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RAS meets SLE*

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*Comment on Crowley SD, Vasievich MP, Ruiz P *et al*. Glomerular type 1 angiotensin receptors augment kidney injury and inflammation in murine autoimmune nephritis. *J Clin Invest* 2009; 119: 943–953

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Role of the type 1 angiotensin receptor AT_1 in immune-mediated glomerular injury

The renin-angiotensin system (RAS) plays an important role in the pathogenesis of glomerular diseases. To delineate more precisely the role of RAS in creating renal injury, knockout mouse strains lacking the angiotensin type 1 or type 2 receptors (AT_1 and AT_2) have proven very informative.

Hence, in their elegant study that was published in the April 2009 issue of the *Journal of Clinical Investigation*, Crowley et al. have tested the effect of a targeted disruption of the AT_1 receptor on the glomerular disease process in a mouse lupus nephritis model [1]. MRL-*Fas*$^{lpr/lpr}$ mice develop a severe lupus-like autoimmune syndrome that is characterized by severe proliferative immune-complex glomerulonephritis, autoantibody production and arthritis, in addition to a peculiar lymphoproliferative phenotype.

In their study, a unique MRL-*Fas*$^{lpr/lpr}$ mouse strain that lacks the major type 1 angiotensin receptor (AT_{1A}) was generated to examine the role of angiotensin in the pathogenesis of autoimmune glomerular injury. Despite the absence of hypertension, AT_{1A} deficiency did not protect against disease but worsened kidney pathology and proteinuria, and accelerated mortality in these mice. Transplantation of AT_{1A}-deficient bone marrow into MRL-*Fas*$^{lpr/lpr}$ did not affect survival, suggesting that the enhanced disease severity was not a consequence of immune cell alteration. Furthermore, AT_{1A}-deficient MRL-*Fas*$^{lpr/lpr}$ mice did not display increased extrarenal tissue injury, and the lymphoproliferative phenotype as well as the circulating antinuclear antibodies were not changed.

How could this worsened disease in AT_{1A}-deficient MRL-*Fas*$^{lpr/lpr}$ mice be explained? Unlike humans, rodents are known to express a second type 1 angiotensin receptor (termed AT_{1B}), in particular in glomerular podocytes. Mice with AT_{1A} deficiency display a higher renin production and an enhanced activity of RAS. Evidence is then provided in this study for exaggerated AT_{1B} receptor activation in podocytes, manifesting as podocyte injury and increased production of inflammatory mediators. Treatment with the angiotensin receptor blocker (ARB) losartan that blocks both type 1 angiotensin receptors indeed reduced glomerular injury. Thus, it appears that the glomerular type 1 angiotensin receptor AT_{1B} mediated the augmented kidney injury and inflammation in AT_{1A}-deficient MRL-*Fas*$^{lpr/lpr}$ mice. Alltogether, the data suggest that an activation of AT_1 receptors may be sufficient to augment autoimmune glomerular injury and inflammation in the absence of hypertension.

SLE, hypertension and the RAS

In addition to the more direct effects of angiotensin II on the cardiovascular system, the RAS promotes immune and inflammatory tissue injury (Figure 1). Thus, it has been shown for example that activation of the type 1 angiotensin receptor AT_1 augments alloreactivity in experimental allograft transplantation [2]. Most of the actions of angiotensin II to enhance inflammation and tissue injury appear to be mediated by the AT_1 receptor. Activation of the opposing angiotensin receptor AT_2 is generally felt to mediate protection from inflammation [3]; however, in other situations, activation of AT_2 has also been linked to inflammation, such as increased chemokine expression in the kidney [4].

It is well known that the extent of hypertension has a major impact on target organ damage in human SLE [5]. Association studies in patients with lupus nephritis have linked high blood pressure to accelerated progression of renal failure. Case series have shown a general benefit of RAS inhibition in patients with SLE [6], but so far no controlled trials with ACEi or ARB have been performed. Although there are no such randomized trials in humans

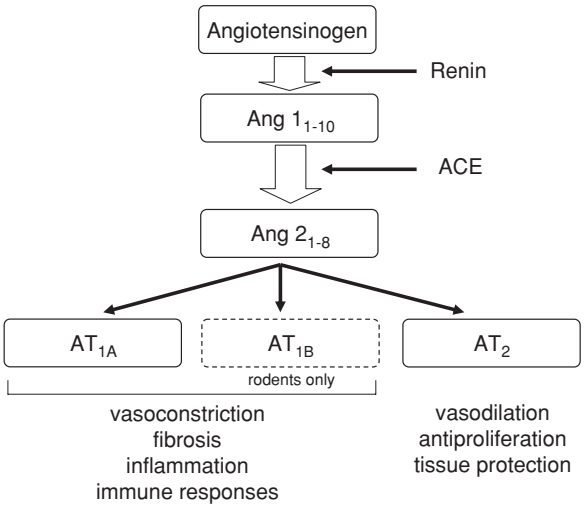

Fig. 1. Pathophysiological alterations that are mediated by the different AT receptors. In humans, there is an AT_1 and an AT_2 receptor that have antagonizing functions. In rodents, there is an alternative AT_1 receptor termed AT_{1B} that is expressed in glomeruli by podocytes, and which is felt to have similar functions as the AT_{1A} receptor.

with SLE, it is felt that RAS inhibition confers protection in human lupus nephritis.

Animal models that apply pharmacological blockade of the RAS or targeted deletion of the angiotensin receptor genes have proved quite useful to gain a better understanding of how RAS promotes immune/inflammatory renal injury. Studies in lupus mice have revealed that inhibition of RAS with ACEi or ARB is beneficial, reducing glomerular injury and albuminuria, and TGF-β production, the latter being a major mediator of fibrosis [7,8]. However, the role of RAS in regulating immune responses is complex, and further experimental studies are needed to elucidate the mechanisms of angiotensin-mediated autoimmune renal injury.

Previous studies have shown that AT_{1A} receptor knockout mice display marked stimulation of renin expression, increased circulating levels of angiotensin II, but with rather low-normal blood pressure. This marked activation of RAS would predict exaggerated stimulation of the residual elements of the system, including activation of other receptors of RAS. In the study by Crowley *et al.*, it was anticipated that elimination of the major angiotensin receptor AT_{1A} would be protective on murine lupus nephritis. Yet it was found that the autoimmune nephritis was accelerated. In mice, but not in humans, there is a second AT_1 receptor—AT_{1B}—whose expression was preserved in this model. As in the murine kidney, the AT_{1B} receptor is exclusively expressed by glomerular podocytes, and the AT_{1A}-deficient MRL-*Fas*$^{lpr/lpr}$ mouse strain provides a fortuitous model wherein the renal AT_1 receptor expression is limited to the glomerulus. Thus, it could be concluded that the systemic activation of RAS in this lupus mouse line promoted more severe injury by stimulating the residual glomerular AT_{1B} receptors.

Role of RAS inhibition in immune/inflammatory renal injury

From this experimental study, one would like to extrapolate that the blockade of RAS with ACEi or ARB is very useful to protect the kidney in autoimmune injury such as in patients with lupus nephritis, or in patients with other immune complex-mediated glomerulonephritides. This has in fact been shown in previous experimental studies, and is shown again here by the fact that the ARB losartan prevented the enhanced disease process in lupus mice with AT_{1A} deficiency [1,8]. One does not need to mention the numerous studies that have documented the beneficial effects of ACEi or ARB in various glomerular diseases, including immune-mediated entities such as IgA nephritis or membranous GN, or non-immune glomerular diseases such as diabetic nephropathy.

What needs to be stated is the fact that the mechanisms by which RAS promotes immune or inflammatory glomerular damage may be far more complex than previously thought, and may not be operating solely through the AT_1 receptors. Various components of RAS, including prorenin, renin, angiotensin$_{1–7}$ to name a few, and the non-AT_1 receptors AT_2, Ang1–7 receptor (Mas) and others may target the immune system and renal parenchymal cells within the glomerulus in a sophisticated way, not to mention the complex interplay with other systems that include the kallikrein–bradykinin system, the NO system and the prostaglandins and thromboxanes. A dysbalance in these systems may cause different patterns of glomerular injury. Thus, one could speculate that in the future there might be more refined therapeutic strategies to influence these interacting systems. Despite decades of intense research, RAS is still always good for a surprise, and the study by Crowley et al. provides another elegant example of this ever increasingly complex system.

In conclusion, activated RAS has a direct negative impact on glomerular injury processes, occurring independently of its effect on blood pressure. Currently, the pharmacological blockade of RAS with ACEi or ARB, and perhaps direct renin inhibitors, appears to be the best available strategy to improve the negative impact of RAS activation on glomerular injury and loss of renal function.

Conflict of interest statement. None declared.

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