Angiotensin II Stimulates Monocyte Chemoattractant Protein-1 Expression in Rat Mesangial Cells

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The influx of bone marrow-derived monocytes into kidney tissue is one of the initial events that occurs in the process of progressive renal injury. Monocytes/macrophages are frequently present in glomeruli and interstitium of experimental and human renal diseases[1-7]. These infiltrated monocytes/macrophages may mediate glomerular injury, and also act as effector cells through their secreted products, such as enzymes, oxygen radicals, platelet activating factor, coagulation products, eicosanoids and nitric oxide, which may lead to tissue injury, crescent formation, stimulation of responses in glomerular cells or hemodynamic changes[6].

Angiotensin II(ANG II) plays a role in the progression of renal disease through the hemodynamic and metabolic mechanisms. ANG II has a growth effect on mesangial and tubular epithelial cells[8, 9], and stimulates the synthesis of structural components of the extracellular matrix in mesangial cells in vitro[8, 10], which contribute to glomerulosclerosis and interstitial fibrosis. Systemic infusion of ANG II for 7 days induces recruitment of inflammatory cells as well as moderate hypertension and marked glomerular, tubulointerstitial, vascular damage and proliferation of resident glomerular and interstitial cells[11]. In a rat model of acute ureteral obstruction, monocyte/macrophage and T lymphocyte infiltration in renal parenchyma accompanies increasing levels of ANG II, which is markedly decreased by angiotensin converting enzyme inhibitor, suggesting a role of ANG II for the immune cell infiltrate[12-14].

Monocyte chemoattractant protein-1(MCP-1) is a potent chemotactic factor for monocytes, T lymphocytes and basophils[15-17]. Role of MCP-1 for the progression of renal disease has recently been reviewed[18, 19]. MCP-1 released by mesangial cells plays a direct role in promoting the influx of leukocytes into the injured tissue and contributing to the progression of inflammatory renal injury. MCP-1 is constitutively expressed in monocytes and renal cells, such as mesangial, epithelial and glomerular endothelial cells[20-23], as well as expressed in a variety of human and experimental glomerulonephritis, ureteral obstruction and chronic rejection of rat renal allografts[24, 28]. MCP-1 production in monocytes and renal cells is further stimulated by various inflammatory cytokines and proteins, such as interferon-γ, interleukin-1, tumor necrosis factor-α, IgG aggregates, thrombin, low density lipoprotein, lipopolysaccharide, nitric oxide and antibody to neutrophil cytoplasmic antigens[21, 29-35]. On the other hand, glomerular MCP-1 expression is reduced by prostaglandin E1 in a rat model of anti-thymocyte antibody-induced glomerulonephritis[36].

We studied the effect of angiotensin II on the MCP-1 production in cultured rat mesangial cells. Chemotactic activity in serum-free medium conditioned by mesangial cells was measured in modified Boyden chambers with freshly isolated human monocytes. Mesangial cells constitutively release chemotactic activity into serum-free medium in a time-dependent manner between 4-72 hours. This activity was equally neutralized 70% by anti-rat MCP-1 or anti-murine JE antibody.

Angiotensin II stimulates chemotactic activity released by mesangial cells in a dose-dependent manner between 10^{-9} M-10^{-6} M. The effect of angiotensin II was also time-dependent with continuous increase in the release of MCP-1 up to at least 48 hours. The effect of ANG II was seen when mesangial cells were treated with ANG II for 9 hours, washed and then incubated in fresh serum-free medium without ANG II excluding a direct effect of ANG II on monocyte chemotaxis. The chemotactic activity released by both unstimulated and angiotensin II-stimulated cells was also neutralized by 70% in the presence of MCP-1 antibodies. Northern blot analysis revealed that angiotensin II(10^{-6} M) stimulates MCP-1 gene expression in a time-dependent manner with a peak effect between 16-24 hours. To determine the mechanism of the increase in MCP-1 mRNA levels, cells were treated with ANG II(10^{-6}M) for 16 hours followed by transcription inhibitor, 5,6-Dichlorobenzimidazole-1-β-D-ribofuranoside(DRB), 10μg/ml, and Northern blot analysis was performed. DRB completely inhibited both constitutive and ANG II-induced MCP-1 mRNA expression. MCP-1 gene transcription was directly measured using nuclear run off transcription assay. ANG II stimulates newly transcibed MCP-1 mRNA synthesis up to at least 24 hours.

We conclude that rat mesangial cells secrete monocyte chemotactic activity constitutively that can be attributed mostly to MCP-1. ANG II transcriptionally regulates gene expression and protein secretion of MCP-1. Angiotensin II may play a role in the recruitment and activation of monocytes to the glomerulus through the release of MCP-1.

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