as the therapeutic targets for diabetic nephropathy. Kato et al. [27] assessed expression of genes regulating monocyte transmigration in the glomeruli of diabetic rats. The time-dependent increase of MCP-1 expression was dramatically suppressed by treatment with the AT1 receptor antagonist candesartan and it was closely associated with effects on proteinuria and glomerular MΦ number [27]. However, whether the manipulation of MCP-1/CCR2 is beneficial or harmful with respect to the progression of human and experimental diabetic nephropathy remains to be investigated.

**Concluding remarks and future directions**

The MCP-1/CCR2 system is involved in the pathogenesis of diabetic nephropathy. We can answer the above question ‘Does MCP-1 play a role in diabetic nephropathy?’ in the affirmative. This suggests that interventions targeting the chemokine/chemokine receptor systems may be a promising strategy in diabetic nephropathy. A number of chemokine receptor antagonists is currently under development. The selective blockade of chemokines/chemokine receptor systems, particularly the MCP-1/CCR2 system, may be useful in the treatment of diabetic nephropathy in the future.

**References**


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