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EDITORIAL

Lipoxygenases in renal injury—Loading the matrix

A matrix of multiple coordinated pathways perpetuates renal injury. Genetic, hemodynamic, and cellular factors act together resulting in progression of glomeruloscelrosis and tubulointerstitial fibrosis, culminating in end-stage renal disease. Many of the actors in this tragedy have been identified by studies in humans, animal models of renal disease, and cell culture studies. For instance, in diabetic nephropathy, the primacy of hyperglycemia was established by the salutary effects of glucose control on progression of renal disease. Success of pharmacologic agents that interfere with either the production or the cellular actions of angiotensin II in slowing the progression of a variety of renal diseases attests to the importance of angiotensin II in pathogenesis of renal disease. However, the precise cellular mechanisms by which angiotensin II inflicts harm are not fully understood. Angiotensin II is versatile and affects both the hemodynamic and cellular pathways mentioned above [1]. Angiotensin II induces cell hypertrophy and promotes synthesis of extracellular matrix proteins, processes that are linked to progression of renal disease [2]. Mechanisms underlying these effects include stimulation of synthesis of growth factors such as transforming growth factor β [2], transactivation of epidermal growth factor (EGF) signaling pathway [3], and generation of free radicals [4]. In this issue of *Kidney International*, Kim et al [5] describe yet another mediator of angiotensin II in cell injury (i.e., products of 12/15-lipoxygenase (LO) activity).

Generation of prostaglandins from arachidonic acid and their effects on kidney function are well known. Arachidonic acid is also a substrate for another group of enzymes that catalyze the addition of molecular oxygen at distinct carbon atoms on the polyunsaturated fatty acid molecule (i.e., the 5-, 12-, and 15-LOs). LOs generate 5-, 12-, or 15-hydroxyeicosatetraenoic acids (HETEs), of which two stereoisomers (S and R) exist. Products of 5-, 12/15-LOs are expressed in renal tissue and may originate in infiltrating hematopoietic cells or resident renal cells, including mesangial cells [6]. In rodents, 12/15 LO performs the functions of 15-LO. Products of 15-LO include 15-(S)-HETE and, in association with 5-LO, lipoxin A4, which exert anti-inflammatory effects in experimental glomerulonephritis. Lipoxin A4 antagonizes the effects of leukotriene D4 and causes vasodilatation and increase in glomerular filtration. Thus, leukotrienes generated by 5-LO on the one hand, and 15-HETE and lipoxins on the other, may play opposing roles in immune-mediated glomerular injury. Recently, a role for 12/15 LO in non-immune renal disease has been proposed. Increased mRNA and protein expression of 12/15-LO was found to be associated with augmented fibronectin content in glomeruli of rats with established type 1 diabetes [7]. However, it was unclear whether this association was casual or causal. Even if pathogenetically important, where 12/15-LO fits into the matrix of processes that injure the kidney was not known and has been addressed by Kim et al [5] in this issue.

Several agents known to be involved in renal injury, such as high glucose and angiotensin II, share the property of stimulating the activity of 12/15-LO and generation of 12(S)-HETE in mesangial and vascular smooth muscle cells. Kim et al [5] explored the role of 12/15-LO in angiotensin II- and serum-induced changes in mesangial cell function that are of importance in renal injury (i.e., syntheses of DNA, total protein, and fibronectin). In contrast to their effects on wild-type mesangial cells, angiotensin II and serum failed to stimulate DNA, general protein, and fibronectin syntheses in mesangial cells from 12/15-LO knockout mice. The authors explored the signaling mechanisms involved. Whereas stimulation of fibronectin synthesis by serum and angiotensin II was associated with activation of p38 MAP kinase in wild-type mesangial cells, these effects were absent in 12/15-LO knockout cells. One mechanism by which p38 MAP kinase regulates gene expression is by activation of cyclic AMP response element binding protein (CREB), a transcription factor. While there was an indication that serum-stimulated increase in CREB binding to DNA was reduced in 12/15-LO knockout cells, this parameter was unaffected by angiotensin II. Thus, the p38 MAP kinase-CREB axis may apply only to serum stimulation of fibronectin synthesis in mesangial cells but not to angiotensin II, which appears to recruit other pathways for promoting synthesis of the matrix protein. However, the important observation by the authors that angiotensin II was fully capable of stimulating Erk-1/-2 type MAP kinase in 12/15-LO knockout mesangial cells excludes this pathway as well in angiotensin II stimulation of DNA, protein, or fibronectin syntheses. Having excluded two important MAP kinase pathways, it will be interesting to identify signaling pathways that are involved. One obvious choice is the phosphatidylinositol 3-kinase (PI 3-kinase)-Akt pathway, as it has been shown to be important in stimulation of general protein synthesis in renal tubular epithelial cells by growth factors such

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as insulin-like growth factor (IGF)-I and vascular endothelial growth factor (VEGF) [8]. PI 3-kinase may be activated by tyrosine kinases such as receptors for growth factors including EGF. It would be of interest to examine if angiotensin II effects depend on intermediary growth factors such as transforming growth factor (TGF)-β or transactivation of EGF receptor [3]. The PI 3-kinase-Akt axis regulates protein translation by modulating the phosphorylation state of crucial eukaryotic factors and their binding proteins [9]. Additionally, relevant to the work reported by Kim et al, TGF-β–induced fibronectin synthesis has been found to involve activation of PI 3-kinase and Akt in mesangial cells [10]. The authors suggest that failure of DNA synthesis stimulation by serum in 12/15-LO knockout cells is due to impairment in induction of c-fos, an early growth response gene. It is not entirely clear that this is the sole mechanism, as induction of c-fos, while not as intense in the 12/15-LO knockout cells, was more prolonged than in the wild-type cells. Together, these observations suggest an important place of 12/15-LO in the matrix of processes that leads to cell injury in mesangial cells. However, more needs to be understood. For instance, Kim et al [5] showed that generation of superoxide in resting cells depended on the integrity of 12/15-LO. The relevance of this important pathway to DNA, protein, or fibronectin syntheses remains to be shown. This may particularly apply to diabetic renal disease, as mitochondrial free radical generation has been proposed as a unifying pathway for target tissue injury in diabetes [11]. Glutathione depletion promotes nitric oxide–induced cell death by recruitment of 12-LO pathway [12]. Glutathione depletion is inimical to target tissues in diabetes, as it makes them more susceptible to oxidative injury [11] and occurs when mesangial cells are exposed to high glucose [13]. This is another potential area for exploration. As the study by Kim et al [5] employed an in vitro model, the next logical step should be studies on evolution of renal disease such as diabetic nephropathy in 12/15 LO knockout mice.

Discovery of 12/15-LO as a mediator of angiotensin II–induced mesangial cell injury could be of importance to diabetic and nondiabetic renal disease, as angiotensin II antagonists exert salutary effects on both types of renal disease. This finding also opens up the possibility of pharmacologically interrupting 12/15 LO pathway as a therapeutic strategy. Identification of important constituents such as 12/15-LO that make up the pathogenic matrix will help develop comprehensive strategies for interrupting these pathways in the management of progressive renal disease.

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