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STATE OF THE ART: REVIEW OF LIPIDS AND PROGRESSIVE RENAL DISEASE

Recent advances in statins and the kidney

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Recent advances in statins and the kidney.

Background. Experimental and clinical studies have suggested a correlation between the progression of renal disease and dyslipidemia. Indeed, apolipoprotein B-containing lipoproteins have been demonstrated to be an independent risk factor for the progression of renal disease in humans. Interventional strategies in experimental models of renal disease have clearly demonstrated a beneficial effect on renal structure and function in a variety of models of renal disease. Investigations into the mechanisms whereby reduction of lipids by lipid-lowering agents benefits renal disease have suggested that the 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors, the so-called statin class of lipid-lowering agents, may have additional effects on the biology of inflammation that are germane to the progression of renal disease.

Methods. Both *in vivo* and *in vitro* studies that investigated secondary mechanisms of statin effects are reviewed. In addition, new studies that investigated the effects on novel cellular mechanisms are presented.

Results. Lipid-lowering agents appear to have biologically important effects in modulating a variety of intracellular signaling systems involved in cell proliferation, inflammatory responses that involve macrophage adhesion, recruitment, and maturation. In addition, the effects on fibrogenesis have been recently defined. These latter effects may influence not only the development of glomerulosclerosis, but also interstitial fibrosis. These potentially major effects of lipid-lowering agents appear to be related to the effects on intracellular synthesis of nonsterol isoprenoids, which are involved in prenylation of critical small molecular weight proteins involved in cell signal transduction.

Conclusions. In addition to the beneficial effects of the reduction in serum lipids, statins and other lipid-lowering agents may influence important intracellular pathways that are involved in the inflammatory and fibrogenic responses, which are common components of many forms of progressive renal injury.

Experimental evidence suggests that lipids are important modulators of progressive renal disease. In recent years, the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, so called "statins," have demonstrated beneficial effects in different models of progressive renal failure. Lovastatin ameliorated the extent of glomerular injury in 5/6 nephrectomy Sprague-Dawley rats [1], obese Zucker rats [2], Dahl-sensitive rats [3], guinea pigs (abstract; Gröne et al, *J Am Soc Nephrol* 3:739, 1992), and the puromycin aminonucleoside model of the nephrotic syndrome [4]. Lovastatin also retarded the development of polycystic kidney disease in the Han:SPRD rats [5], ischemic renal failure in high-cholesterol–loaded rats [6], and hypertension in spontaneously hypertensive rats [7]. Simvastatin suppressed the cell proliferation in rats with anti–Thy-1.1 nephritis [8]. Interestingly, some of the beneficial effects of statins can be seen independent of the cholesterol reduction (abstract; Kauffman et al, *FASEB J* 319:8, 1994) [4, 9]. These beneficial effects of statins on these *in vivo* animal models have been investigated using *in vitro* studies. In this regard, the effects of statins on the interaction of inflammatory cytokines, cell proliferation, and intracellular signaling pathways have recently been reported.

STATINS AND INFLAMMATORY CHEMOKINES

Macrophages participate in the uptake and metabolism of lipids in glomeruli, which may play a critical role in the pathogenesis of lipid-induced glomerulosclerosis [10–12]. The mechanisms whereby monocytes are recruited to glomeruli are poorly understood; however, mesangial cells stimulated by lipids [13] or inflammatory cytokines have been shown to produce important monocyte chemokines such as monocyte chemoattractant protein-1 (MCP-1) and macrophage-colony stimulating factor (M-CSF) [14, 15]. We have reported that lovastatin can reduce *in vitro* mesangial cell expression and the production of MCP-1 [16, 17] and M-CSF, as well as vascular cell adhesion molecule-1 (VCAM) and intracellular adhesion molecule-1 (ICAM-1), which are integral adhesion molecules [18]. Moreover, lovastatin inhibited the activation of transcription factor nuclear factor-κB (NF-κB), which plays a major role in the gene expression involved in mesangial cell inflammatory responses [19], suggesting that statins have modulating effects on the intracellular signaling pathways activated by inflammation.

Key words: fibrinogen, dyslipidemia, apolipoprotein, lipid-lowering agents.

STATINS AND CELL PROLIFERATION

We and others have reported that mesangial cells proliferate in response to various growth factors such as platelet-derived growth factor (PDGF), insulin, and insulin-like growth factor-1, as well as lipoproteins such as low-density lipoprotein (LDL), intermediate density lipoprotein (IDL), and very low-density lipoprotein (VLDL) [20–22]. *In vitro* experiments have shown that statins inhibit proliferation of cultured mesangial cells [23, 24], renal epithelial tubular cells [25], and vascular smooth muscle cells [26–28]. Although statins inhibit intracellular cholesterol synthesis, they also inhibit the formation of intermediate metabolites of the mevalonate pathway [23], particularly the nonsterol isoprenoids, which appear to be essential in cell replication.

INVOLVEMENT OF STATINS IN THE SIGNALING PATHWAYS

Mevalonate was reported to be an important product of HMG-CoA reductase for the progression of a cell cycle [29–31]. Recently, however, the important roles of the mevalonate metabolites such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) have been demonstrated to be indispensable anchors of small G proteins, such as p21ras, that allow it to bind to the cell membrane [32–34]. Binding of certain growth factors to its receptor induces p21ras activation in combination with Grb2-Sos-Shc binding to the receptor and p21ras. The signal is transmitted to the nucleus through a pathway that consists of Raf, MAPK-ERK kinase, and the mitogen-activated protein (MAP) kinase cascade. In the nucleus, the transcription factors such as activated protein-1 (AP-1), NF-κB, NF-interleukin-6 (NF-IL-6), and Egr-1 are induced, as well as early response genes, and subsequent cell proliferation or differentiation occurs. Reduction of FPP and GGPP by statins may effectively block the p21ras-mediated mitogenic signaling event [19, 35]. Lovastatin suppressed the expression of c-fos and c-jun in conjunction with a reduction in membrane-bound p21ras. In addition, it has been shown in renal tubular epithelial cells to functionally impair AP-1 binding to DNA [25]. This could, in part, contribute to the reported beneficial effect of statins on reducing tubulointerstitial inflammation in models of progressive renal disease. Lovastatin has recently been shown to inhibit isoprenylation of p21RhoA, a small G protein, and thereby induce apoptosis by inhibiting mitotic and postmitotic signals in cultured mesangial cells [36]. Similarly, atorvastatin decreased isoprenylation of p21RhoB, a small G protein, and induced apoptosis in vascular smooth muscle cells in culture [37]. Thus, statins appear to regulate cellular signaling pathways involved in proliferation and apoptosis.

In recent years, the involvement of statins in the cell-cycle regulation has received considerable attention. Lovastatin induced p27kip1, a cyclin-dependent kinase inhibitor, resulting in a cell-cycle arrest at G1 phase [38, 39]. These effects of statins on nuclear events may be explained by the observation that pravastatin inhibited geranylgeranylation of p21RhoA and p21RhoB, two small GTPase(s). Isoprenylation of these factors is essential for p27Kip1 degradation and subsequent cell-cycle progression from the G1 to S phase [40]. In our study, lovastatin reduced DNA synthesis by inducing p27Kip1 and suppressing cyclin D1 and E expression in cultured rat vascular smooth muscle cells [41].

Additional cellular effects of statins have been reported in recent studies. For example, simvastatin has been shown to improve vascular hemodynamic responses, suggesting a direct or indirect effect on endothelial-derived nitric oxide [42]. Atorvastatin and simvastatin were able to prevent the reduction in mRNA expression and protein levels of endothelial cell nitric oxide synthase after exposure to oxidized LDL [43]. Pravastatin [44] and lovastatin [45] have also been reported to improve vasomotor tone and endothelial function in patients with coronary artery disease in association with cholesterol reduction. The inhibitory effects of lovastatin and fluvastatin on platelet activation have been shown to reduce platelet aggregation via altered platelet lipid composition [46].

Thus, both *in vitro* and *in vivo* studies have demonstrated that statins may have important effects on the pathophysiology of progressive renal disease by modifying monocyte infiltration, mesangial cell proliferation, and mesangial matrix expansion, as well as tubulointerstitial inflammation and fibrosis. These effects appear to be related, at least in part, to inhibition of small G-protein isoprenylation involved in early gene products, transcription factors, and modulation of the cell-cycle regulatory proteins. Although these data need further study in humans, statins may be an important and beneficial therapeutic strategy for progressive renal diseases.

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APPENDIX

Abbreviations used in the paper are: AP-1, activator protein-1; Egr-1, early growth response factor-1; ERK, extracellular signal-regulated protein; Grb2, growth factor receptor-bound protein 2; HMG-CoA, 3-hydroxy-methylglutaryl coenzyme A; ICAM-1, intracellular adhesion molecule-1; LDL, low density lipoprotein; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage-colony stimulating factor; MEK, MAPK-ERK kinase; NF-κB, nuclear factor-κB; PDGF, platelet-derived growth factor; Shc, SH2 containing protein; Sos, son of sevenless; VCAM-1, vascular cell adhesion molecule-1.

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