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mPGES-1 Deletion Retards Renal Disease Progression but Exacerbates Anemia in Mice with Renal Mass Reduction

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Abstract

Microsomal prostaglandin E synthase-1 (mPGES-1) is a cytokine-inducible enzyme responsible for generation of PGE_2 during the inflammatory response. In the present study, we investigated the role of mPGES-1 in the development of chronic renal failure (CRF) in mice with 5/6 nephrectomy (Nx). After 4 weeks of Nx, wild-type (WT) mice with renal mass reduction exhibited increased blood urea nitrogen (BUN), plasma creatinine (Cr) and phosphorus concentrations, and defective urine concentrating capability, all of which were significantly attenuated by mPGES-1 deletion. The Nx WT mice developed a 2.6-fold increase in urinary albumin excretion, accompanied by glomerulosclerosis and reduction of nephrin and WT-1 expression in the remnant kidney. In contrast, the Nx KO mice had normal albuminuria with improvement of glomerular injury. Nx-induced increases in circulating and renal TNF-1α, and renal IL-1β and MCP-1 expressions were all remarkably attenuated or abolished by mPGES-1 deletion. Paradoxically, the Nx KO mice developed worsened anemia, accompanied by impaired erythropoietin (EPO) synthesis. The co-induction of mPGES-1 and COX-2 but not COX-1 mRNA expressions, along with increased PGE_2 synthesis, was demonstrated in the remnant kidney of WT mice. mPGES-1 deletion remarkably reduced renal PGE_2 content and urinary PGE_2 excretion after renal ablation but had a limited effect on the baseline PGE_2 production. We conclude that: (1) mPGES-1 deletion ameliorates CRF in the mouse model of renal mass reduction, and (2) mPGES-1 deletion paradoxically exacerbates anemia in this model likely via suppression of EPO synthesis.

Keywords

Prostaglandin E_2; chronic renal failure; microsomal prostaglandin E synthase-1; cyclooxygenase-2; and proteinuria

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Conflict of Interest/Disclosure

None.

Introduction

Chronic kidney disease (CKD) is a progressive loss of renal function, eventuating in renal replacement therapy-dialysis or kidney transplantation [1]. The number of patients suffering from CKD is growing as reflected by the increasing cases of renal replacement therapy. There are 26 million American adults with CKD and millions of others are at increased risk. Unfortunately, there is no specific treatment unequivocally shown to slow the progression of CKD. Renal mass reduction in the rodents leads to systemic hypertension, CRF, proteinuria, and glomerulosclerosis, mimicking the major features of human CKD. This model in recent years contributes to the elucidation of the pathophysiology and the development of new therapies for this disease.

Prostaglandin E_2 (PGE_2) is a major product of arachidonic acid metabolism that is sequentially catalyzed by cyclooxygenase (COX) and prostaglandin E synthase (PGES). PGE_2 is a pleiotropic hormone involved in multiple physio-pathological processes, particularly in the inflammatory response. In recent years, the investigation of PGE_2 function has been facilitated by the identification of PGES. To date, at least three major forms of PGES have been cloned and characterized: membrane-associated PGES (mPGES)-1, mPGES-2, and cytosolic PGES (cPGES) with mPGES-1 being the best characterized PGES [2 3]. Like COX-2, mPGES-1 expression in inflammatory cells is highly inducible in response to pro-inflammatory stimuli. Moreover, mPGES-1-deficient mice exhibit blunted pain and inflammatory responses [4]. In light of the pro-inflammatory properties of mPGES-1, this enzyme has been viably viewed as a alternative target for development of analgesics [3]. Emerging evidence supports a potential physiological role of mPGES-1 in renal control of fluid metabolism and blood pressure [5–9]. However, there is scant information regarding a possible role of mPGES-1 in renal inflammatory diseases. The goal of the present study was to examine the role of mPGES-1 in a mouse model of CRF.

Methods

Animals

mPGES-1 null mice were originally generated by Trebino *et al.*[4] This mouse colony was propagated at the University of Utah and maintained on a mixed DBA/1lacJ × C57/BL6 × 129/SV background. The −/− mice were bred using homozygous females to homozygous males. Nonlittermate WT mice which were derived from the same mPGES-1 colony after approximately 20 intercrosses were used as controls. The use of nonlittermate controls was due to the ease of breeding and maintaining the colonies. Male mice (3–4 months old) were used for all experiments. All protocols employing mice were conducted in accordance with the principles and guidance of the University of Utah Institutional Animal Care and Use Committee.

Generation of the Nx mouse model

Under the isoflurane anesthesia, mPGES-1 +/+ and −/− mice underwent a surgery to remove five sixths of total renal mass by resecting the right kidney and cauterizing the upper and

lower poles of the left kidney as described previously [10]. The sham-operated animals were used as controls.

Specific methods

The methods of measurements of blood pressure and hematocrit (Hct), histological analysis, qRT-PCR, immunoblotting, enzyme immunoassay, and statistical analysis are shown in the online supplemental materials at "http://hyper.ahajournals.org".

Results

Assessment of renal function

mPGES-1 WT and KO mice were subjected to 5/6 nephrectomy (Nx) (termed "Nx WT" and "Nx KO", respectively). Renal function was significantly deteriorated in both groups 4 weeks following Nx. The Nx WT mice exhibited renal dysfunction as evidenced by parallel increases in blood urea nitrogen (BUN), plasma creatinine (Cr), and decreased creatinine clearance (Ccr) as compared with the sham control group (Fig. 1A–C). As compared with the Nx WT mice, the indices of renal dysfunction were significantly attenuated in the Nx KO mice (Fig. 1A–C). Similar results were obtained for plasma phosphorus concentration, another index of renal dysfunction (Fig. S1A). Plasma calcium concentration remained constant among all groups (data not shown). In parallel with the overall improvement of renal function, body weight loss was also less in the Nx KO mice (Fig. S1B). Urinary albumin excretion was increased 2.6-fold in the Nx WT mice and this increase was completely blocked in the Nx KO mice (Fig. 1D).

Assessment of glomerular damage

Considering the important role of the podocyte in the development of albuminuria in various forms of CKD, we assessed renal expression of podocyte markers, including the Wilms' tumor 1 gene (WT1) and nephrin, by qRT-PCR. The Nx WT mice exhibited a marked reduction of mRNA expressions of both WT1 and nephrin in the remnant kidney, a sign of podocyte injury (Fig. 2A&B). In contrast, the reduction of both podocyte markers was completely prevented in the Nx KO mice (Fig. 2A&B). The changes in WT1 expresison was confirmed by immunohistochemistry (Fig. 2C). The podocyte number as assessed by counting WT1 positive cells was significantly reduced in the Nx WT mice but was nearly normalized in the Nx KO mice (Fig. 2D).

The remnant kidney weight was not different between the genotypes (Fig. 3A&B). The glomerular morphology was evaluated by Periodic acid-Schiff (PAS) staining and quantified by the semi-qantitative scoring. The Nx WT mice had increased matrix deposition in the glomerulus, a sign of glomeruloslerosis, which was less in the Nx KO mice (Fig. 3C&D).

Assessment of urine concentrating capability and blood pressure

Disturbance of fluid metabolism is an important feature of CRF. We therefore performed metabolic studies to evaluate the status of fluid metabolism in the two genotypes after renal ablation. Significant increases in water intake and urine output were observed in the Nx WT mice and these increases were less in the Nx KO mice (Fig. S2A&B). Water balance

estimated by subtracting water intake by urine output was not different between the two genotypes (Fig. S2C). We then measured urine osmolality as an index of urine concentrating capability. A significant decrease in urine osmolality was observed in the Nx WT mice and this decrease was partially attenuated in the Nx KO mice (Fig. S2D). These results suggest improvement of urine concentrating capability by mPGES-1 deletion after ablation. The levels of key Na^+ and water transporters such as aquaporin-2 (AQP2) and Na^+-K^+-2Cl cotransporter (NKCC2) are an important determinant of urine concentrating capability. We therefore examined the changes of expression of key water and Na^+ transporters in the remnant kidney. AQP2 mRNA and protein levels were upregulated in parallel in the remnant kidney and there was no difference between the genotypes (Fig. S3A&B). A similar pattern was observed for AQP1 mRNA (Fig. S3C). Interestingly, increases in AQP3 and NKCC2 mRNA levels in the remnant kidney were observed in the KO but not WT mice (Fig. S3D&E). Renal mass ablation produced a modest increase in systolic blood pressure (SBP) as determined by tail-cuff plethysmography and there was no difference between the genotypes (Fig. S4).

Assessment of inflammation

In light of the well established role of mPGES-1 in the inflammatory response, we tested whether mPGES-1 deletion affected the expression of pro-inflammatory cytokines or chemokines such as TNF-α, IL-1β, and MCP-1 in the remnant kidney. ELISA detected a significant increase in TNF-α protein expression in the remnant kidney of WT mice as compared with the sham control. This increase was completely abolished in the Nx KO mice (Fig. S5A). Similarly, qRT-PCR demonstrated parallel increases in mRNA expression of TNF-α, IL-1βand MCP-1 in the remnant kidney of WT mice as compared with the sham control; the increases of the pro-inflammatory indices were all completely blocked or significantly suppressed in the absence of mPGES-1 (Fig. S5B–D).

Assessment of anemia

Anemia is an important symptom of CRF. Therefore, we assessed the extent of anemia by examining Hct and spleen weight. The Nx WT mice exhibited small but significant decreases in Hct and increases in spleen weight (Fig. 4A&B), suggesting modest anemia. An accelerated anemia was demonstrated in the Nx KO mice as evidenced by a greater fall in Hct and more severe splenomegaly (Fig. 4A&B). To gain insight into this observation, we analyzed EPO mRNA expression in the remnant kidney by qRT-PCR and plasma EPO concentration by ELISA. EPO mRNA in the remnant kidney of WT mice increased 19-fold, which was reduced by 50% in the absence of mPGES-1 (Fig. 4C). Plasma EPO exhibited a similar pattern of changes except for a trend of difference between the genotypes (Fig. 4D).

The activation of mPGES-1 in the remnant kidney

To gain further evidence for involvement of mPGES-1 in kidney disease progression, we tested whether mPGES-1 expression or activity was stimulated in the remnant kidney. Despite the significant reduction of the kidney mass, the Nx WT mice generated PGE_2 output almost comparable to the sham control group (Fig. S6A), suggesting increased PGE_2 synthesis after renal ablation. Indeed, PGE_2 content was increased 3-fold in the remnant kidney of WT mice as compared with the sham control (Fig. S6B). mPGES-1 deletion led

to a 37% and 67.8% reduction of urinary PGE_2 excretion at baseline and after ablation, respectively, and a 77.6% reduction of PGE_2 content in the remnant kidney (Fig. S6A&B). In light of the potential role of thromboxane A_2 (TXA_2) in the pathogenesis of CKD, we determined the level of thromboxane B_2 (TXB_2), a stable product of TXA_2, in the remnant kidney. Unexpectedly, TXB_2 level tended to be lower than the sham group irrespective of the genotype (Fig. S6C). As expected, however, TXB_2 level was unaffected by mPGES-1 deletion (Fig. S6C). qRT-PCR detected parallel increases in COX-2 and mPGES-1 mRNA expressions in the remnant kidney contrasting to unaltered COX-1 expression (Fig. S6D–F).

Discussion

A large body of evidence consistently demonstrates a pathogenic role of COX-2 in mediating kidney injury in animal models of 5/6 nephrectomy as well as other glomerular diseases[11–14]. COX-2 activity generates five biologically active prostanoids, including PGE_2, prostaglandin D_2 (PGD_2), prostaglandin I_2 (PGI_2), thromboxane A_2 (TXA_2), and prostaglandin $F_2\alpha$ ($PGF_2\alpha$). The contribution of a specific prostanoid to COX-2-mediated kidney injury still remains to be determined. The availability of mPGES-1 null mice offers a novel tool to assess the involvement of PGE_2 in progressive kidney disease in vivo. We demonstrated that mPGES-1 deletion almost abolished proteinuria and also remarkably improved renal dysfunction induced by renal ablation, similar to COX-2 inhibition. Moreover, mPGES-1 expression was induced in parallel with COX-2 in the remnant kidney. These results strongly suggest a specific coupling between COX-2 and mPGES-1 in mediating kidney injury after renal ablation. Consistent with the present study, Stitt-Cavanagh et al. elegantly demonstrates a maladaptive role of the EP4 receptor in podocyte injury by analyzing the phenotype of mice with either podocyte-specific overexpression or deletion of this EP subtype following renal ablation [10]. Whereas, podocyte-specific EP4 deletion produces a partial attenuation of proteiuria without an effect of WT1 expression, contrasting to a more robust effect of mPGES-1 deletion on these parameters. The difference in the magnitude of changes in proteinuria and podocyte marker expression with the two different approaches may suggest involvement of other EP subtypes as well. In support of this possibility, Bek et al. demonstrate that cultured podocytes express the EP1 receptors that may be responsible for PGE_2-elicited intracellular calcium response [15]. Besides PGE_2, TXA_2 is shown to mediate kidney injury induced by renal ablation with variable reports. For example, treatment with two distinct thromboxane synthase inhibitors, OKY1581 [16] and FCE 22178 [17], decrease the excessive renal TXA_2 synthesis, reduce proteinuria, and ameliorate the renal disease progression and hypertension in rats with subtotal renal mass reduction. However, treatment with the selective TXA_2 receptor antagonist GR 32191 in the renal ablation model fails to influence progressive kidney disease [18]. Interestingly, thromboxane receptor deletion but not podocyte-specific EP4 knockout in COX-2 expressing mice reduces proteinurian and improve renal pathology in a mouse model of adriamycin-induced kidney disease [13]. It seems possible that COX-2 may differentially couple with thromboxane or PGE_2/EP4 to mediate renal disease progression depending on the type of injurious insults.

Chronic renal insufficiency is often associated with polyuria as a result of impaired urine concentrating capability. We demonstrated that mPGES-1 deletion significantly improved

renal ablation-induced impairment of urine concentrating capability as evidenced by reduced water intake and urine volume, and elevated urine osmolality. Our results agree with the study of Sanchez et al. who report improvement of urine concentrating capability in the subtotal nephrectomy rats after treatment with COX-2 inhibitors [19]. The mechanism by which prostanoid synthesis inhibition improves urine concentrating capability after renal ablation is unclear. The similar compensatory upregulation of AQP2 expression in the remnant kidney between mPGES-1 WT and KO mice has ruled out a primary role of AQP2. On the other hand, AQP3 and NKCC2 mRNA expressions in the remnant kidney of mPGES-1 KO but not WT mice were significantly elevated as compared with their sham controls. It seems possible that the upregulation of renal AQP3 and NKCC2 expression may in part account for the improved urine concentrating capability in mPGES-1 KO mice with renal mass reduction.

Inflammation plays an important role in progressive kidney disease in both human and animal models of renal failure [20,21]. This is particularly evidenced by the increased levels of pro-inflammatory cytokines such as TNF-α in patients with chronic kidney disease [22] and in 5/6 nephrectomized rats [23]. TNF-α is also responsible for production of other cytokines and chemokines such as IL-1β, RANTES, MIP2, MCP-1, TGF-β1, leading to inflammatory injury in the kidney. Consistent with previous reports [23], we observed significant increases of circulating TNF-α and renal TNF-α mRNA in WT mice after renal ablation. In contrast, the increases of TNF-α along with IL-1β and MCP-1 were significantly ameliorated or completely abolished by mPGES-1 deletion. These results are compatible with the well-known pro-inflammatory properties of mPGES-1. It seems conceivable that mPGES-1 may influence progressive kidney disease via mediating inflammation. Another explanation is that mPGES-1-derived PGE_2 may mediate hyperfiltration in the remnant nephron, a maladaptive response to renal mass reduction [24]. This possibility is suggested by the observation that prostaglandin synthesis inhibition nearly normalized glomerular and tubular function in remnant nephrons but did not affect function of control nephrons [25]. However, since the remnant kidney weight was not different between the genotypes, our results do not support a role of mPGES-1 in mediating the structural hypertrophy induced by renal ablation. Assuming that the structural hypertrophy is the consequence of the functional hypertrophy, one can speculate that mPGES-1 may not be a critical determinant of hyperfiltration in the remnant nephron. Functionally, in the present study, mPGES-1 deletion leads to an increase but not a decrease of glomerular filtration rate, again arguing against the role of mPGES-1-derived PGE_2 in mediating hyperfiltration induced by renal ablation. This finding reinforces the pathogenic role of PGE_2 in ablation-induced kidney injury.

In support of the pathogenic role of mPGES-1 in kidney injury induced by renal ablation, mPGES-1 expression the remnant kidney is induced in parallel with COX-2 but not COX-1, supporting a specific coupling between mPGES-1 and COX-2 in progressive kidney disease. Despite the 75 % renal mass reduction, urinary PGE_2 excretion in nephrectomized mice was comparable to that in the sham group, suggesting increased PGE_2 synthesis in the remnant kidney. This was subsequently confirmed by measurement of tissue PGE_2 content. mPGES-1 deletion produces only a partial attenuation of urinary and renal PGE_2 levels at basal condition but remarkably reduce these parameters after renal ablation. These results

strongly suggest that mPGES-1 becomes a dominant contributor of renal PGE_2 synthesis in the remnant kidney.

In contrast to the overall improvement of renal function in nephrectomized mPGES-1 KO mice, these animals exhibited exacerbated anemia as evidenced by a greater fall of Hct and more severe splenomegaly. In light of the critical role of EPO in regulation of erythropoiesis, we examined renal and circulating EPO levels. Increased EPO levels were demonstrated after renal ablation, possibly reflecting a compensatory response to anemia; the increases were significantly ameliorated by mPGES-1 deletion. Together, these results support an important role of mPGES-1-derived PGE_2 in pathological regulation of erythropoiesis after renal ablation. Consistent with this notion, a significant number of in vitro and in vivo studies report a stimulatory effect of PGE_2 on erythropoiesis and/or EPO synthesis [26–29]. Thus, the impaired EPO synthesis may in part account for the worsened anemia associated with CRF in the absence of mPGES-1. An alternative explanation is that PGE2 may act directly on the bone marrow independently of en effect on EPO production. In support of this possibility, COX-2 KO mice are shown to exhibit enhanced anemia associated with decreased bone marrow cell counts and reduced numbers of erythroid and colony forming cells in the absence of changes in EPO levels [30]. However, our results disagree with the study of Zhang et al. who report suppressed EPO synthesis in a mouse model of subtotal nephrectomy-induced CRF [31]. This study is limited in that the analysis of EPO expression is solely dependent on conventional RT-PCR, which is not a quantitative method. The discrepancy may also arise from the differences in the stages of renal failure or genetic background. It has been reported that the EPO synthesis response to haemodiluton is well preserved in mild CRF but was impaired in advanced CRF [32]. Indeed, the plasma EPO level is not low or even increased in the patients with mild or modest CRF [33–36].

In summary, mPGES-1 deletion improves renal function, urine concentrating capability, and albuminuria, accompanied by a marked attenuation of renal inflammation, in a nephrectomy mouse model of CRF. Paradoxically, the null mice exhibit worsened anemia and suppressed EPO synthesis after renal mass reduction. These results suggest a complex role of mPGES-1-derived PGE_2 in different pathological processes in progressive kidney disease.

Perspectives

Inflammation plays a major role in the pathogenesis of CKD. The present study for the first time demonstrates that mPGES-1 contributes to kidney disease progression likely due to its pro-inflammatory properties. Conversely, this enzyme partially mediates the compensatory EPO synthesis thereby mitigating the extent of anemia. These results suggest that mPGES-1 inhibition may offer a new therapeutic intervention for CKD but caution should be paid to worsened anemia. On the other hand, the side effect of mPGES-1 inhibition may indicate erythropoiesis-stimulating potential of PGE_2 that may have a therapeutic implication for anemia management for patients with or without CRF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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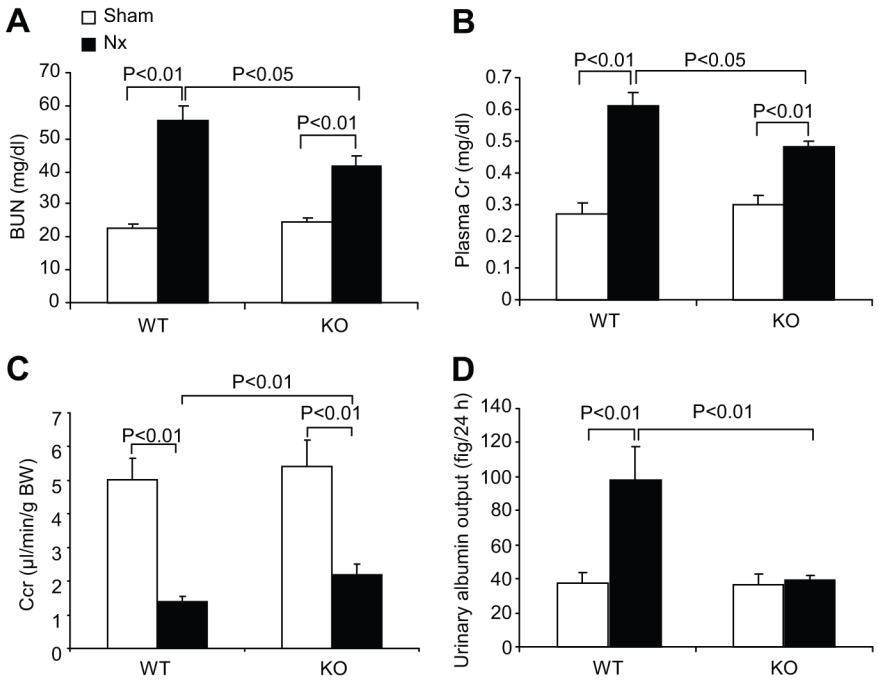

Fig. 1.

BUN (A), plasma Cr (B), creatinine clearance (Ccr) (C), and urinary albumin excretion (D) in mPGES-1 +/+ and −/− mice 4 weeks following renal ablation. Ccr was determined to reflect glomerular filtration rate and was normalized to body weight. Urine albumnin was measured by ELISA. Sham-operated animals were used as controls. N = 6–9 per group. Data are mean ± SE.

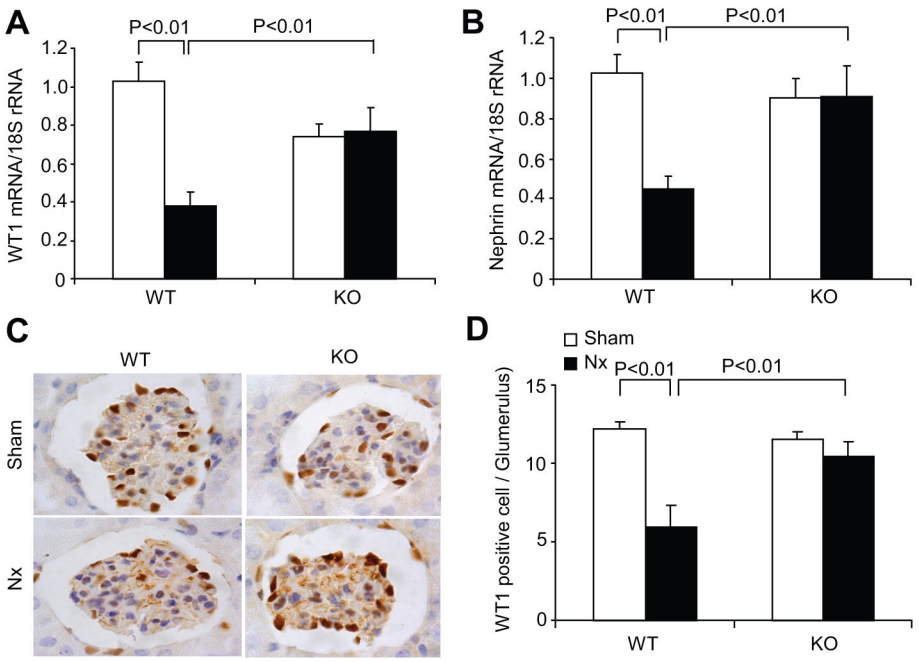

Fig. 2.

Assessment of expression of podocyte markers in mPGES-1 +/+ and −/− mice after renal ablation. mRNA expressions of WT1 (A) and nephrin (B) were determined by qRT-PCR and normalized by 18S rRNA. WT1 positive cells as evaluated by immunostaining were used to reflect the number of podocyte (C, representative micrographs of WT1 immunostaining; D, the number of WT1 positive cells per glomerulus). N = 6–9 per group. Data are mean ± SE.

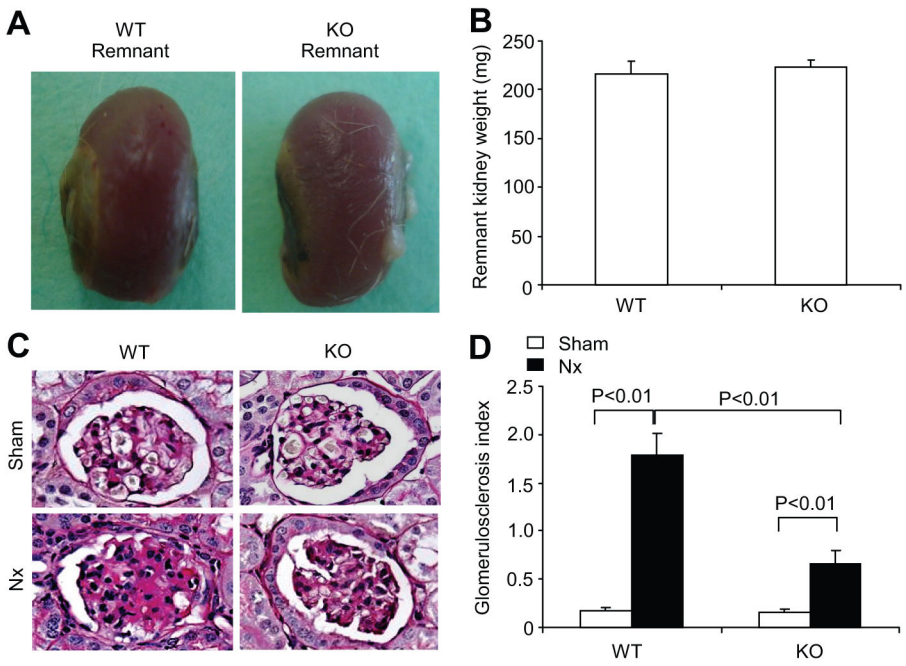

Fig. 3.

Kidney morphological anlaysis. (A) The gross appearance of representative remnant kidneys in mPGES-1 +/+ and −/− mice. (B) The remnant kidney weight between the genotypes. (C) Representative micrographs of perjodic acid Schiff (PAS) stained paraffin sections. (D) Glomerularsclerosis index. N = 6–9 per group. Data are mean ± SE.

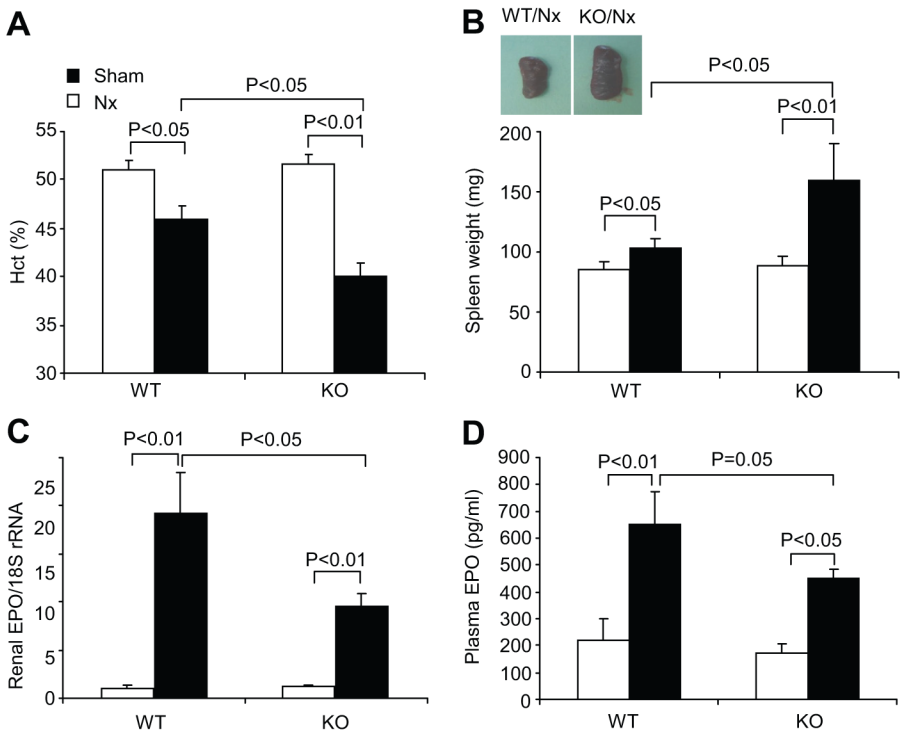

Fig. 4.

Anemia and EPO production in mPGES-1 +/+ and −/− mice after renal ablation. (A) Hematocrit (Hct). (B) Spleen weight. The images show the remnant kidney from mPGES-1 +/+ and −/− mice. (C) qRT-PCR analysis of renal EPO mRNA expression. (D) ELISA analysis of plasma EPO. N = 6–9 per group. Data are mean ± SE.