Dual Role of Microsomal Prostaglandin E Synthase 1 in Chronic Kidney Disease

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Chronic kidney disease (CKD) is typically thought of as a progressive loss of glomerular filtration rate. However, CKD is also a systemic disorder in which loss of glomerular filtration rate or functional renal mass leads to dysregulation of extracellular fluid and electrolyte balance, impaired bone and mineral metabolism, and hematologic abnormalities, such as anemia and platelet dysfunction. Identification of biological mediators that reduce progressive renal injury and attenuate anemia of chronic renal failure is a crucial step in developing treatments for the 26 million people with CKD in the United States.

Prostanoids are the subject of intense interest as potential therapeutic targets in renal disease because of their critical roles in regulation of blood pressure, renal blood flow, glomerular filtration rate, and inflammation. Individual prostanoids are derived from the metabolism of arachidonic acid by the sequential actions of cyclooxygenase (COX) and specific prostanooid synthases. In addition to COX activity, the biological effects of prostanoids are dependent on a number of other factors, including the tissue distribution and expression of individual prostanooid synthases and prostanoids receptors. The most abundant prostanoid in the kidney, prostaglandin E₂ (PGE₂), is produced by 3 isoforms of prostaglandin E synthase (PGES): membrane PGES-1 (mPGES-1), mPGES-2, and cytosolic PGES. The biological effects of PGE₂ are mediated by activation of 4 receptor subtypes (EP1, EP2, EP3, and EP4). Like COX-2, the expression of mPGES-1 increases in response to inflammatory stimuli, and mPGES-1 is functionally coupled and colocalized with COX. Recent studies have demonstrated that renal mPGES-1 and PGE₂ play a role in the regulation of water balance and blood pressure. Although COX inhibition was reported previously to prevent progression of renal injury in a remnant kidney model, the roles of mPGES-1 and PGE₂ in chronic renal failure remain poorly characterized.

In this issue of Hypertension, Jia et al shed new light on the complex role of mPGES-1 and PGE₂ in the pathogenesis of chronic renal failure and its associated anemia in an experimental model of CKD. The authors’ primary goal was to test that hypothesis that mPGES-1 and PGE₂ contribute to progression of renal injury after renal mass reduction. Wild-type (WT) and mPGES-1 knockout (KO) mice were studied 4 weeks after 5/6th nephrectomy. Renal tissue PGE₂ concentrations were significantly increased after renal mass reduction in WT mice, and this was associated with concomitant increases in mPGES-1 and COX-2 gene expression in the remnant kidney. In WT mice, 5/6th nephrectomy led to a significant reduction in renal function and urinary concentrating capability and significant increases in glomerulosclerosis and albuminuria. These changes were all significantly attenuated in the mPGES-1 KO mice. In fact, albuminuria remained unchanged in comparison with sham-operated mPGES-1 KO mice. Although systolic blood pressure increased after 5/6th nephrectomy in both groups, there was no significant difference in blood pressure between the WT and mPGES-1 KO mice. In contrast to the salutary effect on renal injury, mPGES-1 KO unexpectedly worsened anemia in the remnant kidney model. Renal mass reduction resulted in a significant increase in renal erythropoietin (EPO) gene expression and circulating EPO levels in WT mice. However, these changes were significantly attenuated in the mPGES-1 KO mice and resulted in more severe anemia after 5/6th nephrectomy despite relatively preserved renal function. The authors concluded that mPGES-1 promotes progression of renal failure by promoting inflammation but ameliorates anemia by increasing EPO synthesis (Figure).

The results of the current study by Jia et al raise several important questions about the roles of mPGES-1 and PGE₂ in chronic renal failure. First, and perhaps most importantly, how does mPGES-1 KO differ from COX inhibition in this context? Selective inhibition of COX-2 and nonselective inhibition of COX-1 and COX-2 have also been shown to mitigate renal dysfunction after renal mass reduction. However, genetic KO or pharmacological inhibition of COX-2 as a method to decrease renal PGE₂ production has several drawbacks. COX-2 KO mice develop cardiac fibrosis and renal dysplasia, whereas mPGES-1 KO mice have essentially normal renal and cardiac phenotypes. From a therapeutic perspective, COX-2 inhibition is associated with adverse cardiovascular effects, making their use in CKD less attractive. On the other hand, it has been suggested that mPGES-1 inhibition should be associated with fewer cardiovascular adverse effects, because mPGES-1 is expressed in...
endothelial cells to a lesser extent than COX-2. Second, are the deleterious effects of mPGES-1 and PGE2 on remnant kidney function mediated only by augmentation of the inflammatory response? PGE2 has been implicated in the pathogenesis of increased glomerular capillary pressure after renal mass reduction. In the present study, Jia et al reported that mPGES-1 KO impaired anemia. In particular, PGE2 has been shown to directly increase erythroid colony forming units in normal mouse bone marrow. In conclusion, the results of the study by Jia et al indicate that mPGES-1 KO impaired EPO synthesis in the remnant kidney. However, there are other potential mechanisms through which mPGES-1 KO could promote anemia. In particular, PGE2 has been shown to directly increase erythroid colony forming units in normal mouse bone marrow.

In conclusion, the results of the study by Jia et al indicate that mPGES-1 and PGE2 are induced after renal mass reduction and promote inflammatory renal injury and progressive renal dysfunction. In contrast, mPGES-1–derived PGE2 may attenuate anemia in chronic renal failure by increasing renal EPO synthesis. These findings suggest that inhibition of mPGES-1 may be a novel therapeutic strategy for the prevention of renal disease progression, whereas stimulation of mPGES-1 may have benefit in the treatment of anemia in CKD.

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References
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