Tumor necrosis factor-α: a reno-protective cytokine? Focus on “Tumor necrosis factor-α suppresses angiotensinogen expression through formation of a p50/p50 homodimer in human renal proximal tubular cells”

Akira Takaguri and Satoru Eguchi
Cardiovascular Research Center and the Department of Physiology, Temple University School of Medicine, Philadelphia, Pennsylvania

Under physiological conditions, angiotensin II (ANG II) controls cardiovascular and body fluid homeostasis primarily by influencing electrolyte reabsorption and vascular tone. However, ANG II is also implicated in many pathophysiological conditions, including hypertension, atherosclerosis, heart failure, and diabetes. Although it was originally defined as a circulating “endocrine” hormone produced through the renin-angiotensin system (RAS) (so-called “circulating RAS”), it is now widely accepted that ANG II can be locally produced in many target organs and tissues in an autocrine or paracrine manner. This ANG II-producing system is known as local RAS or tissue RAS and is controlled independently from the circulating RAS (5). Human angiotensinogen (AGT) gene encodes the 452 amino acid substrate of renin to yield ANG I, which is then processed by angiotensin-converting enzyme (ACE) to generate ANG II. The renin-AGT enzymatic reaction is the rate-limiting step of the cascade. Small increase in either renin or AGT may thus increase ANG II production. Several single nucleotide polymorphisms in AGT are reported to be associated with cardiovascular diseases. In evolutionary history, higher levels of AGT may have been necessary in the salt-poor environment of Africa. The −6A variant in the AGT promoter (as compared with −6G variant) was identified as the ancestral allele, and it is associated with increased AGT (1). Once ANG II is generated, it exerts the physiological and pathophysiological effects primarily by binding to the AT1 receptor. In addition to Gq-dependent intracellular Ca2+ elevation and protein kinase C activation, activation of the AT1 receptor leads to increased reactive oxygen species, activation of various protein tyrosine and serine/threonine kinases, and of small G proteins such as Ras and RhoA, which may require heterotrimeric G protein (Gq and G12/13)-dependent and -independent mechanisms (i.e., β-arrestin) (3). It is noteworthy to mention that both tissue and local RAS now include newly discovered additional regulatory systems, hormonal factors, and their receptors (ACE2, Ang1–7, Mas receptor) making the research field quite exciting but challenging (2).

Intensive investigations have been undertaken to clarify how the tissue RAS is regulated and is associated with cardiovascular and kidney diseases. As such, the importance of the intrarenal RAS in regulating arterial pressure, sodium reabsorption, and renal blood flow has been well documented. Renal-specific overexpression of AGT causes systemic hypertension without a change in circulating ANG II (1). However, there is still a void of knowledge in the definitive molecular events critical for an upregulation of the RAS within disease states, which is believed to be a critical point of intervention. Interestingly, infusion of ANG II to the circulation is known to lead to paradoxical upregulation of AGT in the kidney, contributing to increased levels of intrarenal ANG II (4). Although the mechanism of paradoxical AGT upregulation remains unsolved, it seems to involve inflammatory cytokines induced by ANG II in kidney (4).

An article by Satou et al. (10) identifies a novel signal transduction mechanism by which an inflammatory cytokine, tumor necrosis factor-α (TNF-α) downregulates AGT expression in cultured renal proximal tubular cells. The results of the study suggest that the AGT downregulation is due to the coincident TNF-α activation of inhibitor κB (IκB) kinase leading to degradation of IκB and subsequent nuclear translocation of nuclear factor-κB (NF-κB) complex subunits (10). Specifically, translocation of a dominant noncanonical p50/p50 repressor complex of NF-κB complex subunits results in suppression of AGT expression in the tubular cells. Although Satou’s group and others have reported a negative regulation of AGT by TNF-α in this cell line and several tissues, respectively (10), this study is the first to answer why TNF-α stimulation did not stimulate AGT expression by the expected NF-κB-dependent transcriptional upregulation. Unlike TNF-α,
the authors’ group has recently demonstrated that interleukin-6 (IL-6) was able to upregulate AGT expression in the tubular cells (9). Since both TNF-α and IL-6 have been shown to be induced by ANG II in the kidney (10), one can propose parallel feedback mechanisms by which TNF-α is a break in the system and IL-6 is an accelerator. Most likely cross-talk occurs on the AGT promoter regulatory sites (Fig. 1). Under pathological conditions, the balance may be shifted to the IL-6 mechanism, leading to a paradoxical ANG II upregulation.

Although the findings presented in this paper as well as the authors’ past publications support the above hypothesis and demonstrate attractive targets of intervention for renal diseases where deteriorative activation of tissue RAS is the problem, additional clarification of the system is strongly desired. The p50/p50 complex has been reported to stimulate the NF-κB-dependent transcription if the complex is associated with Bcl-3 (11). An additional component of the complex may be the determinant, which dictates when the p50/p50 acts as a repressor. Also, in vivo studies should be performed to elucidate the source and stimuli of renal TNF-α production under relevant pathological conditions. In addition to monocytes and macrophages, diverse intrinsic renal cells, including endothelial, mesangial, glomerular, and tubular epithelial cells, have been demonstrated to synthesize and release this cytokine, therefore, TNF-α could subsequently exert its pleiotropic biological activities on different renal structures in a paracrine or autocrine manner. Also, potential renal production of TNF-α by advanced glycation end products should be of concern, since TNF-α has been implicated in the microvascular diabetic complications, including nephropathy (7). The known adverse effects of TNF-α include mesangial production of endothelin-1, recruitment of leukocytes/macrophages infiltration to the kidney by stimulating expression of adhesion molecules, and production of reactive oxygen species and other cytokines, chemokines, and growth factors (7).

Beyond the renal pathophysiology, TNF-α is widely believed to participate in endothelial dysfunction, atherosclerosis, and insulin resistance in diabetes and obesity (6). TNF-α converting enzyme TACE/ADAM17, which produces mature TNF-α and other growth factors, is activated by ANG II and is a novel therapeutic target against cardiovascular diseases (8). However, clinical trials with anti-TNF-α treatments toward these diseases remain inconclusive (6). Further evaluation of the TNF-α signal transduction in regulation of AGT expression, especially in vivo, seems likely to aid our understanding of the critical regulation of intrarenal and other local RAS and perhaps also lead to better treatments for cardiovascular and renal diseases associated with enhanced local RAS activities.

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REFERENCES