Lipid-Induced Glomerular Injury

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It is widely recognized that once a critical number of nephrons has been damaged, a progressive loss of renal function occurs even if the original cause of renal injury is no longer present [1]. The final pathological picture, i.e. glomerulosclerosis, is remarkably similar regardless of the etiology, suggesting that different causes can ultimately merge into a common pathway of progressive glomerular damage. Several mechanisms have been proposed for this continuous decline in renal function. Hemodynamic factors, coagulation disorders and metabolic abnormalities may all play important roles in the pathogenesis of glomerulosclerosis [1]. Although the potential involvement of lipids in renal damage was suggested by Virchow [2] more than a century ago, there has not been a renewed interest in this issue until recent years [3]. Investigations during the last decade have provided relevant contributions to our understanding of how lipids can contribute to the process of glomerulosclerosis [4, 5].

Experimental Evidence

A number of experimental models support a role for lipids in the progression of renal disease. Animals from different species placed on a high cholesterol diet develop hypercholesterolemia and modest glomerulosclerosis [6]. The extent of glomerular injury, in general, correlates with the circulating cholesterol level [6]. Different animal models of hyperlipidemia secondary to proteinuria or other metabolic abnormalities are also associated with glomerulosclerosis and progressive renal injury [5, 6]. Therapeutic interventions with several unrelated antilipemic agents in experimental models of progressive renal disease have slowed the loss of function and prevented the development of glomerulosclerosis [7]. The magnitude of glomerular injury induced by hypercholesterolemia in otherwise normal kidneys appears relatively modest. However, the presence of preexisting glomerular disease [8,9], reduction of the number of nephrons [10,11], or hypertension [12,13] will increase the extent and severity of glomerulosclerosis.

Clinical Evidence

Although lipid abnormalities are almost a constant feature of kidney diseases [14], few clinical studies have addressed the role of hyperlipidemia in the pathogenesis of progressive renal insufficiency in humans. However, certain lipid disorders appear clearly associated with the development of spontaneous glomerular injury. Patients with a deficient lecithin-cholesterol acyltransferase activity develop abnormally large lipid-laden lipoproteins, glomerular lipid deposition and renal failure [15]. Another rare disorder, the so-called

lipoprotein glomerulopathy, has been recently reported from Japan [16,17]. The most distinctive feature of the disease is the presence of intraglomerular lipoprotein thrombi. In every case, apoprotein (apo) E levels are increased and an unusual apo E phenotype is present, apo E2/3 in most cases. The authors suggest that the abnormal apoprotein rather than increased lipids per se is responsible for the disorder. Taken together, these syndromes indicate that unusually large and/or abnormally composed lipoproteins may contribute to renal injury.

The infrequent occurrence of renal damage in the majority of patients with common hyperlipidemias suggests that additional factors are required for lipid-mediated renal injury. In this regard, several reports have suggested that lipids can be modulators of renal damage in nephropathies of different etiologies. Intraglomerular lipid or lipoprotein deposition was detected more frequently than previously thought in different forms of glomerulopathies [18, 19]. Interestingly, patients with apo B and apo E deposition in

their glomeruli had more severe proteinuria, greater hyper-cellularity and more advanced glomerulosclerosis [19,20]. A possible role of apo B and apo E deposition in the progression of mesangial injury has also been proposed [20]. Apo (a), the unique protein moiety of lipoprotein (a) [Lp(a)], has also been found in glomeruli from patients with different renal diseases [21]. The presence of apo (a) was associated with a higher prevalence of glomerulosclerosis, suggesting a role for apo (a) and possibly Lp(a) in glomerular damage. Recently, Samuelsson et al. [22] have reported a positive correlation between triglycerides, very low density lipoprotein cholesterol and apo B and the decline in glomerular filtration rate (GFR) as measured by radioisotopic methods in patients with moderate renal insufficiency. The strongest correlation was found for apo B levels. When elevated apo B levels were associated with hypertension there was a more rapid reduction in GFR, suggesting that both factors can act synergistically to promote the progression of renal insufficiency.

In patients with diabetes mellitus, a possible contributing role of lipids in diabetic nephropathy has also been proposed. Indeed, albuminuria was correlated in different reports with increased total cholesterol [23-26], low-density lipoprotein (LDL) cholesterol [25], apo B [24], triglycerides [25] and Lp(a) [27-30], and reduced high-density lipoprotein (HDL) cholesterol [31]. Whether these abnormalities are a cause, a consequence or an epiphenomenon of diabetic nephropathy is at present unknown. Interestingly, two recent reports from Japan described a reduction in albuminuria of diabetic patients after 2 months of therapy with pravastatin [32, 33], a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. In another uncontrolled study, Rabelink et al. [34] reported a partial remission of the nephrotic syndrome in 7 patients treated with simvastatin (another HMG-CoA reductase inhibitor) for 48 weeks. Chan et al. [35] treated 14 patients with glomerulonephritis and heavy proteinuria with increasing doses of lovastatin for 6 months. They reported an increase in GFR determined by plasma radioisotope Cr-EDTA clearance in a subset of patients at the end of 6 months of therapy. This apparent beneficial effect was restricted to patients with GFR over 70 ml/min and was not associated with any other significant changes in renal plasma flow, filtration fraction, serum creatinine, or proteinuria [35]. Other short-term studies have not found a beneficial effect of lovastatin [36-39] or simvastatin [40] on renal function in patients with proteinuria-associated hypercholesterolemia. Obviously, properly designed, prospective, randomized studies are

needed to determine if antilipemic therapy in kidney patients can have a renal protective effect.

Mechanisms of Lipid-Induced Glomerular Injury

The process of glomerulosclerosis is frequently characterized by increased mesangial cellularity and matrix accumulation leading finally to sclerotic glomeruli. The increased cellularity is probably a result of mesangial cell proliferation as well as an increased influx of circulating monocytes.

Effects of Lipoproteins on Mesangial Cell Proliferation The glomerular mesangium is separated from the capillary lumen by a fenestrated endothelium without basement membrane [41]. Thus, conditions are appropriate for a direct interaction between circulating lipoproteins and mesangial cells. Mesangial cells exhibit receptors for native and possibly modified LDL [19,42-44]. Recently, the effects of LDL in vitro on mesangial cell proliferation were shown to be biphasic. Low concentrations induced mesangial cell proliferation whereas higher concentrations resulted in mesangial cell toxicity [42-44]. In addition, the degree of mesangial cell proliferation induced by different growth factors was significantly increased in the presence of LDL [45]. At doses of LDL that induced minimal proliferation, insulin, insulin-like growth factor 1 and platelet-derived growth factor (PDGF) caused marked proliferation. Conversely, at doses of growth factors that caused minimal effects, the addition of LDL provoked marked proliferation [45]. Certain growth factors for mesangial cells (PDGF, endothelin 1) increased mesangial cell expression of LDL receptors, providing a molecular basis for a synergistic effect [44]. By this mechanism, lipoproteins may modulate the degree of glomerular mesangial proliferation in different pathophysi-ological circumstances in which local production of growth factors occurs [41, 46, 47]. Indeed, in two different human studies apo B and apo E deposition correlated with the degree of mesangial proliferation [19,20]. Finally, LDL can be oxidized by mesangial cells [48]. Oxidized LDL can, in turn, produce mesangial cell injury. In fact, LDL oxidation could be the mechanism by which high concentrations of LDL are rendered toxic to mesangial cells [48].

Interaction between Lipoproteins and Macrophages Macrophages have been shown to be important in glomerulopathies of different etiologies [49]. An early influx of macrophages into the glomerulus has also been demonstrated in early stages of different models of lipid-mediated injury [9,11]. Importantly, different maneuvers that deplete circulating monocytes, such as essential fatty acid deficient-diet or total body irradiation, have been shown to reduce the number of infiltrating macrophages and lessen glomerular

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injury [9]. The interactions between macrophages and lipo-proteins within the glomerulus are reminiscent of those described in the arterial wall in the process leading to atherosclerosis [4,14, 50]. In brief, macrophages can release reactive oxygen species and oxidize LDL. Oxidized lipo-proteins can be trapped into the mesangium more efficiently [43] and contribute again to the recruitment of monocytes directly [51] or through the induction of the synthesis of chemoattractants such as monocyte chemoat-tac-tic peptide 1 (MCP-1) or colony-stimulating factor 1 [52,53]. Recently, Magil et al. [54] have been able to detect oxidized lipoproteins within the glomerulus by using different monoclonal antibodies against oxidized LDL. Macrophages and perhaps mesangial cells can take up oxidized LDL through the

scavenger receptor and become foam cells [55]. Macrophages as well as foam cells can release growth factors and cytokines resulting in a new cycle of mesangial cell proliferation [49]. In fact, the degree of mesangial cell proliferation has been shown to correlate with the number of infiltrating macrophages [9]. Thus, increasing evidence suggests that macrophages play a central role in modulating lipid-induced mesangial injury.

Effects of Lipoproteins on Matrix Turnover Lipoproteins can also contribute to glomerulosclerosis by modulating mesangial matrix turnover. Clinical and experimental data suggest that both increased synthesis and reduced degradation contribute to matrix expansion. Recently, human glomerulosclerosis has been shown to be associated with increased collagen mRNA expression [56]. In different animal models, evidence for both increased synthesis [53, 57] and reduced degradation [58] has been found. In vitro, LDL stimulate mesangial cells to produce increased amounts of fibronectin [52] and collagen [59]. Transforming growth factor β_1 (TGF- β_1) has been proposed to play a major role in different processes characterized by matrix accumulation [60]. Interestingly, TGF- β_1 and fibronectin mRNA expression were found to be upregulated in glomeruli of cholesterol-fed nephrotic rats [57]. Infiltrating monocytes as well as mesangial cells could be the source of TGF- β_1 . We have shown that both native and oxidized LDL in vitro upregulate mesangial cell mRNA expression for TGF- β_1 [unpubl. data]. Thus, TGF- β_1 could be a major mediator of lipid-induced mesangial matrix expansion [57].

Effects of Lipoproteins on Vascular Tone

There is still another way by which lipids can contribute to renal damage. Hyperlipidemia can induce vascular dysfunction prior to the development of atherosclerosis [61, 62], and possibly contribute to increased blood pressure. Epidemiological studies have shown that patients with essential hypertension have higher serum cholesterol and triglyceride levels and lower HDL cholesterol [63, 64]. This association has been observed in both men and women and the level of blood pressure was directly associated with the level of cholesterol. One potentially contributing mechanism appears to be a deficiency in endothelium-derived vascular relaxation [65, 66]. The endothelial dysfunction can be reversed by the parenteral administration of L-arginine [67, 68], the physiological precursor of the endothelium-dependent relaxing factor nitric oxide (EDRF/NO). Indeed, a reduced plasma L-arginine concentration has been reported in hypercholesterolemic patients [69]. Chin et al. [70] have shown that oxidized lipoproteins can impair the EDRF activity. Their data are in accordance with a direct inactivation of EDRF/NO by the oxidized lipid moiety of LDL [70]. Other vasoactive compounds could be involved in the hypercholesterolemia-associated endothelial dysfunction. An increase in thromboxane A₂ [71] and endothelin [72] has been reported in hypercholesterolemic patients. Lipid-induced vascular dysfunction could thus contribute to increased glomerular pressure, resulting in glomerular damage.

Renal Protective Mechanisms of Antilipemic Agents

The most obvious beneficial effects of antilipemic agents are directly related to their ability to decrease circulating lipids. By this mechanism antilipemic drugs could attenuate lipid-induced mesangial cell proliferation and matrix accumulation. As a result of a reduced availability of substrate, the production of oxidized lipoproteins will also be diminished. Consequently, less monocytes will be recruited and the formation of foam cells and the release of growth factors and cytokines will be curtailed. Indeed, as mentioned earlier, a

number of unrelated antilipemic agents have been shown to be beneficial in different models of lipid-induced renal disease [5,14].

Besides these evident mechanisms, certain antilipemic agents also exhibit salutary effects unrelated to their lipid-lowering properties. For instance, probucol has been shown to reduce renal damage [8, 73] in spite of its rather limited ability to lower LDL cholesterol and its possible deleterious effect by decreasing HDL cholesterol. The clear benefit from probucol has been considered to be related to its antioxidant properties [74,75].

In recent years, a new group of antilipemic drugs has received considerable attention. HMG-CoA reductase inhibitors, called statins, have been shown to be potent cho-

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lesterol-lowering agents without important side effects [76]. The study of the effects of statins in different biological systems is generating important information regarding not only lipid disorders but also some important events in cell biology, particularly cell proliferation. The production of mevalonate from HMG-CoA is the rate-limiting step in the cholesterol biosynthetic pathway [77]. By inhibiting this step, statins reduce the intracellular pool of cholesterol and cause an upregulation of LDL receptors. The increased uptake of circulating lipoproteins through the LDL receptor is considered the major mechanism by which statins decrease blood lipids [76]. Interestingly, HMG-CoA inhibitors such as lovastatin have been shown to reduce glomerular injury independently of cholesterol levels [78]. It should be emphasized that cholesterol is only one among the many products of the mevalonate pathway. Mevalonate metabolism yields a series of isoprenoid compounds, such as farnesol, that are incorporated into isoprenylated proteins. It is conceivable that the biological role of these proteins can be modulated by reducing the availability of their isoprenoid moiety following HMG-CoA reductase inhibition. In fact, lovastatin has been shown to inhibit mesangial cell proliferation independent of the availability of cholesterol [79]. Thus, lovastatin may directly lessen glomerular injury by reducing mesangial cell proliferation. p21-ras proteins (the product of the oncogen ras) are involved in controlling cell proliferation and need to be farnesylated to become active [77]. It is tantalizing to speculate about the possible role of p21-ras proteins as a link between the antiproliferative effects of lovastatin and its effects on the mevalonate pathway. In this regard, we have found that lovastatin down-regulates mesangial cell mRNA for IL-6 and production of this peptide [unpubl. data], an important cytokine involved in mesangial cell proliferation. The relevance of the isoprenoid intermediates in the mevalonate pathway is underscored by the fact that many effects of lovastatin can be reversed by the addition of mevalonate or farnesol but not by cholesterol [79, 80].

Increasing experimental information is emerging concerning many other effects of HMG-CoA inhibition. For instance, lovastatin has been shown to decrease in vitro mesangial cell production of MCP-1 [81]. This effect was correlated with a parallel reduction in vivo in the number of glomerular infiltrating macrophages [Kim, unpubl. data], providing another potential way of glomerular protection. The mechanisms by which interferences in the mevalonate pathway can lead to reduced production of MCP-1 are not known.

The mevalonate pathway has also been proposed to play a connecting role between essential hypertension, diabetic

nephropathy, and lipid abnormalities. Patients with diabetic nephropathy show a lipid profile similar to patients with essential hypertension [82]. Interestingly, in both groups, an increased Na⁺/H⁺ and Na⁺/Li⁺ antiport activity has been found [82, 83]. HMG-CoA inhibitors can

reduce the increased antiport activity [83]. This effect can be reversed in vitro by mevalonate, again suggesting a possible role of isoprenoids [83]. Thus, according to Ng and Davies [83], an overstimulated mevalonate pathway could underlie the metabolic and vascular abnormalities found in essential hypertension and diabetic nephropathy and could be of critical importance for the development of vascular and renal lesions.

As mentioned above, most of the information of the beneficial effects of HMG-CoA inhibition comes from in vitro studies and from animal models. Carefully designed controlled studies are needed to define the precise role of HMG-CoA inhibitors in preventing or slowing the progression of renal disease in humans.

In summary, increasing experimental and clinical evidence suggests that lipids can be important modulators in progressive kidney disease. Experimental studies are providing meaningful information on the mechanisms of lipid-induced renal injury and mesangial cell biology. Anti-lipemic agents are emerging as potentially important drugs in modulating the progression of glomerulosclerosis. However, their precise role in treating patients with progressive kidney disease remains to be established.

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