Mechanisms of Disease Reversal in Focal and Segmental Glomerulosclerosis

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It is well known that progression of chronic kidney disease can be ameliorated or stabilized by different interventions, but more studies indicate that it can even be reversed. Most data suggest that current therapy, especially renin-angiotensin system inhibition alone, is not sufficient to initiate and maintain long-term regression of glomerular structural injury. In this article, we review the potential reversal of glomerulosclerosis and evidence from both human and animal studies. We discuss mechanisms that involve matrix remodeling, capillary reorganization, and podocyte reconstitution. In the future, a multipronged strategy including novel anti-inflammatory and antifibrotic molecules should be considered to potentiate regression of glomerulosclerosis.

Key words: Glomerulosclerosis, Regression, ECM, Capillary, Podocyte

Introduction

Progression of chronic kidney disease is a major health problem. Interventions have focused on control of blood pressure and inhibition of the renin-angiotensin system (RAS) but have only resulted in slowing down progression. Over the last years, multipronged intervention has resulted in amelioration of progression and even stabilization of CKD. However, recent observations in humans and in experimental models point to the possibility of regression of sclerosis, which led to a shift in paradigms regarding progressive scarring from a view of sclerosis as a fixed, inevitable outcome in progressive kidney diseases to an understanding of sclerosis as a dynamic, ongoing process that may be modulated.[1-5] Regression of existing glomerulosclerosis requires degradation of extracellular matrix (ECM) accumulation and regeneration of parenchyma. The lesion of glomerular sclerosis is not only a phenomenon of primary focal and segmental glomerulosclerosis (FSGS) but is also a ubiquitous secondary injury underlying the progressive deterioration of many different types of kidney diseases. We will review evidence and mechanisms of regression of glomerulosclerosis, using the term "FSGS" to include this secondary progressive sclerosis.

The Potential Reversal of FSGS

Although lower animals can regenerate nephrons after injury, in mammals, after term birth, no new nephron units can be generated.[6] The tubular epithelium has ample regenerative capacity. Thus, after acute kidney injury, restoration of parenchyma and function is possible. However, even the tubule has limitations, and acute kidney injury has recently been recognized as a major risk factor for CKD.[7] This has been linked to loss of normal cell cycle progression during repair, and loss of tubular epithelial cells, with fibrosis resulting rather than generation of new tubular epithelial cells. However, portions of glomeruli can potentially be restored by capillary lengthening and/or branching. By using 3-dimensional reconstruction of individual glomerular capillary tufts, Remuzzi and colleagues[8] found that after 10 weeks of angiotensin-converting enzyme inhibition, at 60 weeks of age, more than 20% of glomeruli were completely free of sclerosis, whereas at 50 weeks of age practically all glomeruli had some degree of sclerosis. These data suggest that space previously occupied by glomerulosclerosis was now occupied by new capillary tissue. Our mathematical modeling indicated that individual glomerular tufts with sclerosis occupying more than 50% of the capillaries are doomed to progression. Conversely, glomeruli with less than 50% sclerosis of the tuft are capable of growing new capillary loops.[9] Not all glomerular cells have equal capacity for regeneration. Although endothelial cells and mesangial cells readily proliferate after injury, the podocyte has limited, if any, regenerative capacity.

Evidence of Disease Reversal in Human CKD

There are very few studies with repeated biopsies to directly prove regression of sclerosis in humans, and none specifically for primary idiopathic FSGS. However, some clinical observations support the possibility of remodeling of sclerosis. Proof of principle of regression of existing glomerular injury was shown in a small study of diabetic patients with moderately advanced diabetic nephropathy whose diabetes was cured by pancreas transplant.[2] The severity of the diabetic nephropathy was unchanged at 5 years; however, at 10 years, both glomerular lesions and tubulointerstitial lesions had regressed.[10] The African American Study of Kidney Disease and Hypertension (AASK) showed that many CKD patients have a nonlinear glomerular filtration rate (GFR) trajectory or a prolonged period of nonprogression, which indicates that CKD need not be relentlessly progressive.[11] Nondiabetic nephrotic patients who were treated with the angiotensin-converting enzyme inhibitor (ACEI) ramipril

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for 2 years as part of the REIN (Ramipril Efficacy in Nephropathy Core and Follow-up) study achieved stabilization of their rate of GFR decline, to a yearly loss similar to normal aging. Interestingly, in a small subset of these patients, GFR even improved, and thus, they have not reached ESRD.[3] Full remission of proteinuria and stabilized kidney function in response to long-term ACEI were also observed in a small number of patients in another long-term follow-up study of diabetic patients with nephropathy.[12] These findings support that remission and even regression of the functional parameters of CKD can occur in humans with diabetic or nondiabetic kidney disease. However, whether these functional improvements were contributed to in part by any regression of structural injury remains unknown.

Mechanism of Disease Reversal in FSGS Models

Reversal of glomerulosclerosis may occur through various steps, including matrix remodeling, capillary reorganization, and podocyte reconstitution. We will review experimental evidence of mechanisms of such processes.

Effects on Matrix

To achieve regression of sclerosis, matrix degradation must exceed matrix synthesis. A delicate balance between ECM synthesis and degradation affects progression and potential regression of glomerulosclerosis. Key factors that promote collagen synthesis include, but are not limited to, blood pressure, angiotensin II, transforming growth factor-β (TGF-β), platelet-derived growth factor-B, and numerous other growth factors. Angiotensin has been a central focus for mechanisms of progression, linked not only to its effects on systemic and glomerular hypertension but effects on matrix synthesis and cell proliferation. ACEI has shown superior effects on kidney disease progression in various human diseases and in animal models compared with other antihypertensive agents, even in conditions without systemic hypertension. These findings suggest that angiotensin II may have effects beyond blood pressure in progressive kidney disease, and conversely, the effects of ACEI or angiotensin type 1 receptor blocker (ARB) might extend beyond antihypertensive mechanisms.[13] Aldosterone has both genomic and nongenomic actions to promote fibrosis, independent of its actions to increase blood pressure by mediating salt retention.[14] It enhances angiotensin induction of plasminogen activator inhibitor-1 (PAI-1) and also has direct actions on fibrosis.[15]

CLINICAL SUMMARY

- Glomerulosclerosis at early, segmental stages can be reversed.
- Monotherapy with renin angiotensin blockade is insufficient to effect regression of sclerosis.
- Mechanisms of regression of sclerosis involves coordinated matrix remodeling, capillary reorganization/growth, and podocyte reconstitution.

Models of progressive glomerular disease in rodents have shown the potential for regression. Indeed, we showed that higher doses of ACEI than required to normalize both systemic and glomerular hypertension had greater benefits on established glomerulosclerosis in the remnant kidney, a secondary FSGS model, than usual antihypertensive dose.[4] Although there was no further impact on systemic or glomerular pressures, as shown by micropuncture studies, two-thirds of these animals achieved regression of glomerulosclerosis with high-dose angiotensin inhibition. Regression was evidenced by less extensive and less severe sclerosis after 4 weeks of therapy than that seen at the time of biopsy, when intervention was started, 8 weeks after injury was initiated. Animals with regression had better preserved podocytes, more capillary branching, and less matrix accumulation. There was also corresponding less tubulointerstitial fibrosis.[16] Aldosterone inhibition also resulted in regression of sclerosis in this model.[5]

These inhibitors of the renin-angiotensin aldosterone system (RAAS) also decreased expression of PAI-1. PAI-1, a member of the superfamily of serine protease inhibitors, inhibits tissue-type and urokinase-type plasminogen activators and, thus, prevents activation of plasminogen to plasmin. Plasmin not only lyses fibrin but also can degrade ECM. PAI-1 is produced from multiple sources, including endothelium, vascular smooth muscle cells, liver, platelets, and tubular epithelial cells.[17] Angiotensin induces PAI-1, via the angiotensin type 1 (AT1) receptor, independently of blood pressure effects. High levels of PAI-1 have been linked to excess fibrosis in both humans and in experimental models. We found elevated PAI-1 expression at sites of sclerosis and absence of PAI-1 when regression was achieved. In contrast, TGF-β messenger RNA was not decreased when regression was achieved, and its local expression level was not linked to sclerosis. However, these findings do not rule out a role for TGF-β signaling in progression, through for instance, connective tissue growth factor or phosphorylation of Smad2, or a role for its inhibition in regression of sclerosis. Interestingly, 2 key matrix metalloproteases, MMP-2 and MMP-9, were not linked to regression. In contrast, the high level of PAI-1 in animals with progressive glomerulosclerosis was associated with low levels of plasmin. High doses of ACEI or ARB that resulted in regression restored plasmin levels toward normal. These data support that RAAS inhibitors may in part modulate glomerulosclerosis by effects to degrade ECM.

Regression by high-dose RAAS inhibition was not only limited to this remnant kidney model but also was observed in the primary podocyte injury–induced FSGS model of puromycin aminonucleoside nephropathy and in age-related glomerular and vascular sclerosis. In the chronic puromycin aminonucleoside model, regression of sclerosis with intervention with either ACEI or low protein diet was inferred by comparisons of different groups of rats at various time points.[18] We also showed regression of early biopsy-proven glomerulosclerosis lesions in this model, with less sclerosis observed in kidneys at sacrifice in the same rats after treatment with high-dose