Histol Histopathol (1998) 13: 169-179
DOI: 10.14670/HH-13.169
http://www.hh.um.es

Histology and Histopathology
From Cell Biology to Tissue Engineering

Invited Review

Hyperlipidemia and kidney disease: Concepts derived from histopathology and cell biology of the glomerulus

V.S. Kamanna, D.D. Roh and M.A. Kirschenbaum
Nephrology Section, Department of Veterans Affairs Medical Center, Long Beach, California
and the Division of Nephrology and Hypertension, Department of Medicine, University of California, Irvine, USA

Summary. The association between hyperlipidemia and renal disease was noted by Virchow as early as the 19th century. Subsequently, similar histopathological lipid depositions were confirmed in diverse human and experimental renal diseases. Although, no studies have been established in man to suggest a causal relationship between lipids and the pathogenesis of renal disease, compelling evidence accumulated in experimental animals suggests a direct role of lipids in the initiation and progression of glomerular disease. These studies showed that cholesterol-feeding to various experimental animals induced the development of glomerular injury. Furthermore, the treatment of hyperlipidemic animals with lipid lowering drugs prevented the development of glomerulosclerosis.

In this article, we will review recent advances made in understanding various aspects of lipid-mediated renal injury including biochemical mechanisms of hyperlipidemia, a possible direct role of hyperlipidemia in the pathogenesis of renal disease, pathobiological accumulation of lipids and lipoproteins, biochemical and histological similarities between systemic atherosclerosis and glomerulosclerosis, and cellular processes involved in the development of glomerular disease. Furthermore, we will define cellular and molecular hypotheses that provide putative mechanisms by which hyperlipidemia and atherogenic lipoproteins induce series of cytoregulatory peptide-mediated events involved in the development of glomerular disease.

Key words: Hypercholesterolemia, Atherogenic lipoproteins, Cytokines, Growth factors

Offprint requests to: Vaijinath S. Kamanna, Ph.D., Assistant Professor of Medicine, Director, Nephrology Research Laboratories (151), Department of Veterans Affairs Medical Center, 5901 East Seventh Street, Long Beach, CA 90822, USA

Background

Historically, the association between lipid abnormalities and the pathogenesis of renal disease was first suggested in 1860 by Virchow (1860) when he described extensive fatty metamorphosis in renal autopsy tissue obtained from patients with Bright's disease. In 1916, Munk (1936) observed similar lipid deposition within the kidney of young patients with nephrotic syndrome and coined the term *lipoid nephrosis* to highlight what appeared to be a unique association between systemic lipid abnormalities and the pathogenesis of renal disease in patients with nephrotic-range proteinuria. In subsequent years, investigators noted lipid deposition within the tubular, vascular and prominently in glomerulus of patients with diabetic nephropathy (Kimmelstiel and Wilson, 1936; Newburger and Peters, 1939). The pronounced histopathological accumulation of lipids within the glomerulus led investigators to suggest that the combination of hyperlipidemia and elevated glomerular pressure may contribute to the exaggerated mesangial expansion noted in established diabetic nephropathy (Wilens and Elster, 1951). Furthermore, the possibility of abnormalities in lipoprotein metabolism, as an important pathobiological factor in the development of renal disease was shown in patients deficient in lecithin:cholesterol acyl transferase (LCAT), an enzyme associated with the esterification of HDL-cholesterol and transfer of cholesteryl esters to LDL and VLDL (Hovig and Gjone, 1974; Ohta et al, 1986). These patients manifested multiple lipoprotein abnormalities, had an abnormal lipoprotein composition, and eventually developed renal injury with proteinuria, glomerulosclerosis, and progressive renal failure.

Although clinical interests in this area have continued for many decades, only recently have research effort been directed toward understanding the nephrotoxicity of lipids and the identification and management of hyperlipidemia in patients with renal disease (Moorhead et al., 1982; Keane et al., 1988). In this

article, we will review recent concepts emerged from histological, cellular and molecular biology of the glomerulus, in understanding the pathobiological role of lipids and atherogenic lipoproteins in the development of glomerular and tubular injury.

Association between hyperlipidemia and renal disease

The common abnormalities in lipids and lipoproteins seen in renal disease vary considerably and include type IV and IIb hyperlipidemia that manifest hypertriglyceridemia, hypercholesterolemia, increased LDL and decreased HDL levels (Dieplinger et al., 1986; Grundy, 1990; Joven et al., 1990; Appel, 1991). Increased levels of serum cholesterol and LDL are defining lipid abnormalities seen in patients with the nephrotic syndrome. Nephrotic patients also exhibit hypertriglyceridemia that develops later during their disease and is not an essential component of the syndrome. Elevated levels of serum triglycerides and triglyceride-rich VLDL, IDL, LDL particles and decreased concentrations of HDL are also seen in patients with chronic renal disease. Besides the hypertriglyceridemia in patients undergoing hemodialysis (HD) and peritoneal dialysis (PD), elevated levels of LDL are often seen in patients on PD treatment. Serum levels of other lipoproteins purported to increase the risk of atherosclerotic cardiovascular disease including lipoprotein (a) is also increased in both uremic patients receiving either HD or PD treatment (Levine and Gordon, 1994). In addition to these conventional abnormalities in lipoprotein metabolism, uremic patients exhibit varied heterogeneity in lipoprotein chemical composition and size including, the presence of an abnormal second pre-beta lipoprotein, an abnormal triglyceride-rich lipoprotein containing excess sialylated apo C-III, increased chylomicron remnant and IDL particles, heterogeneity in the distribution of LDL particles, and abnormalities in size and composition of both LDL and HDL (Gherardi et al., 1977; Hovig et al., 1978; Holdsworth et al., 1982; Joven et al., 1993). These lipoprotein abnormalities have been shown to be atherogenic in patients without renal disease and thus are likely to contribute to the high prevalence of premature atherosclerosis in uremic patients. Measurement of serum apolipoprotein levels in uremic patients revealed reduced concentrations of apo AI and AII, normal to increased levels of apo B, reduced levels of apo E, and increased concentrations of apo CII and CIII (Attman et al., 1987; Grutzmacher et al., 1988). Hyperlipidemia is also a common metabolic abnormalities seen in patients with kidney transplantation (reviewed in Manske and Kasiske, 1991). Most renal transplant patients manifest hypertriglyceridemia and hypercholesterolemia despite normal HDL levels. Atherosclerotic cardiovascular disease is a major cause of morbidity and mortality in renal transplant patients. Analogous to human renal disease, hyperlipidemia is seen in various non-immune-mediated experimental renal diseases including renal ablation, models of diabetes mellitus (e.g., streptozotocin-treated rats, obese Zucker rats, db/db mice, obese spontaneously hypertensive rats, etc), puromycin aminonucleoside- or adriamycin-induced nephrotic syndrome, Dahl salt-sensitive hypertensive rats and spontaneous or diet-induced hypercholesterolemic animals (reviewed in O'Donnell and Schmitz, 1991). In most of these experimental models, hyperlipidemia occurs in association with renal insufficiency, albuminuria, and accelerated development of glomerulosclerosis. In recent years, this clear association between hyperlipidemia and renal disease led to investigations aimed at understanding lipid-mediated renal injury including the biochemical mechanisms of hyperlipidemia, the direct role of hyperlipidemia in the initiation and progression of renal disease, the pathobiological accumulation of lipids, biochemical and histological similarities between systemic atherosclerosis and glomerulosclerosis, and the atherogenic lipoprotein-mediated activation of cellular and molecular events involved in the pathogenesis of progressive kidney disease.

Biochemical mechanisms of hyperlipidemia in renal disease

The biochemical mechanisms associated with hyperlipidemia in different forms of renal disease vary considerably and are summarized in Table 1. Many studies suggested that the generalized increased synthesis of proteins including lipoproteins in response to hypoalbuminemia and low plasma oncotic pressure may contribute to the hyperlipidemia in nephrotic syndrome (Marsh and Sparks, 1979; Appel et al., 1985). Increased hepatic cholesterol synthesis and HMG-CoA reductase activity was also noted in experimental nephrotic syndrome (Goldberg et al., 1982). Consistent with these observations, lipoprotein turnover studies revealed an overproduction of LDL particles in patients with nephrotic syndrome (Joven et al., 1990). Additional studies also noted defective LDL metabolic clearance rate through LDL receptor pathway in patients with nephrotic syndrome (Warwick et al., 1990). Abnormalities in liporegulatory enzymes (e.g., lipoprotein lipase and LCAT) may also contribute to the hyperlipidemia in nephrotic syndrome (reviewed in Appel, 1991). Furthermore, urinary losses of HDL and its apolipoproteins seen in nephrotic rats may contribute to the abnormalities in lipoprotein metabolism in these animals (Feltz and Mayerle, 1974; Saku et al., 1988). However, recent studies indicated that the rate of albumin synthesis in nephrotic patients on a low-protein diet was similar to control rates despite the plasma cholesterol and triglycerides in these patients (Kaysen et al., 1987). Increasing the rate of albumin synthesis by increasing the dietary protein did not alter the plasma lipid levels suggesting that the albumin synthesis and lipid levels were not dependent mechanisms. In contrast, these authors suggested that the urinary loss of albumin

Table 1. Proposed biochemial mechanisms of hyperlipidemia in kidney disease.

RENAL DISEASE	METABOLIC ABNORMALITIES	REFERENCES
Nephrotic syndrome	Increased apo-B containing lipoprotein and cholesterol synthesis	Appel et al., 1985; Marsh and Sparks, 1979
	Defective LDL metabolic clearance	Goldber et al., 1982; Joven et al., 1990
	Decreased LPL and LCAT enzyme activities	Appel, 1991
	Urinary loos of HDL and apo-A-I and A-II	Feltz and Mayerle, 1974; Saku et al., 1988
End stage renal disease	Decrease fractional catabolic rate of LDL	Horko et al., 1995
	Decreased LPL and LCAT enzyme activities	Appel, 1991
	Defective LDL particle for LDL receptor interaction	Gonen et al., 1985; Horkko et al., 1992
	Abnormalities in LDL receptor function and decreased receptor gene expression	Portman et al., 1992
	Decreased synthetic rates of HDL and apo A-I	Fu et al., 1990
	Serum subfraction (HD and PD) reduced ability for apo A-I synthesis by hepatocytes	Kamanna et al., 1994; Shah et al., 1996
	Serum subfraction (PD) increased ability for apo B synthesis by hepatocytes	Sha et al., 1996
Renal transplant	Prednisone-induced augmentation of insulin action and increased VLDL synthesis	Manske and Kasiske, 1991
	Cyclosporin-induced interaction with LDL and defective binding with apo B/E receptors	Manske and Kasiske, 1991; Markell and Friedman, 1989
	Cyclosporin-induced decreaed bile acid synthesis	Princen et al., 1987

or unknown liporegulatory substances, rather than hypoalbuminemia or low plasma oncotic pressure, stimulated hepatic lipogenesis.

Decreased clearance of apo B-containing lipoprotein particles is the predominant biochemical mechanism involved in hyperlipidemia of patients with uremia (Horkko et al., 1995). The fractional catabolic rate of LDL in uremic patients undergoing hemodialysis was modestly decreased when compared to control subjects, but the clearance of LDL in the CAPD patients was markedly decreased in comparison to the controls. Parallel to these studies, low levels of LPL and LCAT activities were also observed in uremic patients (reviewed in Appel, 1991). Additional studies have suggested that the LDL particles isolated from uremic patients are structurally and functionally altered in a way that its ability to interact with apo B/E receptors and its *in vivo* clearance is decreased (Gonen et al., 1985; Horkko et al., 1992). Furthermore, abnormality in LDL receptor function and decreased mRNA expression of LDL receptors was observed in lymphocytes isolated from uremic patients (Portman et al., 1992). The decreased HDL levels in uremic patients have been attributed to the decreased synthetic rates of apo AI and HDL (Fu et al., 1990). Recently, we have shown that the subfractions (mol wt, 500-2000 Da) isolated from both HD and PD patient serum decreased apo AI synthesis by human hepatocytes suggesting the pathobiologic role of uremic factors in HDL metabolism (Kamanna et al., 1994; Shah et al., 1996). Similar studies showed that the serum subfraction isolated from PD but not HD patient increased apo B synthesis by human hepatocytes implicating a putative biochemical mechanism of increased LDL and apo B in PD patients as compared with HD patients (Shah et al., 1996).

The lipid metabolism abnormalities in renal transplant patients are thought to be due to immunosuppressive medications used in these patients. In this regard, a positive correlation was noted between serum cholesterol levels and daily or cumulative prednisone concentrations used in renal transplant patients (Ibels et al., 1978; reviewed in Manske and Kasiske, 1991). Furthermore, the withdrawal of prednisone was shown to decrease serum cholesterol levels in these patients (Reisman et al., 1990). A similar elevation in serum cholesterol was observed in endogenous hypercortisolism (Cushing's syndrome) and in other disease states in which exogenous corticosteroids were used (reviewed in Manske and Kasiske, 1991). The biochemical mechanisms associated with corticosteroid-induced hyperlipidemia are multifactorial including augmentation of insulin action leading to increased hepatic synthesis of VLDL particles, stimulation of adipocyte hormone-sensitive lipase facilitating the release of stored triglycerides as free fatty acids for increased VLDL synthesis, alterations in LDL receptor function, and stimulation of insulin-mediated lipoprotein lipase leading to the increased conversion of VLDL to LDL and hypercholesterolemia (reviewed in Manske and Kasiske, 1991). Similarly, the use of cyclosporin as an immunosuppressant in renal transplant recipients, caused an increase in serum cholesterol levels independent of its suppressive effects on glomerular filtration (Harris et al., 1986; Raine et al., 1988). Parallel studies performed in non-renal patients (e.g., patients with amyotrophic lateral sclerosis or psoriasis) also showed increased serum cholesterol levels in cyclosporine treated patients as compared with controls (reviewed in Manske and Kasiske, 1991). The mechanism associated with cyclosporine-induced hypercholesterolemia has been attributed to its ability to bind to LDL leading to a defective interaction with LDL receptors (Markell and Friedman, 1989; Manske and Kasiske, 1991). Cyclosporine was shown to inhibit 26-hydroxylase, an

enzyme in bile acid synthesis, thus leading to reduced excretion of cholesterol in bile and systemic hypercholesterolemia (Princen et al., 1987).

Management of hyperlipidemia of kidney disease

The growing acceptance that hyperlipidemia is one of the major risk factors for atherosclerotic cardiovascular disease has launched increased interest in the identification and management of abnormalities in plasma lipids and lipoproteins in patients with kidney disease. Various lipid lowering agents (e.g., bile acid sequestrants, nicotinic acid, HMG-CoA reductase inhibitors, fibric acids, probucol) have been used to manage abnormalities in lipid and lipoprotein metabolism in patients with diverse renal disease (Grundy, 1990). However, few clinical trials have compared their relative efficacy in renal insufficiency, nephrotic syndrome, patients on HD or PD treatment, and in renal transplantation. Recent comparative studies by meta-analysis indicated that specific antilipidemic therapies generally had similar effects in different renal diseases when compared with hyperlipidemic patients without renal disease (Massy et al., 1995). For example, HMG-CoA reductase inhibitors resulted in a comparable reduction of LDL-cholesterol in patients with nephrotic syndrome, renal transplantation, renal insufficiency, and those undergoing dialytic therapy. Parallel to the general population, fibric acid analogues had less of an effect on lowering LDL-cholesterol, but caused greater reductions in triglycerides in many forms of kidney disease. Although these studies evaluated the efficacy of hypolipidemic agents and provided beneficial effects on lowering plasma lipid levels that may lower the risk for atherosclerotic coronary events in ESRD patients, none of these studies examined the long-term benefits of treatment on the progression of either renal disease or atherosclerotic cardiovascular disease in these patients. Considering these observations, long-term clinical studies addressing the role of hypolipidemic agents in reducing clinical manifestation of both glomerular injury and coronary events may provide fundamental clues in the treatment of ESRD patients based, in part, on their lipid and lipoprotein profile.

Histopathological evidence of lipids and lipoproteins in renal disease

Although systemic lipid and lipoprotein abnormalities in renal disease have been examined extensively, only recently have studies evaluated the evidence of lipid and lipoprotein glomerulopathy in human biopsy specimens as a histologic end points to support lipid-mediated renal injury. Examination of renal biopsy specimens revealed that many human biopsy specimens contained lipoprotein glomerulopathy (Avram, 1989). The author strongly stated that - *should other renal centers search, they will also find lipids in their own biopsy material*. For example, renal biopsy specimens from a patient with idiopathic focal glomerulosclerosis and mild renal insufficiency exhibiting massive proteinuria and hypoalbuminemia revealed abundant lipid vacuoles surrounded by mesangial sclerosis and monocytic debris of focal and segmental glomerulosclerosis. Additionally, renal biopsy specimens from a diabetic patient with azotemia also manifested lipid deposition with a sclerotic glomerulus and extensive hyalinosis. Mesangial hypercellularity was also common histological finding in these patients. Furthermore, many other human renal biopsy specimens from patients with heroin nephropathy, idiopathic proteinuria, focal sclerosis, nephrotic syndrome, diabetic nephropathy, chronic glomerulopathies, transplant nephropathy, familial lecithin cholesterol acyltransferase deficiency, hepatorenal syndrome, etc also showed significant lipid deposits in various phases of renal disease (Avram, 1989). Lee and colleagues (1991) examined the evidence of lipids and apo B accumulation in renal biopsy materials from 631 patients with diverse renal diseases. Although only 8.4% of total patient population showed ultrastructurally detectable lipid deposits, many patients showed lipid deposition in glomerular lesions of patients with focal segmental glomerulosclerosis (20%), membranoproliferative glomerulonephritis (33%), diffuse sclerosing glomerulonephritis (27%), and hemolytic uremic syndrome (33%). Indirect immunofluorescence staining revealed glomerular apo B deposition in considerably high percentage of patients with minimal lesions (33%), focal segmental glomerulosclerosis (17%), membranous nephropathy (60%), membranoproliferative glomerulonephritis (62%), IgA nephropathy (16%), and hereditary nephrosis (50%). The distribution of lipids and apo B was either diffuse or in focal and segmental patterns. Consistent with these findings, Sato et al. (1991) demonstrated the deposition of apo B in 14 of 35 patients with primary glomerular disease and 8 of 13 patients with secondary glomerular disease. Apo E was detected in approximately 50% of both primary and secondary glomerular diseases. Furthermore, these authors have shown that patients with glomerular deposition of apo B exhibited severe proteinuria and patients with apo E deposition showed higher incidences of glomerular adhesion and interstitial changes when compared with controls. The patient group with the glomerular deposition of both apo B and apo E exhibited more severe mesangial hypercellularity, higher incidences of interstitial changes and glomerular sclerosis. Apo B or E was not detected in control renal biopsy specimens from non-tumorous tissue of renal cell carcinoma patients (Sato et al., 1991).

Beside these human studies, there is a wealth of histopathologic data supporting the glomerular deposition of lipids in various experimental models of renal disease including, puromycin aminonucleoside or adriamycin-induced nephrotic syndrome, renal ablation, endogenous hyperlipidemia in Zucker obese rats, and dietary lipid-induced glomerular disease (French et al.,

1967; Kasiske et al., 1985; Grond et al., 1986; Al-Shebeb et al., 1988; Keane et al., 1988; Groene et al., 1989; Van Goor et al., 1991; Kamanna and Kirschenbaum, 1993). Based on these histopathological observations in human and experimental renal disease, several investigators speculated that certain histologic features accompany focal segmental glomerulosclerosis including glomerular accumulation of proteins, the exaggerated presence of lipids (e.g., cholesterol and cholesterol esters), and the presence of macrophages that strikingly resemble the lesions of systemic atherosclerosis.

Biochemical and histopathological similarities between atherosclerosis and glomerulosclerosis

Recognizing the pathobiological importance of lipids and atherogenic lipoproteins in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD) and since abnormalities in lipids and lipoproteins are often seen in patients with both atherosclerosis and kidney disease, a general consensus has developed among investigators linking these two diseases dependent, in part, on disturbances in lipoprotein metabolism (Moorhead et al., 1982; Kamanna et al., 1993). Additionally, recognizing that the kidney is perfused by a significant portion of the cardiac output, it has been speculated that similar lipid-induced vascular events as seen in larger vessels may participate in diseases of the glomerular microvasculature. Studies in experimental animals and man strongly suggest that many biochemical and histological features that accompany glomerulosclerosis are similar to those observed in the systemic vascular lesions of atherosclerosis (Grond et al., 1986; Avram, 1989). The common cellular events observed in these two disease processes include: (a) the deposition of lipids, LDL, and oxidatively-modified LDL in both atherosclerotic plaques and glomerulosclerotic lesions, (b) the influx of monocytes into the artery in atherosclerosis and into the glomerulus in glomerulosclerosis, (c) the formation and accumulation of lipid-laden foam cells in both lesions, (d) the proliferation of smooth muscle cells in atherosclerosis and mesangial cells in glomerulosclerosis; and (e) the expansion of the extracellular matrix (Diamond, 1991; Kamanna et al., 1993). Thus, glomerulosclerosis can be classified as an extension of the atherosclerotic process into the glomerular capillary and is characterized by an accumulation of lipid-rich foam-like cells within the mesangium and the exaggerated expansion of the mesangial matrix resulting in the disturbances in the structural and functional integrity of the glomerulus.

Role of hyperlipidemia in the progression of glomerular disease

Despite the common association between hyperlipidemia and renal disease seen in end-stage renal disease (ESRD) patients and experimental models of renal disease, the major link between hyperlipidemia and glomerular disease is predominately derived from experimental animal models of atherosclerosis. Cholesterol-feeding to experimental animals, an intervention used to induce accelerated atherosclerosis in herbivores, has been shown to provoke the development of glomerular injury (French et al., 1967; Diamond and Karnovsky, 1987; Al-Shebeb et al., 1988; Groene et al., 1989). Additionally, in the obese Zucker rat, a genetic variant that exhibits endogenous hyperlipidemia, proteinuria, mesangial expansion and subsequent glomerulosclerosis develop sequentially (Kasiske et al., 1985; Kamanna and Kirschenbaum, 1993). Furthermore, the treatment of hyperlipidemic animals with specific lipid-lowering drugs or by modifying their dietary lipid intake prevented or reversed the development of both glomerulosclerosis and atherosclerosis (Kasiske et al., 1988a,b). Similar relationships between hyperlipidemia and kidney disease have not been defined in humans. Furthermore, the Watanabe heritable hyperlipidemic rabbit, a LDL-receptor deficient model of atherosclerosis, develops massive atherosclerotic lesions but not renal lesions (Goldstein et al., 1983; Raij et al., 1988). As noted above, feeding a cholesterol-rich diet to normal rabbits and various animal species can markedly result in the development of renal lesions. It appears that the structural and functional alterations in atherogenic lipoproteins rather than mere hyperlipidemia may determine nephrotoxicity of lipids and lipoproteins.

Cellular and molecular events involved in the pathogenesis of glomerular disease

The enhanced accumulation of circulating monocytes within the mesangium, proliferation of intrinsic glomerular cells, and the exaggerated deposition of mesangial extracellular matrix proteins (ECM) are characteristic cellular pathobiologic features involved in the development of diverse forms of renal disease. The enhanced migration and accumulation of circulating monocytes within the mesangium in response to the injury or activation of the glomerulus are predominant cellular processes seen early in and before any histological glomerular abnormalities. The accumulation of monocytes and their transformation into tissue macrophages has been described in both immunologic- and nonimmunologic-mediated glomerular injury in humans and various experimental models of renal disease (Schreiner et al., 1978; Magill and Cohen, 1989; Saito and Atkins, 1990).

Thus, the adhesion of circulating monocytes to the glomerular capillary endothelium and their subsequent transmigration into the mesangium, appear to be prerequisite early histopathological events in the initiation of glomerular injury. Based on recent studies, this process can be divided in two phases, a) adhesion of the leukocytes to the endothelium of the capillary wall, and b) entry of the leukocytes into the vessel wall. Evidence from several laboratories primarily derived

from *in vitro* studies suggest that the adhesive phase of this process is mediated by the coordinated interactions of four classes of adhesion molecules that include selectins (e.g., p-selectin, E-selectin, L-selectin), carbohydrate-containing selectin ligands, integrins, and immunoglobulin-like molecules (Arnaout, 1990; Pober and Cotran, 1990; Springer, 1990; Baccarini and Stanley, 1991; Bevilacqua et al., 1993; Briscoe and Cotran, 1993; Brady, 1994). In response to capillary endothelial activation, the upregulation of specific selectin molecules triggers the initial attachment of phagocytes to the endothelium through the interaction of selectins with cognate carbohydrate-containing ligands. Although selectin-induced adhesion is relatively resistant to shear stress of the vascular bed, this cellular process is not sufficient to immobilize phagocytes onto the endothelium. Whereas, selectin-mediated slowing of the motion of phagocytes causes them to roll onto the endothelium establishing a closer cell-to-cell contact. Subsequently, both endothelium and phagocytes are subject to the local activation signals from vascular intrinsic cells and extravascular tissue (e.g., glomerulus) leading to the expression of new surface integrin molecules on phagocytes and immunoglobulin-like molecules (adhesion molecules) on the endothelium. The receptor-mediated interaction of phagocyte integrins with adhesion molecules on endothelium has been thought to immobilize finally and firmly attach phagocytes to the endothelium. Very late activation antigen-4 (VLA-4) and the CD11/CD18 are major integrins associated with leukocyte-endothelial adhesion. VLA-4 and CD11/CD18 are ligands for endothelial vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2) and are shown to play an important pathobiologic role in monocyte recruitment involved in vascular and glomerular disease.

Although cellular and molecular mechanisms involved in the next phase of endothelial transmigration of phagocytes are not clearly understood, monocyte chemoattractant peptides appear to lead the way in facilitating the diapedesis of mononuclear cells into the mesangium. Cytoregulatory peptides, including macrophage-colony stimulating factor (M-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), and human monocyte chemotactic protein-1 (MCP-1) or JE, the murine homologue of human MCP-1 (JE/MCP-1), are major soluble gene products that induce monocyte chemoattraction, differentiation and proliferation (Rollins et al., 1989; Cushing and Fogelman, 1992). JE/MCP-1 seems to be a relatively specific chemoattractant for monocytes and accounts for most of the monocyte chemotactic activity secreted by vascular cell.

Beside monocyte infiltration, mesangial cell proliferation and accumulation of ECM proteins are characteristic features of progressive glomerulosclerosis. Glomerular mesangial cell proliferation has been shown to be a critical histopathological finding seen in various human renal diseases and experimental models of glomerular injury (Striker et al., 1991; Floege et al., 1993). Platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and other cellular mitogenic factors have been proposed to play a major role in mesangial cell hypercellularity noted in some glomerular diseases (reviewed in Abboud, 1995). Transforming growth factor-ß (TGF-ß), in an autocrine or paracrine fashion, appears to be implicated in the enhanced expression of mesangial matrix. TGF-ß has been shown to regulate various aspects of ECM metabolism including increased ECM synthesis and to inhibit matrix degradation (reviewed in Border and Ruoslatti, 1992).

Although, these pathobiological processes are universally seen in the pathogenesis of glomerular disease, the endogenous factors that initiate the cascade of cellular and molecular events involved in the development of glomerular disease are not clearly understood. Based on many *in vivo* and *in vitro* studies, it has been proposed that the activation of glomerular capillary wall and intrinsic glomerular cells, in response to proinflammatory cytokines (e.g., TNF-α IL-1, etc.) can serve as a critical signaling molecule for the initiation and progression of monocyte infiltration into the mesangium and the pathogenesis of tissue inflammation and injury and are extensively reviewed elsewhere (Vilcek and Lee, 1991; Egido et al., 1993; Kamanna et al., 1996; Pai et al., 1996a,b). However, in this review, we define the cellular and molecular hypotheses that provide a putative mechanism(s) by which hyperlipidemia and atherogenic lipoproteins induce series of cellular processes involved in glomerular disease.

Glomerular cell activation in response to atherogenic lipoproteins

Recent concepts emerged from *response-to-injury and response-to-cellular activation hypotheses* to understand vascular disease provided valuable clues to delineate the pathobiologic role of atherogenic lipoproteins in the pathogenesis of atherosclerosis (Ross et al., 1977; Pober, 1988). Based on various *in vitro* and *in vivo* studies, atherogenic lipoproteins, specifically, oxidatively-modified LDL have been shown to induce vascular cell activation leading to cytoregulatory peptide-mediated vascular injury. Recognizing the vascular organization of the glomerulus, we and others have proposed that atherogenic lipoproteins may participate in cellular pathobiologic events of the glomerular microvasculature similar to those seen in larger blood vessels. Parallel to atherosclerotic lesions, increased monocyte accumulation in many glomerular diseases (Magil and Cohen, 1989) is associated with enhanced glomerular expression of adhesion molecules (e.g., ICAM-1, VCAM-1, etc), MCP-1 and M-CSF (Bloom et al., 1993; Rovin et al., 1994; Tang et al., 1994). Thus, the initiation of glomerular disease appears to be dependent, at least in part, on the transformation of

Table 2. Glomerular responses to activation by atherogenic lipoproteins.

ACTIVATION STIMULUS	CELLULAR LOCALIZATION AND GENE EXPRESSION	PATHOBIOLOGICAL CONSEQUENCE	REFERENCES
Kidney disease associated with hyperlipidemia	Increased glomerular/tubular epression of ICAM-1, VCAM-1, MCSF, MCP-1, PDGF	Monocyte accumulation within the mesangium	Bloom et al., 1993; Rovin et al., 1994; Tang et al., 1994
In vitro ox-LDL and its components	Endothelial cell ICAM-1 expression	Monocyte adhesion to endothelial cells	Ha et al., 1995a,b
In vitro LDL and ox-LDL/mm-LDL	Mesangial cell expression of MCP-1 and M-CSF	Monocyte chemoattraction, infiltration and proliferation	Rovin and Tan, 1993; Pai et al., 1995; Kamanna et al., 1996
In vitro LDL, mm-LDL, ox-LDL	Mesangial cell PDGF and ECM protein expression	Mesangial cell proliferation and matrix expansion	Roh et al., 1994 Ha et al., 1995

glomerulus from a normal homeostatic state to an activated state characterized by quantitative changes in the expression of specific gene products (e.g., cytokines, growth factors, etc.) that in turn empower the glomerulus to perform new pathobiological functions (Table 2). Although the elaborated glomerular expression of adhesion molecules and monocyte chemoattractant peptides has been implicated in the pathogenesis of renal injury, the endogenous factors that regulate the synthesis and release of these molecules into the mesangium and modulate monocyte recruitment and growth are not fully understood.

The possibility that atherogenic lipoproteins, by activating intrinsic glomerular cells, may induce a series of cellular events associated with glomerular disease (Kamanna et al., 1993; Kirschenbaum et al., 1996) becomes even more relevant since the blood within the glomerular capillary is separated from the mesangium merely by a fenestrated endothelium without intervening basement membrane thus providing a conducive interactive tissue site for atherogenic lipoproteins and glomerular cells. To address this question, we have performed a series of studies examining the role of atherogenic lipoproteins (e.g., native LDL; oxidatively modified-LDL, ox-LDL; and minimally modified-LDL, mm-LDL) in the transformation of glomerular cells from a normal to an activated state to synthesize various new proinflammatory molecules involved in renovascular disease using glomerular endothelial and mesangial cells as an *in vitro* model system. The incubation of glomerular endothelial cells with either ox-LDL or lysophosphatidylcholine, a major component of ox-LDL, but not of native LDL, stimulated monocyte adhesion and endothelial cell expression of ICAM-1 (Ha et al., 1995a). Co-incubation of cells with neutralizing antibodies for ICAM-1 or VCAM-1 inhibited ox-LDL-mediated increases in monocyte adhesion suggesting the involvement of ICAM-1 and VCAM-1 in lipoprotein-mediated cellular responses (Ha et al., 1995b).

As noted in the cellular and molecular mechanism sections of this review, the signals generated at the interface of endothelium-monocyte or within the mesangium, through the synthesis of soluble monocyte chemoattractant peptides, may play a critical role in the attraction of circulating monocyte to the endothelium and their subsequent transendothelial migration. Additional studies were designed to examine whether atherogenic lipoproteins modulate the synthetic properties of glomerular mesangial cells to produce MCP-1 and M-CSF, specific cytoregulatory peptides implicated in monocyte chemoattraction, differentiation and proliferation within the glomerulus. These studies indicated that the activation of glomerular mesangial cells with either native, ox-LDL or mm-LDL markedly increased the expression of M-CSF and MCP-1 (Rovin and Tan, 1993; Pai et al., 1995; Kamanna et al., 1996). The media obtained from mesangial cells pretreated with lipoproteins enhanced the growth of bone marrow progenitor colonies and induced monocyte chemotaxis suggesting that the secretory products are biologically active in stimulating cellular responses. These cellular responses could be attenuated by the addition of either anti-M-CSF or MCP-1 respectively showing the involvement of M-CSF and MCP-1 in lipoprotein-mediated cellular events. Furthermore, the conditioned media obtained from lipoprotein-activated mesangial cells increased monocyte DNA synthesis that could be attenuated by the addition of anti-M-CSF. Although ox-LDL had a several fold greater activity, native LDL also induced significant mesangial cell M-CSF and MCP-1 and monocyte chemotaxis and proliferation. Comparative vascular and glomerular responses by lipoproteins indicated that the oxidatively modified LDL exhibited similar effects in their ability to alter vascular and glomerular cell MCP-1 and M-CSF expression. However, native LDL had significant stimulatory effects only in glomerular mesangial cells but not in aortic endothelial and smooth muscle cells.

Additional studies were performed to examine the effect of atherogenic lipoproteins on glomerular mesangial cell proliferation and extracellular matrix production. The activation of glomerular mesangial cells with mm-LDL stimulated PDGF expression and facilitated mesangial cell proliferation (Ha et al., 1995a,b). Furthermore, stimulation of mesangial cells with atherogenic lipoproteins resulted in an increased expression of mesangial cell extracellular matrix proteins (Roh et al., 1994). The effect of oxidatively-modified LDL (e.g., ox-LDL or mm-LDL) was more pronounced in modulating cellular events than native

LDL. Thus, these studies showed that the activation of glomerular endothelial and mesangial cells in response to atherogenic lipoproteins stimulated a series of cellular and molecular events associated with monocyte infiltration, mesangial cell proliferation and elaborated extracellular matrix expansion, characteristic histological features of many glomerular diseases (Table 2).

Proposed model illustrating the pathobiological role of atherogenic lipoproteins and cytoregulatory peptides in glomerular injury

Based on the data from our studies and those of others, we constructed a workable paradigm that integrated atherogenic lipoproteins and the cellular and molecular pathobiological events that induce monocyte chemoattraction, migration, and proliferation, mesangial cell proliferation, and mesangial matrix accumulation (Fig. 1). In this model, we have proposed that activation of the glomerular endothelial and mesangial cells in response to atherogenic lipoproteins (e.g., LDL and its oxidized forms) may lead to an elaboration of adhesion molecules and monocyte chemoattractants (e.g., ICAM-1, M-CSF and MCP-1) that can initiate the pathological infiltration of circulating monocytes into the mesangium. Lipoprotein- or cytokine-mediated activation or injury may structurally alter the glomerular capillary endothelium allowing for the leakage of lipoproteins and other macromolecules and the diapedesis of monocytes into the mesangium similar to that proposed in atherosclerosis. The LDL entering the mesangial space may be subjected to oxidative modification by the influence of lipid oxidative products produced by platelets, PMN, monocytes, or injured or activated intrinsic glomerular cells. Oxidatively modified LDL, by its enhanced atherogenic vascular activity, transforms phenotypically quiescent endothelium and mesangial cells to an activated synthetic state to produce enhanced expression of cytokines (e.g., endothelial adhesion molecules and mesangial monocyte chemoattractant peptides) involved in the eárly stages of glomerular injury. Oxidatively-modified LDL also enhances the transformation of macrophages into lipid-rich foam-like cells commonly seen in glomerulosclerotic and other renal lesions.

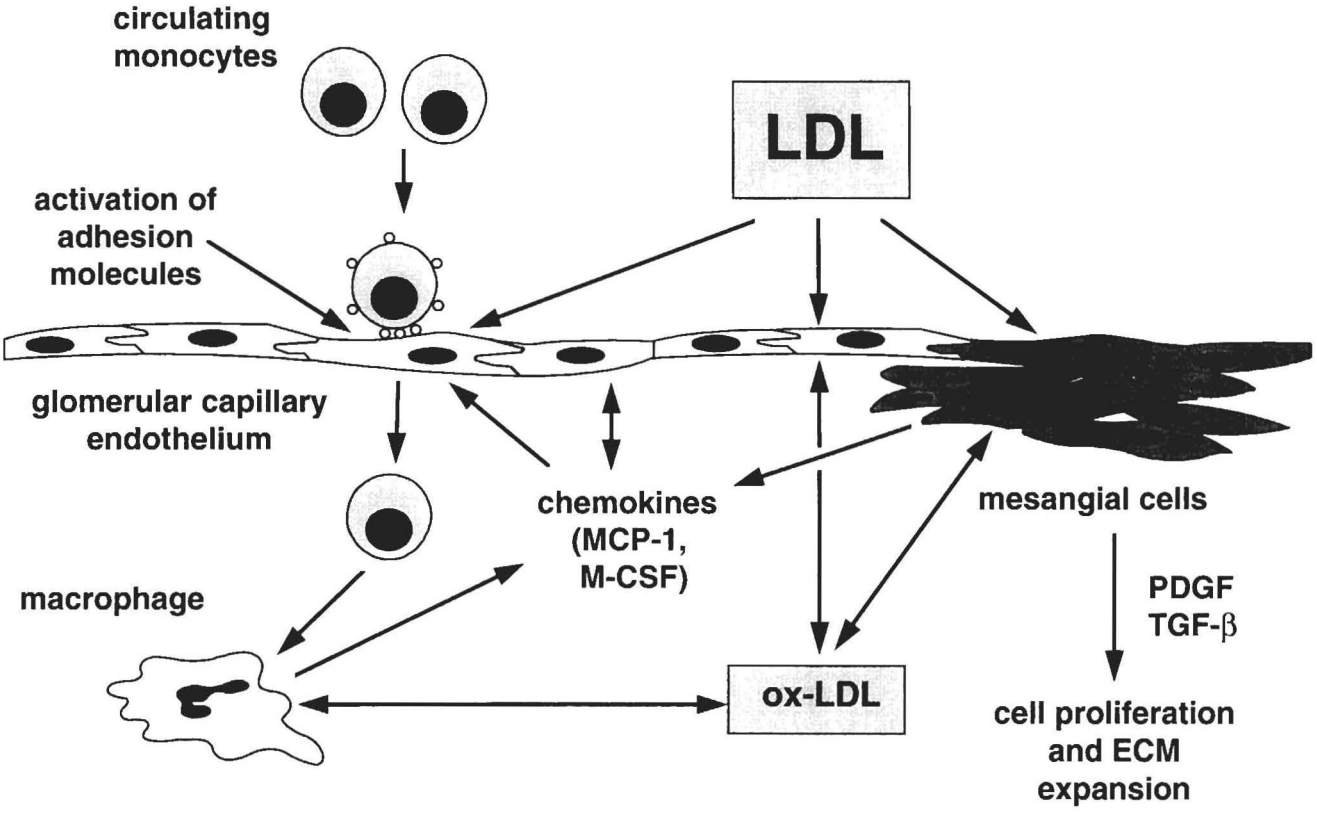

Fig. 1. Proposed model illustrating the pathobiological role of atherogenic lipoproteins and cytoregulatory peptides in glomerular injury. In response to glomerular capillary endothelial cell and mesangial cell activation by atherogenic lipoproteins, mononuclear cells are attracted, adhere, and transmigrate into the mesangium. This process is mediated by the pathological expression of adhesion molecules and monocyte chemoattractant peptides. Atherogenic lipoproteins infiltered into the mesangium may undergo oxidative transformation further facilitating the activation of glomerular cells and the generation of lipid-laden foam-like cells. The early pathobiological events may lead to the enhanced expression of proinflammatory cytokines and growth factors that may result in mesangial cell proliferation, increased production of extracellular matrix proteins, and progressive glomerular injury.

Atherogenic lipoproteins infiltered into the mesangium can interact with resident cells and stimulate the secretion of growth factors and cytokines (e.g., PDGF, TGF-ß, etc) involved in glomerular hyper-cellularity and exaggerated expression of matrix proteins. In this paradigm, atherogenic lipoproteins-mediated cellular expression of adhesion molecules, and chemoattractant peptides appear to have a prominent role in cell-to-cell communication leading to the activation of intrinsic glomerular cells and subsequent pathobiological events associated with renovascular injury. However, additional studies will be needed to confirm these interactions in *in vivo* systems so that they may act as the basis of new and novel treatment strategies to prevent cytokine- mediated glomerular and tubulointerstitial renal disease.

Acknowledgements. This work was supported by a Merit Review from the Department of Veterans Affairs, Baxter Healthcare Corporation, and an Institutional Fellowship from the National Kidney Foundation of Southern California. The authors wish to thank postdoctoral fellows/ visiting scientists, particularly, Drs. Rama Pai, Hunjoo Ha, Babu Bassa, and Zuo-Lun Lin for their significant contributions in various projects.

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