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MCP-1/CCR2 Autocrine Loop in Podocytes

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Monocyte chemoattractant protein-1 (MCP-1) is upregulated in diabetic glomeruli and promotes the development of diabetic kidney disease, evidenced by the ability of the MCP-1 knockout (mouse model) to curtail albuminuria, renal fibrosis, and macrophage accumulation, while preserving kidney clearance function. However, the mechanisms whereby MCP-1 causes diabetic glomerulopathy are not well known, specifically the cellular sources of MCP-1, the stimulants of MCP-1 secretion, and the pathobiological effects of MCP-1 in the kidney. The podocyte was investigated as a source of MCP-1. Conditionally immortalized mouse podocytes showed a >7-fold increase in MCP-1 secretion in response to TGF-β1, an effect that was prevented by a TGF-β type I receptor kinase inhibitor, SB-431542. Furthermore, the TGF-β1-induced MCP-1 in podocytes was completely blunted by LY294002, implicating PI3K as a predominant component of the signaling mechanism. As for a functional impact of the increased MCP-1, the podocyte's motility, assayed by how quickly a cell monolayer could heal a scratch wound, was significantly increased by exogenous MCP-1 and by endogenous MCP-1 release as stimulated by TGF-β1 treatment. Podocyte motility correlated with increases in actin stress fiber formation. All of these effects on podocyte migration were dependent on signaling via the chemokine receptor, CCR2, judging by the ability of the specific CCR2 inhibitor, RS 102895, to block the MCP-1 (or TGF-β-induced MCP-1) effects. The changes in podocyte motility are believed to play a role in the permeability of the glomerular filtration barrier to proteins, since podocytes on a Transwell apparatus displayed increased diffusion of tagged albumin across the monolayer when exposed to MCP-1. The MCP-1-stimulated increase in albumin permeability was reversed by the CCR2 inhibitor. Our data suggest that in diabetes, the podocyte is both villain and victim in the overproduction of MCP-1 and in the maladaptive response to MCP-1 by undergoing mobility and permeability changes. Podocytic MCP-1 expression in the diabetic state is largely stimulated by TGF-β overactivity, acting partly through the PI3K pathway, and MCP-1 effects on the podocyte's motility and permeability are mainly mediated by the CCR2 receptor, all together suggesting that podocytes embody a functional MCP-1 autocrine loop.