Editorial Comments

Angiotensin II, the immune system and renal diseases: another road for RAS?

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Introduction

Recent findings from large clinical trials and experimental studies have emphasized the importance of inhibiting the renin–angiotensin system (RAS) in a wide variety of diseases. They have demonstrated that the benefits of RAS blockade may be due to the inhibition of pressor and non-pressor actions of RAS. Since elevated tissue levels of RAS components have been demonstrated in many diseases, the potential contribution of local RAS to the progression of immune and non-immune conditions has been considered in recent years. Novel components of RAS, such as a renin receptor [1] and an angiotensin-converting enzyme (ACE) 2 molecule [2], have been described in several organs, further indicating that resident and infiltrating cells possess the enzymatic machinery to perform the complete conversion to active angiotensin II (Ang II). Therefore, RAS effects may be partly dependent on the compartment in which Ang II, its major effector peptide, is generated.

There is at present a considerable amount of data indicating pleiotropic effects of Ang II [3]. One of the well-described Ang II actions is as a growth factor that regulates cell growth and fibrosis [4]. Special attention has been paid to transforming growth factor-β in Ang II-mediated fibrosis and hypertrophy [4]. This aspect affords an additional therapeutic rationale to the RAS blockade in progressive renal diseases independently of the aetiology.

However, increasing evidence indicates that RAS may participate not only in the progression, but also in the induction of several diseases [5]. This idea is partly based on the Ang II-related leukocyte extravasation, which is divided into two steps: (i) margination through rolling and adhesion and (ii) migration toward chemotactic stimuli. Clinical and experimental studies have demonstrated that Ang II is involved in the regulation of adhesion molecule expression in many diseases [5]. In addition, Ang II enhances chemokine and chemokine receptor expression in various tissues and cell types [5], suggesting a role of RAS in leukocyte infiltration. Moreover, immunocompetent cells, including T lymphocytes, macrophages and dendritic cells, are equipped with components of the RAS and can participate in the production of Ang II [5–7]. These findings lead to the notion that RAS may influence the prognosis of many renal diseases in association with immune system activation.

Ang II behaves as a cytokine mediating infiltration and activation of immunocompetent cells in renal interstitium

In non-immune primary injury, including proteinuric diseases, urinary obstruction, polycystic kidney disease, diabetes and hypertension, it is well recognized that immunocompetent cell infiltrates are present in the kidney, especially in the interstitium [7]. In these settings, the currently dominant view is that mononuclear cell infiltration does not necessarily require specific antigens, but is rather a manifestation of chemoattractant overexpression [8].

In the pathological conditions mentioned above, an overactivation of RAS, mainly in tubular cells, has been noted [4,5]. RAS blockade by drugs or antisense oligonucleotides decreased interstitial cell infiltration partly via attenuation of chemokines (MCP-1 and osteopontin), adhesion molecules and other mediators [9–11]. Moreover, Ang II itself has chemotactic
properties for mononuclear cells [12]. Therefore, locally activated tubular RAS may directly enhance the interstitial infiltration. However, AT1-deficient mice with overload proteinuria keep a marked interstitial cell infiltration that is not attenuated by an ACE inhibitor, though these animals are protected from interstitial fibrosis [13]. The fact that the cellular infiltration was markedly attenuated by an endothelin-1 receptor A/B antagonist suggests that other mediators, including the vasoactive peptide endothelin, must be implicated in the interstitial cell recruitment [13].

Johnson et al. [14] have hypothesized that salt-sensitive hypertension could be the result of tubulointerstitial damage that would interfere with the physiologic mechanism of pressure-natriuresis. Rodriguez-Iturbe et al. [7] and Johnson et al. [14] extensively studied this phenomenon in models of hypertension caused by a high salt intake following Ang II infusion, clearly suggesting that Ang II is a key mediator in the cellular recruitment occurring in this situation. The continuous hypertension in the model was prevented by mycophenolate mofetil (MMF), coinciding with a marked reduction in the interstitial cell infiltration [15]. Chronic administration of nitro-L-arginine-methyl ester (L-NAME), which suppresses nitric oxide synthesis, produces arterial hypertension characterized by interstitial macrophage and lymphocyte infiltration that was also attenuated by MMF [16]. After stopping chronic L-NAME administration, the blood pressure was normalized and only animals receiving high-salt diet became hypertensive. Interestingly, both models of salt-sensitive hypertension showed interstitial accumulation of Ang II-producing cells, mainly lymphocytes, and oxidative stress that were reduced by MMF in association with the improvement of hypertension [7,15,16]. These findings suggest that Ang II-producing immune cells at sites of renal injury could play an important role in salt-sensitive hypertension. Other recent studies indicate a contribution of the Ang II-producing interstitial infiltrates in different types of hypertension models, such as rats with essential hypertension as well as non-salt-sensitive hypertension and interstitial damage that would interfere with the physiologic mechanism of pressure-natriuresis. However, there are still no data that determine whether these Ang II-producing cells, especially T lymphocytes, also would contribute to the immune amplification in the injured interstitium. It is well known that diverse insults to renal interstitium elicit neoantigen expression, such as altered tubular antigens and heat shock proteins [8]. Thus, it is of great interest to investigate whether the immune response to neoantigens is mediated by Ang II-producing T cells. Indeed, Ang II may be involved in the differential expression of antigen-presenting cells and upregulates their phagocytic activity [5,6,19].

Local RAS amplifies antigen-specific immune responses in glomerular diseases

Our group and Hisada et al. [20–22] demonstrated that Ang II is involved in the pathogenesis of experimental immune-complex glomerulonephritis through NF-κB activation, MCP-1 production and adhesion molecule expression. However, the implication of Ang II in antigen-specific T cell recruitment into the glomeruli, as well as the molecular mechanisms involved, has not yet been demonstrated.

We recently found that the susceptibility of antigen-specific T cell-mediated glomerulonephritis is regulated by renal RAS activation [23]. We used the anti-glomerular basement membrane antibody-induced glomerulonephritis (anti-GBM GN) model that allows the assessment of both humoral and cellular immunity. We previously demonstrated that the immunoglobulin Fc receptor (FcR) is a critical molecule in acute glomerular injury in this disease [24]. We have further clarified that FcR on polymorphonuclear cells (PMN) plays an essential role through initial PMN recruitment and their effector function in the acute glomerular injury [25]. Interestingly, although FeR-deficient mice [γ(–/–)] were protected from initial lethal injury, they still developed glomerular injury characterized by mesangial proliferation, macrophage accumulation and subsequent crescent formation, which were markedly prevented by AT1 antagonists [24]. Th1 cells are major players in the crescent formation of this disease [26]. In addition, antibody deposition onto GBM activates intrarenal and systemic RAS in a dose-dependent manner [21,27]. Using bone marrow chimera between γ(–/–) and AT1(–/–) mice, we noted that CD4+ T cell responses causing the glomerular damage in γ(–/–) mice were dominantly driven by intrarenal RAS activation via AT1 [23]. It is known that Ang II promotes lymphocyte proliferation [28] and may elicit Th1 predominance in vitro and in vivo [29,30]. Thus, the contribution of systemically activated RAS should be carefully elucidated in T cell-mediated glomerulonephritis. However, the functional diversity between Th1 and Th2 cells is partly due to the different chemokine receptor phenotypes. Therefore, to assess potential mechanisms for renal AT1-dependent Th1-trafficking, we examined Ang II-induced Th1-associated chemokine (IP-10 and MIP1α) expression in mesangial cells. Supernatants from Ang II-treated mesangial cells exerted a strong chemotactic activity for T cells and Ang II enhanced the expression of these chemokines in mesangial cells [23]. Therefore, our findings indicate that in immune-complex glomerulonephritis, the locally activated RAS may contribute to the antigen-specific T cell trafficking to inflamed glomeruli, partly via chemokine regulation.

Ang II induces cellular responses through several molecular pathways, including calcium mobilization, free radical generation and activation of protein kinases and nuclear transcriptional factors [4,5]. Emerging data suggest a role of NF-κB as a key mediator of
Ang II-induced inflammatory process [5]. Ang II increases proinflammatory genes under NF-κB control, including chemokines and cytokines [4,5,31]. Recent work has demonstrated that both AT1 and AT2 receptors activate the NF-κB pathway, however, important issues remain unresolved [5,32]. Interestingly, the above-mentioned Ang II-induced Th1 chemokines are differently regulated. IP-10 is NF-κB-dependent, while MIP-1α is dominantly regulated by calcineurin (CaN)-dependent nuclear factor of activated T cells (NF-AT) [23]. NF-AT activity requires a sustained Ca^{2+} stimulus by the Ca^{2+} release-activated Ca^{2+} influx (iCRAC) channel and CaN [33]. Since the physiological mesangial cell function via protein kinase C and calmodulin is closely related with iCRAC, Ang II-induced NF-AT activation in MC could be of interest in the pathogenesis and treatment of immune-complex glomerulonephritis. In fact, South–western histochemistry revealed strong mesangial NF-AT activation after anti-GBM antibody deposition, which was drastically attenuated by AT1 antagonists [23]. CsA and FK 506, which are CaN inhibitors, blocked the morphological and molecular response of primary cardiomyocytes to Ang II [34], indicating that CaN/NF-AT is an important signalling pathway whereby Ang II causes cardiac hypertrophy. Ang II-induced NF-AT pathways may be implicated in the pathological changes of vascular smooth muscle cells, such as phenotypic modulation [35]. Furthermore, the CaN/NF-AT pathway is involved in Ang II-induced lymphocyte proliferation [30]. This observation raises another interesting issue, namely the implication of the Ang II/NF-AT pathway in tubulointerstitial damage. In this regard, it is noteworthy that NF-AT activation was observed in tubular cells and interstitial infiltrating cells in the chronic phase of proteinuric γ(−/−) mice with anti-GBM GN [23].

**Conclusion**

Accumulating data indicate that Ang II could be an inflammatory mediator. This scenario opens the possibility that Ang II contributes to the pathogenesis of renal diseases partially through the infiltration and activation of immunocompetent cells (Figure 1). In some settings, the immune system may be directly influenced by tissue RAS activation. Although future clinical studies are necessary to confirm the relevance of this hypothesis for human disease conditions, this line of research could indicate new directions concerning RAS blockade and immunosuppression in renal diseases.

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