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Mechanisms of Disease Reversal in FSGS

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Abstract

It is well known that progression of chronic kidney disease can be ameliorated or stabilized by different interventions, but more and 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 in order to potentiate regression of glomerulosclerosis.

Keywords

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 chronic kidney disease (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 renal 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 FSGS (focal and segmental glomerulosclerosis), but is

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also a ubiquitous secondary injury underlying the progressive deterioration of many different types of renal 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 (AKI), restoration of parenchyma and function is possible. However, even the tubule has limitations, and AKI 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 three-dimensional reconstruction of individual glomerular capillary tufts, Remuzzi et al. found that after 10 weeks of ACE 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.[8] 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 >50% of the capillaries are doomed to progression. Conversely, glomeruli with <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 AASK study showed that many CKD patients have a non-linear GFR trajectory or a prolonged period of nonprogression, which indicates that CKD need not be relentlessly progressive.[11] Non-diabetic nephrotic patients who were treated with the angiotensin converting enzyme inhibitor (ACEI) ramipril for two years as part of the REIN study (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 renal 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 to other antihypertensive agents, even in conditions without systemic hypertension. These findings suggest that angiotensin II may have effects beyond blood pressure in progressive renal disease, and conversely, that effects of ACEI or angiotensin type 1 receptor blocker (ARB) might extend beyond antihypertensive mechanisms.[13] Aldosterone has both genomic and non-genomic actions to promote fibrosis, independent of its actions to increase blood pressure by mediating salt retention.[14] It enhances angiotensin induction of PAI-1, and also has direct actions on fibrosis.[15]

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 four weeks of therapy than that seen at time of biopsy, when intervention was started, eight 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 plasminogen activator inhibitor-1 (PAI-1). PAI-1, a member of the superfamily of serine protease inhibitors, inhibits tissue-type and urokinase type plasminogen activators (t-PA and u-PA), 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 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 mRNA 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 (CTGF), or phosphorylation of Smad2, or a role for its inhibition in regression of sclerosis. Interestingly, two 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 towards 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 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 ACEI.[19] The sclerosis occurring in aged rats could be remodeled by inhibiting angiotensin II with high dose ARB for 6 months, starting at a time point of moderate injury at 18 months of age.[20]

More recently, elegant studies by Adamczak and Remuzzi have confirmed regression in the remnant kidney model and in the spontaneous nephropathy occurring in the Munich Wistar Fromter (MWF) modelc, with high dose ACEI and combination of ACEI and ARB, respectively. [21, 22] Adamczak's data revealed that remodeling of vascular sclerosis, tubulointerstitial fibrosis and existing glomerulosclerosis is feasible. Regression has also been observed in experimental hypertensive nephropathy by high dose ARB. [23]

To maximize the potential for regression, multi-pronged approaches will probably be necessary. The efficacy of combining ARB with ACEI has been explored in several studies as discussed above. The group of Remuzzi showed that ACEI and ARB, with or without added statins, led to further regression than monotherapy in an experimental model.[24] However, no advantage of combination of ARB and ACEI has been demonstrated in previous animal studies, beyond that achieved with greater blood pressure control.[25, 26] Several clinical trials using dual RAAS blockade failed to show cardiovascular or renal protection, but showed more adverse events, suggesting that dual RAAS blockade for the treatment of CKD cannot currently be recommended.[27–29] The angiotensin type 2 receptor (AT2) counteracts the classic AT1 receptor actions, especially by inducing vasodilation instead of vasoconstriction and also with cell-specific effects, and thus might play a beneficial role in remodeling of sclerosis. There is now unequivocal evidence that the AT2 receptor mediates microvascular vasodilation by nitric oxide (NO) generation in a bradykinin-dependent or independent manner.[30, 31] Vazquez et al. found a time-dependent increase in AT2 receptor expression at 7, 15, and 30 days after 5/6 nephrectomy. Animals

pre-treated with ARB showed a further increase in AT2 receptor expression.[32] Whether AT2 contributes to ARB induced regression of glomerulosclerosis is of interest. We directly explored this hypothesis by adding blockade of the AT2 receptor to AT1 blocker in the remnant kidney model.[33] The added inhibition of AT2 blockade completely prevented the beneficial effects of the ARB. This progressive sclerosis in rats treated with AT2 receptor antagonist was associated with increased PAI-1 in contrast to decrease with ARB. AT1 and AT2 blockers also affected podocytes and collagen synthesis. Cultured wild-type podocytes, but not PAI-1 knockout cells, responded to angiotensin II with increased collagen, an effect that was completely blocked by ARB with lesser effect of the AT2 receptor antagonist. We conclude that the beneficial effects on glomerular injury achieved with ARB are contributed to not only by blockade of the AT1 receptor, but also by increasing angiotensin effects transduced through the AT2 receptor, and that these effects include effects both on matrix and podocytes.

Effects on Capillaries

Although regression of chronic kidney diseases cannot be achieved by growing new glomeruli, we postulate, based on elegant studies by Nyengaard, that segments of glomeruli can regenerate by capillary lengthening and/or branching, whereas the sclerosed segment may be largely reabsorbed.[34]

In the remnant kidney model, regression by high dose ACEI was manifest by decreased sclerosis volume and increased volume of intact capillaries by up to 40%.[8] Mesangial and endothelial cell proliferation was reversed, but the number of podocytes per glomerulus was not changed by ACEI treatment.[35] In our studies by confocal three-dimensional imaging and graph theory analysis, we also found that glomeruli in rats with progressive sclerosis were enlarged, but had reduced number of capillary segments and capillary branch points and decreased complexity of the glomerular network compared with normal glomeruli. In contrast, in rats with regression of sclerosis induced by high dose ARB, glomerular enlargement was due not to increased matrix, but due to increased number of glomerular capillary segments and capillary branch points and restored complexity of the capillary network.[36]

Therapeutic efforts beyond RAAS inhibition must include mechanisms to protect and restore the podocyte. The podocyte is key for glomerular endothelial cell survival, by secreting key angiogenic factors such as vascular endothelial-derived growth factor (VEGF) and angiopoietin-1. Elegant experiments have shown that podocyte VEGF expression is necessary to maintain the endothelium of the glomerulus. In vitro, we showed that injured podocytes treated with ARB had restoration of their angiogenic capability.[37] Thus, endothelial cell health and angiogenesis is crucially interrelated with podocyte health.

Glomerular Epithelial Cells

Podocytes have limited, if any, ability to proliferate due to high expression of a cyclin-dependent kinase inhibitor, $p27^{kip1}$.[38] Podocytes are key to the structural integrity of the glomerulus and to its permselectivity functions, and to maintain the glomerular endothelium (see above). Podocyte loss is closely correlated with progressive glomerulosclerosis. Direct

podocyte injury in genetically engineered rodents demonstrates that injury initially limited to only this cell can result in fully developed sclerosis. In dosing experiments from the group of Wiggins, a threshold for about 20% loss was shown to determine whether repair could occur, or if progressive sclerosis ensued.[39] Interestingly, even when only some podocytes are initially injured, injury can spread to other podocytes, as demonstrated using transgenic chimeric mice where a toxin receptor for human CD25 was expressed in only a subset of podocytes. Injection of toxin that binds to hCD25 resulted in injury even to wild type podocytes, and also increasingly severe sclerosis as injury spread.[40]

Podocytes can be regenerated from local progenitor cells. Parietal epithelial cells (PECs) are postulated to serve as niche stem cells for podocytes, based on marker studies in humans and lineage tracing cells in animal models.[41] Thus, the presence of CD24+/CD133+ cells lining Bowman's capsule supports a stem cell function.[42] Both podocytes and PECS are mobile cells, and their cytoskeletons can respond rapidly to stimuli and allow migration. In injury models, migration of PECs on to the tuft, either along the vascular pole, or by extension along synechiae, has been associated with local increase of matrix, and thus postulated to rather be an injurious profibrotic response. Aberrant Notch-1 expression may contribute to such adverse PEC migration.[43] However, it is possible that migration of such cells could give rise to podocyte-like cells, and perhaps even restore podocytes after injury, depending on the local matrix context. Thus, tissue regeneration may, as in other wound healing settings, depend on the local balance of ECM accumulation and the degradation and resolution of a provisional matrix. Interestingly, the proliferating visceral epithelial cells observed in collapsing glomerulopathy stain with CD44, a marker of activated PECs. In the early phase of recurrence of FSGS in the transplant, when standard microscopy and electron microscopy document only foot process effacement, but no sclerosis, such activated CD44+ cells were increased in the glomerular tuft, and along Bowman's capsule. In contrast, native kidney minimal change disease showed significantly less such activated PECs.[44] Insufficient PEC migration has also been postulated to contribute to age-related sclerosis.[45] However, by using lineage tracing models, PEC migration onto the vascular tuft and differentiation into podocytes only was detected in juvenile mice, but not in aging mice and adult mice with injury induced by subtotal nephrectomy.[46] The biology and pathophysiologic functions of PECs are still controversial. PECs might be reparative or injurious, depending on the type of injury and age of the mouse, or patient.[47] In addition to PECs, cells of renin lineage may also enhance glomerular regeneration by serving as progenitors for glomerular epithelial cells and podocytes.[48]

Podocyte injury can be protected and its regeneration also can be induced by some interventions. High dose ACEI could reverse the spontaneously occurring FSGS lesions in aged MWF rats, linked to podocyte proliferation. These "podocytes" are postulated to result from regeneration from the parietal epithelium.[49] ARB increased glomerular transitional cells in several models of glomerulosclerosis and proteinuria, with cells doublestaining for podocyte and PEC markers, with resulting increased number of podocytes.[50] Podocytes may also be directly protected by glucocorticoids, and this treatment also increased progenitor cells in experimental FSGS induced by anti-podocyte antibody injection. Glucocortocoid also protected podocytes from apoptosis, and thus promoted less injury and increased repair, with ultimately less sclerosis in treated mice.[51] Maintenance of microRNA-30, which

decreased Notch-1 activation and inhibited the cell cycle molecule p53, may contribute to these reparative effects of glucocorticoids.[52]

Novel strategies to Reverse FSGS

Additional preliminary studies have shown that combination of PPARγ agonists and ARB induced more regression of glomerulosclerosis in the 5/6 nephrectomy model than monotherapy with either agent. These additional effects were related to less inflammation and more podocyte protection.[53] Combination therapy with an ACEI, ARB and statin also achieved even better results on sclerosis than monotherapy with any one of these classes of drug.[24] Impressively, combination of ARB with the diuretic hydrochlorothiazide afforded additional protection of function compared to ARB alone when treatment was started at advanced stages of injury in the 5/6 nephrectomy model. Other RAAS targets also provide additional avenues for tissue protection and potential regeneration. Renin inhibition reversed the balance of profibrotic *vs.* antifibrotic mediators in renin transgenic mice, with restoration of tubular epithelial cell and podocyte function and structure.[54] Novel targets include periostin, also linked to disease progression.[55] Although sclerosis was not regressed, progression was completely halted, indicating a potential for modulation even of advanced injury.

Summary

Reversal of glomerulosclerosis can be achieved. High dose ACEI or ARB can slow the progression of chronic kidney diseases, or even partially reverse glomerulosclerosis. However, it appears unlikely that RAS inhibition alone will be sufficient to initiate and maintain long term regression of glomerular structural injury. Future approaches include consideration and targeting additional mechanisms to optimize matrix remodeling, capillary reorganization and podocyte reconstitution. Thus, a multipronged strategy including novel anti-inflammatory and antifibrotic molecules, in addition to standard RAS inhibition, should be considered in order to potentiate regression of glomerulosclerosis.

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