**Progression versus regression of chronic kidney disease**

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**Introduction**

Chronic kidney disease (CKD) is a major cause of morbidity and mortality worldwide, and is characterized by relentless progressive scarring of renal parenchyma that ultimately results in end-stage renal disease with the need for dialysis or transplantation. Scarring is, however, not an inherently irreversible process, as it may be modulated in, for example, skin, heart and large arteries. However, the kidney has unique challenges in remodelling of glomerulosclerosis, in that nephron development ends in late gestation, and generation of new glomeruli is not possible after term birth. The apparent inexorable progression characteristic of CKD is postulated to start with disease-specific initial scarring that then activates compensatory but ultimately maladaptive changes in the remaining nephrons. These compensatory changes include haemodynamic alterations and altered growth responses that promote further scarring and fuel this vicious circle [1]. It is of interest that this sclerotic process is not static, in that even glomeruli with advanced sclerosis have ongoing cell turnover. Thus, there is a potential for modulation of these processes.

**Feasibility of regression—proof of principle in experimental models**

The potential reversibility of glomerulosclerosis has been explored in experimental models. Typically, interventions in experimental studies have started at the time of induction of injurious stimuli, thus precluding examination of mechanisms related to modulation of existing injury. We and others have explored the efficacy and mechanisms of delayed treatment, initiated at a time point of established glomerulosclerosis. Early studies in the 5/6 nephrectomy hypertensive remnant kidney model, with delayed intervention starting at a time point of established sclerosis, as verified by renal biopsy, had suggested that a higher dose of angiotensin-converting enzyme inhibitor (ACEI) had greater effects than the usual antihypertensive doses, despite similar efficacy in normalizing both systemic and glomerular pressures [2]. Glomerular micropuncture studies demonstrated that this greater efficacy on sclerosis was not due to greater haemodynamic effects at either the systemic or glomerular level [1,2]. Remarkably, in some of the rats treated in this manner with high dose ACEI, sclerosis was even less at autopsy than at biopsy 4 weeks earlier [1]. Studies in the puromycin aminonucleoside nephropathy model with sacrifice of rat cohorts at different time points also implied a potential for regression with delayed treatment with low protein diet or ACEIs [3]. Carefully performed studies with sacrifice of subgroups of rats at different times and detailed assessment of possible mechanisms were also done recently by Ritz's group, showing that high dose delayed enalapril treatment could decrease glomerulosclerosis, vascular lesions and tubulointerstitial fibrosis to levels lower than that seen in subgroups sacrificed at the time of initiation of treatment 8 weeks after subtotal nephrectomy [4]. Additional more recent studies by the groups of Ritz, Remuzzi, Zatz and Chatziantoniou, and our own group have explored mechanisms and the potential for modulation of existing glomerulosclerosis [4–9].

**Mechanisms of regression**

*Multipronged interventions*

Although regression was achieved in the above studies with angiotensin inhibition, regression did not occur in...
all animals, and the tissue structure was not completely normalized, suggesting that additional mechanisms promoting sclerosis were still active. Elegant studies from the group of Remuzzi indeed have supported that combination therapy with ACEI, angiotensin type 1 receptor blocker (ARB) and statin therapy could achieve better results than monotherapy with any one of these agents [6]. Dose effects are also important, in that supra-high doses of either ACEI or ARB appear necessary to achieve regression. Although glomerular pressures were lowered similarly by a lower dose and an extremely high dose of the ARB losartan, the highest dose also had beneficial effects in decreasing renal inflammation and restoring glomerular and interstitial injury to pre-treatment levels [7]. Multiple pro-fibrotic mechanisms are activated in progressive sclerosis models, and angiotensin's manifold effects modulate many of these processes.

**Effects on extracellular matrix (ECM)**

The hallmark of sclerosis is increased ECM and obliteration of capillary lumina. Regression of sclerosis, by definition, must result in less ECM and more open capillary loops (Figure 1). Decreased ECM can be contributed to by changes in either ECM synthesis or its degradation, altering net ECM accumulation. In our studies of regression in the remnant kidney model, changes in mRNA and activity of matrix metalloproteases (MMPs) -2 or -9, the key MMPs expressed in the glomeruli, did not account for regression [9]. Expression of mRNA for transforming growth factor (TGF)-β1, a major stimulator of ECM synthesis, was also not decreased by high-dose angiotensin inhibition [9]. It is of interest that angiotensin can directly induce plasminogen activator inhibitor-1 (PAI-1) via the AT1 receptor [1,10]. PAI-1 has major effects in promoting fibrosis by both plasmin-dependent and -independent mechanisms, and may also influence cell migration [11,12]. Regression of sclerosis was tightly linked to the decrease of PAI-1 and tissue inhibitor of metalloprotease-1, TIMP-1, in our studies [9,13]. It is of interest that inhibition of another element of the renin–angiotensin system, aldosterone, by spironolactone, an ineffective anti-hypertensive, decreased PAI-1 levels and induced regression of sclerosis in some animals [13]. *In vitro* studies have shown that aldosterone synergistically affects angiotensin-induced PAI-1 by effects on a GRE motif in the PAI-1 promoter [14]. *In vivo*, spironolactone further decreased PAI-1 beyond the level achieved with angiotensin inhibition [15]. Additional novel contributions to ECM regulation have been discovered by proteomic analysis of normal vs sclerotic vs non-sclerotic glomeruli in the remnant kidney model. We identified thymosin-β4 as a key upregulated molecule in sclerosis, and further demonstrated that

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**Fig. 1. Schema of potential mechanisms of regression of glomerulosclerosis.** ECM degradation, contributed to by AT1RA-induced decreased PAI-1, decreases the area of the scar (brown to grey). Capillary lengthening and branching (orange) occur by capillary growth, mediated by increased VEGF, and angiopoietins-1 and -2 (Ang1 and Ang2). Capillary growth is also enhanced by decreased ECM and AT1RA.
thymosin-β4 was necessary for angiotensin-induced increases in PAI-1 *in vitro* [16].

**Cell responses**

Components of the modulation of injury have also been studied. Not all cells in the glomerulus have equal capacity for remodelling. The podocyte in particular usually has limited ability to proliferate, due to the presence of cyclin-dependent kinase inhibitors. In studies by Ritz’s group, podocyte number/glomerulus was not changed, but podocyte volume was increased. In contrast, the increase of mesangial and endothelial cells occurring after injury was reversed by an ACEI, with a corresponding reduction of glomerular volume and capillary number [5]. In our recent studies in a different variant of the remnant kidney model, we used graph theory analysis of confocal Z-sections through the glomeruli, and analysed vertices and branching patterns. Untreated sclerotic rats showed simplification of capillary branching, with increased capillary branching, approaching normal patterns, when sclerosis was regressed by high dose angiotensin inhibition (Figure 2) [17,18].

The complex interactions of cells within the glomerulus clearly impact on the potential for regression. The interaction between podocytes and endothelium is quite complex. The podocyte normally secretes specific growth factors, including vascular endothelial growth factor-A (VEGF-A) and angiopoietin-1, which are key for maintaining normal glomerular endothelial function and fenestration [19,20]. In models of glomerulosclerosis, glomerular VEGF and capillary density were decreased, while exogenous VEGF treatment ameliorated development of glomerulosclerosis and tubulointerstitial fibrosis [21]. Our recent *in vitro* studies indicate that angiotensin inhibition may also influence podocyte modulation of glomerular endothelial cell growth. Medium from podocytes injured with sublethal doses of puromycin aminonucleoside was ineffective in mediating endothelial cell sprouting and growth, linked to decreased VEGF-A and angiopoietin-1. Endothelial cell growth responses to podocyte-derived media were restored when injured podocytes were treated with ARB. This intervention also normalized podocyte VEGF-A and angiopoietin-1, and, further, these responses were blocked by antibodies inhibiting these angiogenic proteins. These data support that angiotensin inhibition could contribute to regression by yet another mechanism, namely by affecting podocyte modulation of capillary remodelling [22].

**Limits for induction of regression**

Although regression has been demonstrated experimentally, there are limitations to achieving this goal. Mathematical modelling has indicated that individual glomerular tufts with sclerosis occupying >50% were doomed, and progressed despite intervention [1]. Conversely, glomeruli with less than half of the tuft

![Fig. 2. Confocal sections of glomeruli from rats 12 weeks after 5/6 nephrectomy (Nx) vs normal baseline control. In normal rats, glomeruli show complex capillary branching (a), compared with fewer, larger branches in sclerotic glomeruli after 5/6 Nx (b). In rats treated with AT1RA from 8 to 12 weeks after 5/6 Nx, some achieved regression, seen here as restoration of more normal, complex capillary branching, and more normal appearance of podocytes (green, anti-vimentin) (c).](image)
sclerosed could regress the existing sclerosis, resulting in glomeruli with more open capillary loops. Elegant morphometric studies in CKD in children and in rats have indeed demonstrated that both capillary lengthening and branching can occur in glomerular growth after injury [23,24]. Proof of principle of regression has also been shown in human diabetic nephropathy, where cure of the underlying diabetes by pancreas transplant resulted in regression of the existing sclerotic lesions in the kidney and tubulointerstitial fibrosis over a 10 year follow-up period, verified by repeat biopsies [25].

Summary

In summary, current experimental and human data support that there is a possibility for regression of existing glomerulosclerosis that involves alterations of both ECM and glomerular parenchymal cells in a complex coordinated manner. Angiotensin seems to be a key mediator of many of these processes, affecting blood pressure, matrix and podocyte interaction with capillaries. The challenge remains to identify patients at early enough stages where regression could be achieved, and to optimize interventions to target the many processes driving sclerosis, thus unleashing the glomerular potential for remodelling.

Conflict of interest statement. None declared.

References

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