Hypertension is the second leading cause of end-stage renal disease (ESRD) after diabetes mellitus in the United States. In 2009, more than half a million people in the United States had ESRD with $\approx$400,000 on dialysis and $>17,000$ with kidney transplants. Unfortunately, dialysis and transplantation are the only available treatment options for ESRD, making this a costly and devastating disease. A prominent pathological feature of hypertensive kidney disease is inflammation and fibrosis, characterized by fibroblast activation and excessive production of extracellular matrix, leading to destruction of renal parenchyma and progressive loss of renal function. There is growing evidence that hypertension is inextricably linked to vascular and renal inflammation. Activated T cells and macrophages have been found to infiltrate the kidneys of hypertensive animals, and this is mediated, in part, by chemoattractants, such as monocyte chemoattractant protein-1, and inflammatory cytokines, such as tumor necrosis factor-$\alpha$. Human renal biopsy samples also show increased collections of lymphocyte aggregates and interstitial inflammation in hypertensive compared with normotensive individuals. Renal cortical and vascular endothelial nuclear factor $\kappa$B has been associated with renal inflammation and hypertension-induced renal damage. Interestingly, T lymphocytes of the adaptive immune system play a critical role in hypertension and its associated vascular and renal dysfunction. A key question is whether renal inflammation is a cause of hypertension or whether hypertension causes renal inflammation. Data presented in this issue of Hypertension by Xia et al suggest the latter. The authors found that the chemokine CXCL16 is a key mediator of the renal inflammation and damage induced by angiotensin II independent of blood pressure.

Chemokines are a subset of the cytokine family responsible for homing immune cells through interactions with their G-protein-coupled receptors. They are categorized into subfamilies, CXC, CC, C, and CX3C, according to the number and spacing of conserved cysteine residues in the amino terminus of the protein. Chemokines are induced by inflammatory cytokines and result in the exacerbation of the inflammatory reaction by homing of leukocytes to secondary lymphoid organs and other tissues. For example, the chemokine CX3CL1 is increased in psoriatic tissue and leads to the migration of CX3CR1-positive T cells into the psoriatic lesion.

CXCL16 is a recently discovered cytokine belonging to the CXC chemokine family and is unique in that it combines scavenger receptor functions with properties of an inflammatory chemokine. It exists in a transmembrane and soluble form. The transmembrane form is composed of a CXC chemokine domain, a mucin-like stalk, a transmembrane domain, and a cytoplasmic tail. The soluble form results from cleavage at the cell surface and is composed of the extracellular stalk and chemokine domain. The transmembrane form functions as an adhesion molecule for CXCR6-expressing cells and a scavenger receptor for oxidized low-density lipoprotein. The soluble form is a chemoattractant that promotes migration of CXCR6-expressing cells, including T cells, monocytes, and myeloid fibroblasts. Although CXCL16 has been implicated in other forms of renal disease such as lupus nephritis and antiglomerular basement membrane nephritis, its role in hypertension and hypertensive kidney disease was not known.

Xia et al found that CXCL16 was induced in renal tubular epithelial cells in response to angiotensin II in a nuclear factor $\kappa$B-dependent manner. Genetic deletion of CXCL16 did not affect blood pressure but protected against angiotensin II–induced renal dysfunction, proteinuria, and fibrosis. CXCL16 deficiency reduced accumulation of bone marrow–derived fibroblasts, myofibroblasts, F4/80+ macrophages, and CD3+ T cells in the kidneys of angiotensin II–treated mice compared with wild-type mice. Extracellular matrix proteins and proinflammatory cytokines were reduced correspondingly in the CXCL16-deficient mice. Thus, CXCL16 seems to mediate the renal inflammation and fibrosis that accompanies angiotensin II–induced hypertension, and targeting CXCL16 may be a novel therapeutic strategy for hypertensive kidney disease. The Figure illustrates a model for the hypertensive kidney damage mediated by CXCL16.

Prior work has supported a role of CXCL16 in kidney disease. In humans, elevated serum and urine CXCL16 levels were associated with the development of chronic kidney disease and independently associated with glomerular filtration rate. In a separate study, urine CXCL16 was elevated in several strains of mice and patients with lupus nephritis, correlating well with urine protein levels and systemic lupus erythematosus disease activity index scores. On the basis of these results, it is interesting to speculate that serum or urine CXCL16 may serve as a prognostic/diagnostic marker for kidney disease.
for severity of renal dysfunction and progression to ESRD in hypertensive patients.

In humans, hypertension is both a cause and consequence of long-standing renal dysfunction. In ESRD, hypertension is difficult to control because of diminishing glomerular filtration rate and the accompanying salt and water retention. Xia et al. found that deletion of CXCL16 had no effect on the hypertensive response to angiotensin II, at least in the short term. It is possible that the mice lacking CXCL16 might demonstrate reduced hypertension in response to a longer term exposure stimulus, given the important role of the kidney in blood pressure control.

Hypertension is linked intimately to vascular inflammation and atherosclerosis. Interestingly, CXCL16 was described initially as a macrophage scavenger receptor for oxidized low-density lipoprotein and later found to be expressed in human vascular smooth muscle cells. The primary receptor for CXCL16 is CXCR6. The role of CXCL16/CXCR6 in atherosclerosis is controversial. Although CXCR6 deficiency confers atheroprotection, deficiency of CXCL16 in low-density lipoprotein receptor–deficient mice was associated with accelerated atherosclerosis and enhanced macrophage recruitment. This would suggest that CXCL16 is atheroprotective. Recently, Borst et al. found that CXCR6 is highly expressed in platelets, and that CXCL16 stimulation enhanced platelet adhesion to the endothelium in vitro after high arterial shear stress and to injured vascular wall in vivo after carotid ligation, suggesting that CXCL16 is prothrombotic. Thus, the role of CXCL16 signaling in atherosclerosis is still unclear and requires further investigation.

In summary, the work by Xia et al. and prior studies emphasize the role of CXCL16 in renal inflammation and injury in several different models of renal disease: lupus, antiglomerular basement membrane disease, and now hypertensive kidney disease. Novel therapies aimed at inhibiting CXCL16 function or signaling could prove effective in preventing or delaying chronic kidney disease, but the effect of these interventions on atherosclerosis and thrombosis needs to be taken into consideration, particularly given the fact that many hypertensive patients have concomitant coronary artery disease.

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