Perforator blockade, for example, would influence both pathways by maintaining eNOS activity while diminishing superoxide production.

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References


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Glomerular scarring: can we delay or even reverse glomerulosclerosis by RAAS inhibition?

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Summary

In a recent publication, Macconi et al. show that reversal of focal and segmental glomerulosclerosis (FSGS) lesions in aged Munich Wistar Frömter (MWF) rats treated with high-dose angiotensin-converting enzyme inhibitors (ACE) inhibitors is associated with a reconstitution of the number of podocytes [1].

Aged MWF rats spontaneously develop hypertension, proteinuria, and focal and segmental glomerulosclerosis due to an unknown genetic defect. In 2006, the Remuzzi group has shown that treatment of aged MWF rats with very high doses of the ACE inhibitor lisinopril (~10 mg/kg/day) could revert proteinuria, and additional loss of renal function could be prevented effectively [2]. A detailed histological analysis showed that glomerular scarring was effectively reduced by this treatment suggesting that regression of glomerular scars could be achieved in these animals. In a recent paper, Macconi et al. followed up on this important finding and investigated changes in resident glomerular cells. They showed that the absolute podocyte number was decreased from 159 to 109 podocytes per glomerulus in aged MWF rats and that lisinopril treatment could restore the podocyte number to 144 (P < 0.01). As a mechanism for this cell renewal, the authors show that ~10% of podocytes co-expressed the proliferation marker Ki-67 in the treated rats suggesting that podocytes could undergo cell divisions in situ or that these cells could be regenerated from parietal cells. To support the latter notion, the authors show that a significantly higher proportion of parietal podocytes were present in the treated animals. This raises the interesting possibility for the existence of a glomerular regenerative mechanism.

Discussion

Although many groups (including the ones of Remuzzi, Fogo, Ritz, Zat, Weening or Chatziantoniou) agree that regression of glomerulosclerosis is possible [3,4], the mechanism by which this occurs is not clear. Regression of a glomerular scar may occur through various mechanisms. The balance between collagen synthesis could change versus proteolytic mediators. Glomerular capillaries are reorganized and multiplied by longitudinal splitting (‘intussusception’) [5]. The fate of the fibrocellular infiltrate is largely unknown. As a net result, the glomerular scar appears to shrink—but most investigators conclude that a glomerular scar never disappears entirely.

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In their current study, Macconi et al. have shown for the first time that a high-dose treatment with an ACE inhibitor can increase the number of podocytes per glomerulus [6]. A decrease of the number of podocytes beyond a critical threshold has been linked to the development of glomerular sclerotic lesions [7]. A reconstitution of podocytes has also been confirmed recently by the group of Ritz and Hamar [8]. In their interesting study, the authors find that a combination of an ACE inhibitor and an aldosterone antagonist was even more effective in a subtotal nephrectomy model of the rat. However, podocyte number could also be increased significantly using alternative drugs to lower blood pressure (a combination of HCT, reserpine and hydralazine).

How could the reconstitution of podocytes have occurred?

Several mechanisms for replenishment of glomerular podocytes have been proposed, including recruitment of cells from the bone marrow in Alport mice [9,10]. Recently, we have been able to trace genetically tagged parietal cells in young developing mice. We could show that ~10% of the podocytes were recruited from parietal or 'transitional' cells onto the glomerular tuft where they differentiate into podocytes [11]. The group of Romangani showed that the cultured primary parietal cells engrafted into the developing fetal kidneys and differentiated into podocytes [12]. In addition, they could show that the cultured parietal cells ameliorated acute toxic renal failure when injected into the circulation. The study of Macconi et al. suggests that parietal cells could also be recruited in adult animals that have already developed a glomerular pathology. Specifically, the data of Macconi et al. indicate that the renin–angiotensin–aldosterone system (RAAS) is involved in the regulation of this potential regenerative pathway.

The RAAS system

There is a lot of hope that inhibition of the RAAS bears additional effects to lowering systemic blood pressures. This hope is mainly based on the finding that inhibition of angiotensin II dilates the efferent arteriole and thus reduces glomerular filtration pressure. Increased glomerular pressures and hyperfiltration are considered to trigger a maladaptive response resulting in glomerulosclerosis. However, the pathogenetic mechanism by which glomerulosclerosis is induced is still unresolved. In addition, elevated levels of angiotensin II or aldosterone in the absence of systemic hypertension do not have any negative consequences on the kidney. This is illustrated by the low-salt diet of indigenous people, patients with decreased central volume [cirrhosis, minimal-change glomerulopathy (GN)] or the two-kidney one-clip model [13]. The additional renoprotective effects of therapies aiming at inhibiting the RAAS are still controversial. In elegant studies, Griffin and Bidani have shown that the
renoprotective effects of RAAS inhibition depended solely on a more effective control of systemic blood pressure (for review see [14]).

What is in for the practising nephrologists?

The major goal to prevent progression of glomerulosclerosis still remains an effective control of systemic blood pressure. Renal autoregulation is impaired in the remaining glomeruli of chronically diseased kidneys, and glomerular hyperfiltration must be prevented to prevent disease progression (Figure 1). Although the pathomechanism is still incompletely understood, proteinuria can serve at least in part as a surrogate marker for glomerular hyperfiltration. Proteinuria is mostly only partially reversible in patients even with optimal therapy including ACE inhibitors or AT1 blockers, and this might be a consequence of the destruction of the glomeruli by sclerosis. The identification of a regenerative mechanism that might replenish podocytes within the glomerulus of adult patients will open the prospect to develop additional and more specific pharmacological strategies beyond ACE inhibitors to slow or even revert glomerular injury.

References


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Cell therapy for cystinosis*

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Summary

In the September 2009 issue of Blood, Syres et al. [1] report on syngeneic bone marrow cell (BMC) and haematopoietic stem cell (HSC) therapy as a successful treatment in a mouse model of cystinosis, an autosomal recessive metabolic disease caused by a defect in the transport of cystine across the