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Short Communication

Monocyte Chemoattractant Protein 1's Role in Glomerular Pathology

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Introduction

Chemokines represent a family of secreted proteins with an important role in the immune response, being mainly involved in cellular migration processes of leukocytes, but also of other types of cells (endothelial cells, epithelial cells). Chemokines are classified according to their primary amino acid structure and the distribution of the 4 cysteine residues into four families: CXC, CC, CX3C and XC. Chemokines interact at the level of transmembrane receptors linked to the G protein, which are found on the surface of target cells [1].

Monocyte chemoattractant protein 1 (MCP-1/CCL2) is part of the CC chemokine family and is particularly involved in interacting with monocytes. It's made up of 76 amino acids, has a molecular weight of ~ 13 kDa and derives from a precursor of 99 amino acids through proteolytic cleavage. It is part of a subfamily composed of at least 4 members (MCP-1, -2, -3, and -4) [2,3]. MCP-1 acts primarily on the CCR2 receptors located on the target cells, but this interaction is not exclusive. Studies have shown that MCP-1 also interacts with other receptors from the same class: CCR1, CCR3 and CCR5. In addition, the CCR2 receptor can also interact with other chemokines, such as CCL7, CCL8, CCL11, CCl12, CCL12, CCL 24 and CCL26 [4]. CCR2 is part of the G protein-coupled receptor family. It consists of 374 amino acids, and has a short, extracellular amino-terminal end, 7 hydrophobic transmembrane domains interconnected by 3 extracellular loops and 3 intracellular loops and an intracellular carboxy-terminal end. Interaction with MCP-1 is done through the amino terminal end [2].

MCP-1 is produced at the level of several cells: endothelial, fibroblast, smooth muscle, mesangial, monocyte/macrophage. The latter represent the major source of MCP-1 [3]. The main stimuli of MCP-1 production are: pro-inflammatory cytokines (IL-1, IL-4, TNF-α, IFN-γ), growth factors (macrophage colony-stimulating factor (M-CSF), granulocytes- macrophage colony-stimulating factor (GM-CSF), PDGF, VEGF), lipopolysaccharides, reactive oxygen species, oxidized LDL molecules and immune complexes. TGF-β, retinoic acid, glucocorticoids and estrogen play an important role in inhibiting MCP-1 expression [5].

MCP-1 stimulates the migration of monocytes in the affected tissues, but also exerts chemotactic properties on basophils, CD4+ and CD8+ lymphocytes and T lymphocytes, being involved in inflammatory and tissue repair processes [3]. MCP-1 fulfills 3 distinct roles in monocyte migration: it recruits monocytes and monocyte precursors from the bone marrow into the bloodstream, then concentrates at the surface of endothelial cells, and recruits monocytes from the blood and into the inflamed tissue. After migrating into tissues, monocytes undergo differentiation processes and will start secreting pro-inflammatory cytokines, both processes being stimulated by MCP-1 [6]. At the level of the kidney, MCP-1 is synthesized both by local renal cells and by infiltrative leukocytes. MCP-1 is involved in inflammatory processes through the mobilization, localization, recruitment and differentiation of macrophages. In addition, in vitro studies demonstrate the synthesis of MCP-1 at the level of mesangial glomerular cells following stimulation by inflammatory cytokines (IL-1 and TNF-alpha), immune complexes, metabolic factors (glucose, glycosylation products), danger associated molecular patterns (DAMPS) and at the level of podocytes as a result of stimulation by advanced glycosylation products, TNF-α and TGF-β [7]. Renal tubular cells produce MCP-1 in response to IL-1, TNF, [8] thrombin [9] and albumin [10].

The involvement of MCP-1 in renal pathology has been studied in several types of diseases: ANCA-positive vasculitis, Henoch-Schonlein purpura, lupus nephritis, also playing an important role in the progression of chronic kidney disease. At the kidney level, MCP-1 determines the activation of tubular epithelial cells, inflammation and the progression of tubulo-interstitial lesions, with a primary role in the progression of chronic kidney disease. In addition, the direct effect of MCP-1 on smooth muscle cells seems to determine the increase in cardiovascular risk, but also the progression of chronic kidney damage. Studies performed in patients with GNRP showed the presence of MCP-1 in crescents and parietal cells, [11] and the urinary excretion of MCP-1 is higher in patients with crescents compared to other histopathological changes [12].

Studies on human subjects continue to focus on the diagnostic and prognostic value of urinary MCP-1, especially in patients with ANCA-positive vasculitis. The results of the study led by F. Tam et al showed significantly higher urinary values of MCP-1 in patients with active renal vasculitis compared to those with inactive vasculitis, patients with vasculitis without renal manifestations or healthy volunteers. Increased urinary levels of MCP-1 correlated with the ANCA titer and the BVAS score, and did not correlate with the value of proteinuria. The serum values of MCP-1 did not register the same differences between the groups of patients [7]. The results are supported by another study published in 2009 on 82 patients with ANCA-positive vasculitis. The urinary level of MCP-1 correlated with disease activity and represented a poor prognostic factor, the degree of association being stronger than for conventional prognostic markers (CRP, BVAS or ANCA score). The authors take two possible explanations into consideration. Either Urinary MCP-1 can represent a marker of subclinical inflammation with a long evolution to the patient's disadvantage, or it can represent a marker of tubulo-interstitial damage, which correlates with the severity of the disease at the onset and with an unfavorable long-term prognosis [13].

Another study carried out on 23 renal biopsies from patients with Rapidly Progressive Glomerulonephritis determined the distribution of MCP-1 and its receptor CCR-2 at the level of the affected glomeruli. MicroRNA MCP-1 was expressed mainly in crescent cells, parietal epithelial cells, tubular epithelial cells and infiltrative monocytes at the tubulointerstitial level. The microRNA molecule for the CCR2 receptor was described especially at the level of leukocytes in the tubulointerstitial and in smaller numbers at the level of the glomerular ball and of crescent cells, and most of the cells that expressed CCR2B were arranged around crescent cells [14]. Similar results were obtained in groups of pediatric patients with Henoch-Schonlein purpura [15] but also in patients with lupus nephritis. Urinary MCP-1 was correlated with 24-hour proteinuria, anti-DNA dc titer, SLEDAI score, biopsy activity index in a study conducted on 60 patients with SLE. There was also an increase in the urinary MCP-1 titer in the patients who did not register a response to the treatment [16].

Conclusions

MCP-1 represents an important cog in renal pathology, insufficiently known until now. Although current research has gained momentum, and the discoveries made represent important steps in understanding the complex pathophysiological changes in renal pathology, this biomarker cannot yet be used in current practice. Studies are still needed to establish the role of MCP-1 in the diagnosis and establishment of the prognosis in the various kidney diseases.

Conflict of Interest

No conflict of interest.

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