REVIEW

Biology of Progression of Chronic Renal Diseases

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Abstract

A clinically important characteristic of chronic renal disease, regardless of the underlying cause, is its frequently relentless progression to end-stage renal failure. Functional deterioration is often inevitable even after the initial pathological mechanism has apparently subsided. The possibility has therefore been raised for some time that, after a certain degree of renal damage by the initial disease processes, a common pathway leads to the final progressive functional and structural deterioration. Intensive clinical and experimental animal studies, both in vivo and in vitro, carried out during the last decade have identified several potentially important pathophysiologic mechanisms contributing to this progressive destruction of renal architecture. In this article we will review these recent findings and outline the current directions of research in this field.

Key words: chronic renal failure, glomerular filtration, glomerular sclerosis, glomerular mesangium, uremia

The discovery of a scientific explanation and the achievement of effective therapeutic measures to forestall the progressive nature of chronic renal diseases have long been the major issues in nephrology. It has been speculated for some time that the relentless nature of renal deterioration may be due to the failure of a complete elimination of an initial pathogenic insult, which then persists and is not readily unmasked by an available diagnostic procedure. Alternatively, the remarkably similar histological patterns found in the end stage kidneys, resulting from a variety of diseases, suggest the
possibility that many different primary disease states may trigger a common destructive process in nephrons, thereby bringing about relentless functional deterioration. Such a process may involve all nephrons from the start of the disease, triggered directly by the various initial insults, or more indirectly, changes in the internal milieu which alter normal cell function and lead to proliferation, scarring and eventual nephron destruction. Recent studies in animal models of glomerular sclerosis have shown that experimental enhancement and attenuation of hyperlipidemia, which is commonly seen in

Fig. 1 A hypothesis for the pathophysiologic mechanism involved in the progressive destruction of glomerular structure in chronic renal failure. This current and most popular hypothesis stems from the assumptions that 1) a series of maladaptive processes of which the failing kidney is triggered by a loss of selected functioning nephrons as a result of initial pathologic insults; 2) this loss leads to an alteration in function, such as an elevation in filtration rate in the remaining intact nephrons; 3) which is self-inflicted in nature and causes further reduction in the functioning nephron population.
chronic renal failure, led to acceleration and retardation, respectively, of glomerular structural damage. Alternatively, destructive processes may not involve all nephrons from the start. Based on the marked functional internephron heterogeneity seen in many end-stage kidneys of humans and animals, a hypothesis has recently been formulated: the hypothesis (Fig. 1) states that various initial insults may cause loss of a selected population of functioning nephrons, which leads to functional alterations such as an increase in glomerular filtration and pressure in remnant "intact" nephrons. The theory further states that these alterations are self-destructive in nature and induce deterioration in the structure and function of these remnant nephrons, leading to further reduction in the functioning nephron population. Subtotal nephrectomy (or the remnant nephron model), which simulates experimentally this hypothetical reduction in nephron population, leads to destruction of remnant glomeruli in a manner closely resembling end-stage kidneys histologically. Alterations in function in the remnant kidneys, are noted soon after nephrectomy, including an increase in glomerular filtration rate, glomerular pressure and other functions. Since certain experimental maneuvers, such as dietary manipulation of protein intake, have been shown to modify the magnitude of the early functional changes and the degree of later structural changes, it has been proposed that increased glomerular perfusion and elevation of glomerular capillary pressure are at least in part responsible for the subsequent structural damage.

In recent micropuncture studies attempts were made to address the following key issues relating to the pathophysiology of progressive renal injury. 1) Is the "hyperfunction of remnant glomeruli" a phenomenon common to, and a cause of all types of progressive renal failure? 2) Are the effects of several maneuvers, proven to modulate the degree of glomerular structural damage in animal models of chronic renal failure, channeled through their effect on glomerular hemodynamics? The studies obtained evidence indicating that other mechanism(s) are also involved in the development of glomerular sclerosis and progressive renal failure, independent of changes in glomerular hemodynamics. Thus, following administration of puromycin aminonucleoside (PAN) or adriamycin, glomerular filtration and pressure progressively declined while glomerular sclerosis developed in the same nephrons. In the PAN model, administration of an angiotensin 1 converting enzyme inhibitor, which ameliorates almost completely both glomerular hyperfunction and subsequent sclerosis in the remnant kidney, attenuated the development of focal glomerular sclerosis in the PAN model without affecting the early glomerular functional pattern. These findings point to an important notion, i.e., early hemodynamic changes and later structural damage, does not prove a causal linkage between the two. In a separate set of experiments in subtotal nephrectomy, the degree of glomerular sclerosis was assessed at the completion of each experiment and was compared with single nephron GFR (SNGFR) and glomerular capillary pressure (P_{gc}) values obtained earlier at several time intervals in the
same glomeruli. We found no correlation between glomerular sclerosis vs SNGFR or PGE. In some nephrons high glomerular pressure abated before structural damage became discernible. These observations urge us to investigate pathophysiologic mechanisms other than, or in addition to, glomerular hyperfunction, which produce structural damage and chronic renal failure.

Several other processes have been suggested to be involved in progressive destruction of glomeruli (Fig. 2). A relationship has been shown to exist between the amount of macromolecules taken up by mesangium in the early stage of disease and subsequent development of glomerular sclerosis in animals treated with PAN. Colloidal carbon (CC), a representative marker for macromolecules, was injected 4 weeks after the start of the PAN injections when sclerotic lesions had not yet developed. When these rats were examined at 5 months, glomeruli of PAN rats contained significantly more CC than did the glomeruli of the controls. Moreover, glomeruli with sclerosis in the PAN rats contained significantly more CC than non-sclerotic glomeruli in the same kidneys. The abundance of mesangial uptake of macromolecules was speculated to be an early sign of the subsequent development of glomerular sclerosis. Of interest, a specific angiotensin inhibitor was shown to suppress the accumulation of mesangial macromolecules in Pan-treated rats, raising the possibility that the effect of angiotensin inhibition to protect glomeruli from the development of sclerosis may be channeled through a direct effect on the access of macromolecules to the mesangium or through an increased mesangial response to the influx of macromolecules. This notion was further supported by the observation that angiotensin II given exogenously augmented mesangial deposition of ferritin. Increased mesangial uptake of macromolecules is also shown in glomerular sclerosis which develops after renal ablation.

When the barrier function of the glomerular capillary wall is intact, only small amounts of macromolecules pass across the capillary wall into the urinary space. Many of the factors influencing the mesangial kinetics of macromolecules were shown to affect the glomerular capillary sieving function in normal and proteinuric states. However, with regard to the barrier for glomerular capillary sieving and for access to the mesangium, there is a distinct difference, i.e., the existence of glomerular basement membrane (GBM). The GBM, which functions as the major size and charge selective barrier of the glomerular capillary wall, is not interposed between the endothelium and the mesangium, while, it is between the endothelium and the urinary space. Thus, it is conceivable that changes in glomerular sieving function and access of macromolecules to the mesangium could result from different mechanisms. A recent study showed that intravenous administration of a competitive inhibitor of angiotensin II resulted in diminution of mesangial deposition of tracer macromolecules without resulting in an alteration in the urine protein excretion in PAN treated rats. These studies raised the possibility that the factors modulating the glomerular sieving function and mesangial
accumulation of macromolecules are somewhat different. Whether changes in accumulation of macromolecules is due to altered mesangial processing, however, remains unknown.

In addition to alterations in glomerular circulatory dynamics and accumulation of macromolecules within the mesangium, alterations of glomerular epithelial cells are known to precede glomerular sclerosis. In many human and animal forms of glomerular injury effacement of visceral epithelial cells precedes major histological changes in the GBM and mesangium, and is closely associated with a loss of fixed anionic charge. Such early epithelial changes were also noted in a genetic rat model which developed extensive glomerular sclerosis.\textsuperscript{28} Of note, a histochemical study demonstrated\textsuperscript{18} a direct relationship between the degree of glomerular sclerosis and the extent of loss of glomerular polyanions, and moreover, within a given glomerulus, areas of sclerosis corresponded to areas devoid of polyanions. Claufield and Farquhar observed a progressive loss of fixed negative charges from both epithelial cell layer and GBM.\textsuperscript{29} Loss of glomerular anionic charge is also seen in association with gross histological changes soon after subtotal nephrectomy.\textsuperscript{12,22}

The importance of epithelial cell injury is supported by in vitro observations, also. Although the currently available data are conflicting,\textsuperscript{30} some investigators demonstrated in vitro and in vitro that PAN causes a marked loss of heparan sulfate proteoglycan\textsuperscript{31-33} and a defect in glycosylation of podocalyxin, a sialoglycoprotein.\textsuperscript{32} Moreover, studies in glomerular epithelial cells cultured in vitro demonstrated that PAN, added to the cultured medium, altered the morphology, including the localization of anionic sites and the metabolism of epithelial cells.\textsuperscript{34} When heparin was added to a culture medium of glomerular mesangial cells, a marked inhibition of mesangial cell growth was observed.\textsuperscript{35} Moreover, it was noted that a conditioned medium from glomerular epithelial cell cultures contained a heparin-like substance capable of inhibiting mesangial cell growth.\textsuperscript{35} It has therefore been speculated that epithelial cell injury, via alteration of its capacity to regulate mesangial function, may underlie the development of major changes in mesangial structure. A variety of heparin species have been shown to attenuate the development of glomerular sclerosis in experimental models, including subtotal nephrectomy.\textsuperscript{36,37} Epithelial cell injury may occur as a result of abnormal lipid metabolism present in human and animal forms of chronic renal failure. An avid lipoprotein transport system present in glomerular epithelial cells\textsuperscript{38} may contribute to their own injury. The injurious effect of lipids on the glomerulus has recently been demonstrated in rat models of glomerular sclerosis.\textsuperscript{2,3}

Intraglomerular coagulation is another factor considered to be involved in the development of glomerular sclerosis. Aggregation of platelets, as a result of glomerular capillary endothelial injury or in response to substances locally released from invading or resident cells,\textsuperscript{39} may cause release of platelet products such as the platelet
OUTLINE OF SEQUENCE INVOLVED IN GLOMERULAR SCLEROSIS

Initial Events
- Glomerular Hyperfiltration / Hypertension
- Enhanced Intraglomerular Coagulation
- Epithelial Cell Damage
- Accumulation of Macromolecules in Mesangium
- Others

Secondary Events
- Altered Release of Mitogens and/or Anti-mitogens
- Altered Mesangial Environment for Matrix Metabolism

Tertiary Events
- Mesangial Proliferation
- Altered Mesangial Matrix Metabolism

Final Outcome
- Increased Mesangial Matrix (Intrinsic & Extrinsic Constituents) and Glomerular Sclerosis

Fig. 2 Various pathophysiological mechanisms, which are currently believed to be involved in various stages of the destruction of glomerular architecture in chronic renal diseases.
derived growth factor (PDGF), which, in turn, may stimulate the proliferation of mesangial cells and production of the mesangial matrix. Platelet aggregation may also cause intraglomerular coagulation. Recent studies using a model of subtotal nephrectomy have demonstrated that warfarin, a specific thromboxane synthesis inhibitor, and heparin were shown to markedly attenuate the development of glomerular sclerosis.36,37,40,41

Mechanisms involved in the final step of abnormal mesangial matrix accumulation and glomerular sclerosis have become the focus of recent investigations. Three types of cells have been identified in the normal mesangial region.42 They are: 1) intrinsic mesangial cells, 2) resident Ia-antigen bearing cells, and 3) transient monocyte macrophages. The intrinsic mesangial cells constitute the majority of cells found in the mesangium. Their functions have been speculated as: 1) contribution to mesangial contractility,43-45 2) support of glomerular capillaries,46,47 3) endocytosis of various macromolecular substances,48-51 and 4) production of extracellular matrix components, e.g. glycosaminoglycans, and various types of collagens.52-55 In addition to these functions, intrinsic mesangial cells are believed to produce prostaglandin E2 and neutral proteinase, which degrades collagen type IV, a component of GBM.56 A small number (≈5%) of the cells in the mesangium bear Ia-antigen.58,59 These Ia-antigen bearing cells have endocytic activity in vitro,58 and are believed to participate in the local immune response.42,45 Transient monocyte-macrophages constitute another population of cells, although extremely small in number under normal conditions, which are quickly augmented if the need arises.60-63 These cells can become activated during phagocytosis, releasing reactive oxygen, lipoxygenase products, interleukin 1 which stimulates collagen production, fibronectin fragments that are chemotactic for fibroblasts, and collagenase.

Although mesangial sclerosis can be identified histologically from amorphous eosinophilic lesions by periodic acid-Schiff staining, the nature of the sclerotic substance has not been clarified. It is speculated that sclerosis may occur either by excess accumulation of the normal mesangial matrix, or by an accumulation of extrinsic substances in the mesangial matrix. The former can occur by increased production of the constituents of the mesangium or by decreased degradation of these substances. An increase in collagenous protein was demonstrated in the sclerotic glomeruli,64 while the collagen has been shown to be produced by the mesangial cells.52-54 Thus, it is likely that the activation and/or proliferation of mesangial cells in glomerular diseases might result in the overproduction of the mesangial matrix. However, direct evidence for such a process and elucidation of the mechanisms involved are lacking. Recent studies have shed light on the regulation of mesangial cell turn over and metabolism, which may be altered in the process of sclerosis. In addition to a variety of vasoactive substances demonstrated earlier,65,66 preliminary experiments have been reported to indicate the presence of specific receptors on the mesangial cells for several mitogenic substances, including insulin-like growth factor,67 platelet activating factor (PAF),68 PDGF,58-70
and epidermal growth factor (EGF)\textsuperscript{71} although the latter is controversial.\textsuperscript{72} PDGF and EGF have been shown to induce proliferation of mesangial cells\textsuperscript{69,71} and prostaglandin E2 synthesis.\textsuperscript{71} As it has been known to occur following hormonal stimulation in a number of cell types,\textsuperscript{73-75} PAF and PDGF binding resulted in an increase in cytosolic free Ca\textsuperscript{2+} and in phospholipase activity.\textsuperscript{68,70} In view of the fact that angiotensin II also causes similar intracellular events in mesangial cells\textsuperscript{76} and in other target cells,\textsuperscript{75} it appears that certain common intracellular mechanisms may be shared by vasoconstrictors and mitogenic substances. Similarities in biological actions of angiotensin II and EGF have been documented in aortic smooth muscle cells.\textsuperscript{77} It is, therefore, conceivable that some vasoactive substances may exhibit mitogenic potentials, as do PDGF and others, in the progressive glomerular structural changes.

In addition to infiltrating cells, mesangial cells release substances which can modulate their own mitogenesis and induce structural changes. Recently, an \textit{in vitro} study demonstrated the synthesis and release by human mesangial cells of an anti-plasminogen activator.\textsuperscript{78} Furthermore, several investigators observed the release from cultured mesangial cells of a PDGF-like mitogen,\textsuperscript{69,79} thus raising the possibility that structural changes in glomeruli of progressive diseases may involve autonomous activation of mesangial mitogenic processes.

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