Tumor necrosis factor-α receptor type 1, not type 2, mediates its acute responses in the kidney

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Castillo A, Islam MT, Prieto MC, Majid DS. Tumor necrosis factor-α receptor type 1, not type 2, mediates its acute responses in the kidney. Am J Physiol Renal Physiol 302: F1650–F1657, 2012. First published March 28, 2012; doi:10.1152/ajprenal.00426.2011.—Acute administration of tumor necrosis factor-α (TNF-α) resulted in decreases in renal blood flow (RBF) and glomerular filtration rate (GFR) but induced diuretic and natriuretic responses in mice. To define the receptor subtypes involved in these renal responses, experiments were conducted to assess the responses to human recombinant TNF-α (0.3 ng·min⁻¹·g body wt⁻¹ iv infusion for 75 min) in gene knockout (KO) mice for TNF-α receptor type 1 (TNFαR1 KO, n = 5) or type 2 (TNFαR2 KO, n = 6), and the results were compared with those obtained in corresponding wild-type [WT (C57BL/6), n = 6] mice. Basal levels of RBF (PAH clearance) and GFR (inulin clearance) were similar in TNFαR1 KO, but were lower in TNFαR2 KO, than WT mice. TNF-α infusion in WT mice decreased RBF and GFR but caused a natriuretic response, as reported previously. In TNFαR1 KO mice, TNF-α infusion failed to cause such vasoconstrictor or natriuretic responses; rather, there was an increase in RBF and a decrease in renal vascular resistance. Similar responses were also observed with infusion of murine recombinant TNF-α in TNFαR1 KO mice (n = 5). However, TNF-α infusion in TNFαR2 KO mice caused changes in renal parameters qualitatively similar to those observed in WT mice. Immunohistochemical analysis in kidney slices from WT mice demonstrated that while both receptor types were generally located in the renal vascular and tubular cells, only TNFαR1 was located in vascular smooth muscle cells. There was an increase in TNFαR1 immunoreactivity in TNFαR2 KO mice, and vice versa, compared with WT mice. Collectively, these functional and immunohistological findings in the present study demonstrate that the activation of TNFαR1, not TNFαR2, is mainly involved in mediating the acute renal vasoconstrictor and natriuretic actions of TNF-α.

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TNFαR2, and comparing the responses with those in wild-type [WT (C57BL/6)] mice.

**Methods**

All the experimental procedures were approved by and performed in accordance with the guidelines and practices established by the Tulane University Animal Care and Use Committee.

Groups of TNFαR1 KO and TNFαR2 KO, as well as WT mice (9–10 wk old, ~25 g body wt) were purchased from Jackson Laboratories (Bar Harbor, ME). The mice were housed in a temperature- and light-controlled room in the Tulane Vivarium and allowed free access to standard diet (Ralston-Purina, St. Louis, MO) and tap water for ≥3 days before acute renal clearance studies were performed under anesthesia. On the day of experiments, the animals were anesthetized with thiobutabarbital sodium (100 mg/kg ip; Inactin, Sigma, St. Louis, MO), and the renal clearance studies were performed as described previously (32). The mice were placed on a servo-controlled surgical table that maintained body temperature at 37°C, and a tracheostomy was performed. The animals were allowed to breathe air enriched with O2; the exterior end of the tracheal cannula was placed inside a small plastic chamber into which humidified 95% O2, 5% CO2 was continuously passed. The right carotid artery was cannulated with polyethylene (PE-10) tubing connected to a pressure transducer (AcqKnowledge data acquisition system, Biopac) for continuous recording of mean arterial pressure (MAP) and heart rate. The right jugular vein was catheterized with PE-10 tubing for fluid infusion at a rate of 3 ml/min with the help of an infusion pump (CMA). During surgery, an isotonic saline solution containing 6% albumin (bovine serum; Calbiochem, La Jolla, CA) was infused. The bladder was catheterized with PE-90 tubing via a suprapubic incision for urine collection. After surgery, the infusion fluid was started at a rate of 0.3 ml/min to calculate UNaV and fractional excretion of sodium (FENa), respectively. Renal vascular resistance (RVR) is calculated by dividing mean systemic arterial pressure by RBF. The mean of the values ± SE. Statistical differences between basal and treatment periods are considered the responses to TNFα treatment. All values were normalized per gram of kidney weight. Results are expressed as means ± SE. Statistical differences between basal and treatment values in the same set of experiments were analyzed by paired Student’s t-test. Data among the different groups of animals were compared by unpaired Student’s t-test. Differences are considered significant at P < 0.05.

**Results**

Basal levels of renal hemodynamic and excretory function in TNFα receptor gene KO mice. The basal values of MAP, as well as renal hemodynamic and excretory function parameters, in these anesthetized TNFαR1 KO, TNFαR2 KO, and WT mice are summarized in Table 1. The basal value of MAP was
significant lower in TNFαR1 KO than WT mice. However, other renal hemodynamic parameters (RBF, RVR, and GFR) were not statistically different between WT and TNFαR1 KO mice (Table 1). On the other hand, V was slightly lower in TNFαR1 KO than WT mice, which could be due to lower MAP in TNFαR1 KO mice. Similarly, UNaV and FENa were also lower in TNFαR1 KO than WT mice, but the difference did not reach statistical significance, possibly because of wide variability in the basal values. The basal MAP value in TNFαR2 KO mice was not statistically different from that in WT mice. However, the basal values of renal hemodynamic parameters (RBF, RVR, and GFR) were significantly lower in TNFαR2 KO than WT mice. Despite the lower values for the renal parameters in TNFαR2 KO than WT mice, the basal values for the excretory parameters [V, UNaV, FENa, and urinary potassium excretion (UK) V] were similar in both strains of mice. RVR was higher, while RBF and GFR were lower, in TNFαR2 KO than TNFαR1 KO mice. V was also higher in TNFαR2 KO than TNFαR1 KO mice.

Renal hemodynamic responses to TNFα infusion in TNFαR1 KO and TNFαR2 KO mice. Percent changes in the hemodynamic responses (MAP, RVR, RBF, and GFR) to TNFα administration in TNFαR1 KO and TNFαR2 KO, as well as WT, mice are shown in Figs. 1 and 2. As reported previously (32), administration of human recombinant TNFα (0.3 ng·min⁻¹·g⁻¹ iv) in WT mice did not alter MAP (from 98 ± 1.6 to 98 ± 1.8 mmHg, n = 6). However, small, but statistically significant, decreases in MAP in response to human TNFα administration were observed in TNFαR1 KO (from 85 ± 6.0 to 79 ± 5.7 mmHg, P < 0.003, n = 5) and TNFαR2 KO (from 94 ± 4.2 to 85 ± 2.9 mmHg, P < 0.05, n = 6) mice (Fig. 1A). The responses to murine TNFα in TNFαR1 KO mice (from 87 ± 6.2 to 84 ± 5.3 mmHg, P < 0.05, n = 5) are qualitatively similar to the responses to human TNFα. In WT mice (n = 6), human TNFα administration caused an increase in RVR (from 10.7 ± 1.4 to 13.6 ± 1.9 mmHg·ml⁻¹·min⁻¹·g⁻¹, P < 0.05; Fig. 1B). Decreases in RBF (from 10.0 ± 1.3 to 8.0 ± 1.0 ml·min⁻¹·g⁻¹, P < 0.05) and GFR (from 1.12 ± 0.12 to 0.67 ± 0.07 ml·min⁻¹·g⁻¹, P < 0.05) in response to human TNFα were observed in these WT mice (Fig. 2). These responses were similar to those reported earlier from our laboratory (32). In TNFαR1 KO mice, these hemodynamic responses to human TNFα were prevented and, in fact, reversed. Contrary to the responses in WT mice, human TNFα caused a decrease in RVR (from 11.1 ± 1.3 to 8.2 ± 2.2 mmHg·ml⁻¹·min⁻¹·g⁻¹, P < 0.05; Fig. 1B), an increase in RBF (from 8.1 ± 0.9 to 10.1 ± 1.0 ml·min⁻¹·g⁻¹, P = 0.055; Fig. 2A), and no appreciable change in GFR [from 1.38 ± 0.17 to 1.31 ± 0.17 ml·min⁻¹·g⁻¹, P = not significant (NS); Fig. 2B] in these TNFαR1 KO mice (n = 5). In the TNFαR1 KO group, responses to infusion of murine TNFα were qualitatively similar to responses to infusion of human TNFα. RVR decreased (from 15.1 ± 1.9 to 13.4 ± 1.6 mmHg·ml⁻¹·min⁻¹·g⁻¹, P < 0.01), RBF increased (from 6.0 ± 0.9 to 6.6 ± 0.8 ml·min⁻¹·g⁻¹, P < 0.001), and GFR did not change appreciably (from 1.08 ± 0.15 to 1.01 ± 0.11 ml·min⁻¹·g⁻¹, P = NS) in response to murine TNFα in TNFαR1 KO mice. The changes in RVR and RBF were quantitatively somewhat larger in response to human than murine TNFα (−24 ± 6 vs. −9 ± 2% for RVR and 28 ± 11 vs. 11 ± 2% for RBF) in TNFαR1 KO mice. In TNFαR2 KO mice (n = 6), the changes in renal hemodynamic parameters in response to human TNFα were comparable to those observed in WT mice (Figs. 1 and 2). TNFα administration caused decreases in RBF (from 6.5 ± 0.4 to 5.3 ± 0.6 ml·min⁻¹·g⁻¹, 0.05 > P > 0.1) and GFR (from 0.67 ±

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<th>Group</th>
<th>MAP, mmHg</th>
<th>RBF, ml·min⁻¹·g⁻¹</th>
<th>RVR, mmHg·ml⁻¹·min⁻¹·g⁻¹</th>
<th>UNaV, mmol·min⁻¹·g⁻¹</th>
<th>FENa, %</th>
<th>UKV, mmol·min⁻¹·g⁻¹</th>
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<td>WT (n = 6)</td>
<td>98 ± 2</td>
<td>10.2 ± 1.3</td>
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<td>TNFαR1 KO (n = 10)</td>
<td>86 ± 4*</td>
<td>7.1 ± 0.7</td>
<td>13.1 ± 1.3</td>
<td>0.58 ± 0.13</td>
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<td>TNFαR2 KO (n = 6)</td>
<td>94 ± 4</td>
<td>6.4 ± 0.48</td>
<td>15.2 ± 1.0**</td>
<td>0.30 ± 0.06</td>
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0.04 to 0.43 ± 0.05 ml·min⁻¹·g⁻¹, P < 0.01) but a small insignificant change in mean RVR (from 15.1 ± 0.9 to 17.2 ± 2.1 mmHg·ml⁻¹·min⁻¹·g⁻¹) in TNFαR2 KO mice.

Renal excretory function responses to TNF-α infusion in TNFαR1 KO and TNFαR2 KO mice. Percent changes in the renal excretory responses (V, UKV, UNaV, and FENa) to human TNF-α administration in TNFαR1 KO and TNFαR2 KO, as well as WT, mice are shown in Figs. 3 and 4. In WT mice (n = 6), human TNF-α administration caused an increase in V (from 10.4 ± 2.9 to 16.6 ± 2.0 µl·min⁻¹·g⁻¹, P < 0.05; Fig. 3A) but no significant changes in UKV (from 1.2 ± 0.1 to 1.1 ± 0.1 µmol·min⁻¹·g⁻¹, P = NS; Fig. 3B). Increases in UNaV (from 0.83 ± 0.4 to 2.1 ± 0.3 µmol·min⁻¹·g⁻¹, P < 0.05; Fig. 3A) and FENa (from 0.6 ± 0.4 to 2.3 ± 0.4%, P < 0.001; Fig. 3B) in response to human TNF-α were also observed in WT mice. These responses were similar to those reported earlier from our laboratory (32). These diuretic and natriuretic responses to human TNF-α administration were absent in TNFαR1 KO mice (Figs. 3 and 4). The changes during human TNF-α administration in these TNFαR1 KO mice (n = 5) were from 4.1 ± 0.3 to 5.1 ± 0.7 µl·min⁻¹·g⁻¹ (V), from 0.38 ± 0.12 to 0.18 ± 0.04 µmol·min⁻¹·g⁻¹ (UKV), from 0.17 ± 0.03 to 0.10 ± 0.02% (FENa), and from 1.1 ± 0.09 to 1.1 ± 0.07 µmol·min⁻¹·g⁻¹ (UNaV). Immunoanalysis of murine TNF-α in the TNFαR1 KO group also caused changes similar to those observed with human TNF-α. The changes during murine TNF-α administration in these TNFαR1 KO mice (n = 5) were from 4.8 ± 0.9 to 5.2 ± 0.7 µl·min⁻¹·g⁻¹ (V), from 0.77 ± 0.18 to 0.53 ± 0.05 µmol·min⁻¹·g⁻¹ (UNaV), from 0.55 ± 0.20 to 0.38 ± 0.09% (FENa), and from 1.0 ± 0.14 to 0.98 ± 0.10 µmol·min⁻¹·g⁻¹ (UKV). In TNFαR2 KO mice (n = 6), human TNF-α administration caused excretory responses similar to those in WT mice (Figs. 3 and 4): increases in V (from 8.2 ± 0.7 to 15.7 ± 2.1 µl·min⁻¹·g⁻¹, P < 0.05; Fig. 3A), UNaV (from 0.30 ± 0.05 to 1.2 ± 0.3 µmol·min⁻¹·g⁻¹, P < 0.05; Fig. 4A), and FENa (from 0.3 ± 0.06 to 1.9 ± 0.4%, P < 0.01; Fig. 4B) and no significant changes in UKV (from 1.0 ± 0.07 to 1.1 ± 0.1 µmol·min⁻¹·g⁻¹, P = NS; Fig. 3B).

Immunohistochemical analysis of TNFαR1 and TNFαR2 in renal tissues. TNFαR1 and TNFαR2 immunoreactivity and densitometric analysis in renal tissues are illustrated in Fig. 5. Kidney slices from the WT mice show that TNFαR1 was located in proximal tubules and collecting duct cells (Fig. 5A), as well as endothelial and smooth muscle cells of the renal vasculature (Fig. 5B). TNFαR2 immunostaining was also observed mostly in proximal and collecting duct cells, but only in the renal vascular endothelium (Fig. 5, E–G). Immunostaining for TNFαR2 and TNFαR1 was also performed in TNFαR1 KO and TNFαR2 KO mice, respectively. Mean data from the densitometric analysis of the intensity of immunoreactivity of TNFαR1 and TNFαR2 in these kidney sections are illustrated in Fig. 5, D and H, respectively. TNFαR1 immunoreactivity was higher (100 ± 3 vs. 128 ± 6% change in intensity, P < 0.01) in TNFαR2 KO than WT mice (Fig. 5D). Similarly, TNFαR2 immunoreactivity was also higher (100 ± 7 vs. 143 ± 6% change in intensity, P < 0.01) in TNFαR1 KO mice (Fig. 5H).
change in intensity, $P < 0.002$) in TNFαR1 KO than WT mice (Fig. 5H).

**DISCUSSION**

This present investigation describes the renal functional phenotypes in mice that are lacking one of the two known TNF-α receptors, type 1 (TNFαR1 KO) or type 2 (TNFαR2 KO). In the anesthetized condition, MAP was slightly, but significantly, lower in TNFαR1 KO, but not TNFαR2 KO, mice than in genetic background WT (C56BL/6) mice. Renal hemodynamic parameters (RBF, RVR, and GFR) are similar in TNFαR1 KO mice but significantly lower in TNFαR2 KO than...
WT mice. However, V and UnaV were lower in TNFαR1 KO than TNFαR2 KO or WT mice, which could be due to low basal MAP in TNFαR1 KO mice. On the other hand, TNFαR2 seems to play a more regulatory role in maintaining the basal levels of RBF, RVR, and GFR than V and UnaV, as the basal renal hemodynamic parameters were significantly lower in TNFαR2 KO than WT mice. Although it was reported earlier from the experiments with human kidney tissues (1) that TNFαR2 was mainly expressed in renal tubules, the present immunohistochemical analysis in mouse kidneys (Fig. 5B) indicates that this receptor is also located in the vascular endothelium, along with tubular epithelial cells. These immunohistochemical data in the present study show that a deficiency in TNFαR1 leads to upregulation of TNFαR2 in the renal tissues, and vice versa, which indicates a potential interaction of these receptors in regulating TNF-α-induced responses in the kidney. An upregulation of TNFαR1 in TNFαR2 KO mice may have resulted in enhanced or opposed effects of TNF-α on TNFαR1 in the absence of TNFαR2 that caused these reductions in the basal level of renal hemodynamic parameters in these TNFαR2 KO mice. As it was reported that TNF-α inhibits renin gene expression and its production in the kidney (36), it is also possible that an alteration in renin secretion rate might have influenced the basal hemodynamic values in TNFαR2 KO mice, although the exact receptor type involved in the mechanism of renin inhibition by TNF-α has not been characterized. Although we did not measure the renin secretion level in these KO mice, the present findings may indicate that TNFαR2 is involved in mediating TNF-induced inhibition of renin secretion in the kidney; such involvement may indicate that this receptor has a role in the general protective function of TNF-α, as suggested earlier (12, 35).

Chen et al. (7) reported that basal MAP in conscious TNFαR1 KO mice was not significantly different from that in WT mice. However, the results of the present study, which was conducted in anesthetized mice, demonstrate that basal MAP was lower in TNFαR1 KO than WT mice. This apparent discrepancy between the results from our study and the results reported by Chen et al. could be due to differences in the experimental preparations, as anesthetic agents can influence the regulatory function of cytokines and their receptors in maintaining generalized vascular tone (23, 34). In the present study, we also observed that TNF-α at 0.3 ng·kg⁻¹·min⁻¹ caused small, but statistically significant, reductions in MAP in TNFαR1 KO and TNFαR2 KO mice, although it caused no significant change in MAP in WT mice. In our earlier study (32), we observed that TNF-α at >0.3 ng·kg⁻¹·min⁻¹ also resulted in decreases in MAP in WT mice that might be related to direct cardiac effect of TNF-α, leading to the development of systolic dysfunction (33). In the present study, slight decreases in MAP in response to TNF-α in TNFαR1 KO and TNFαR2 KO mice could also be related to such a dose-dependent direct cardiac effect of TNF-α.

Similar to the findings in our earlier study (32), human recombinant TNF-α administration in WT mice in the present study also resulted in an increase in RVR and decreases in RBF and GFR. This form of human recombinant TNF-α was widely used in other earlier in vivo studies (7, 29, 32, 33) conducted in mice. The specificity of human TNF-α action in the mice was demonstrated in our earlier study (32). The renal responses to systemic infusion of TNF-α were completely inhibited in mice pretreated with the TNF-α blocker etanercept (32). In the present study, these renal vasoconstrictor and hypofiltrating effects of TNF-α were absent in TNFαR1 KO mice. Rather, RBF increased and RVR decreased in response to human and murine TNF-α administration in TNFαR1 KO mice. As human and murine TNF-α resulted in qualitatively similar responses in TNFαR1 KO mice in the present study, it can be concluded that activation of TNFαR2 in the absence of TNFαR1 in the mouse could have resulted in the renal vasodilator action in response to TNF-α.

Although mouse TNFαR1 and TNFαR2 are 64% and 62% identical to their human counterparts, it was also suggested that human TNF-α may not bind effectively to the mouse TNFαR2 (28). Such species specificity of TNF-α action was suggested from the findings in an in vitro study (28) that used a competitive binding assay of human and murine TNF-α in a human cell line (TSA 201) transfected with murine TNFαR1 and TNFαR2. However, it was also shown in the same study (28) that human TNF-α was able to compete for at least ~40% of the endogenous TNFαR2 located in some mouse cell lines (particularly the L-M cell line), indicating some variability of human TNF-α action on mouse TNFαR2. Such variable species preference between human and murine TNF-α was also reported in studies using in vitro and in vivo experiments (24). In the present in vivo study, it has also been demonstrated that human and murine TNF-α caused decreases in RVR and increases in RBF, presumably acting via TNFαR2 in these TNFαR1 KO mice. However, these changes in RVR and RBF are quantitatively larger with human than with murine TNF-α, indicating a degree of species preference of the recombinant forms of this cytokine, as reported previously (24).

An enhancement of NO bioactivity could be linked to the renal vasodilator response to TNF-α in TNFαR1 KO mice, as TNF-α infusion has been demonstrated to cause an increase in RBF in mice pretreated with tempol (32). The renal vasoconstrictor action of TNF-α is mediated primarily by O₂⁻ production and, as such, reduces the bioactivity of NO, as described in our earlier study (32). However, the present finding that TNF-α failed to cause a vasoconstrictor response in TNFαR1 KO mice suggests that TNFαR1 may be responsible for induction of O₂⁻ production. It was reported that TNF-α could upregulate expression of Nox2 and Nox4 subunits of NADPH oxidase in the renal tissues and could increase O₂⁻ production (29, 32, 33). Also, endothelin-1 could be involved in mediating the renal responses to TNF-α administration, as other studies demonstrated a possible link between TNF-α and endothelin-1 release (8, 26). Additional experiments are required to examine this issue. TNF-α was also known to induce enhancement in tissue expression of endothelial NO synthase, as well as increases in NO production (29, 33). Although not yet known definitively, this induction of NO by TNF-α could be mediated by the activation of TNFαR2 as part of its protective role in the kidney (12, 35). As the present findings demonstrate that TNFαR2 is located only in the vascular endothelium, but not in vascular smooth muscle cells, and that this receptor is upregulated in TNFαR1 KO mice, it is reasonable to assume that the activation of TNFαR2 induces NO production that is involved in mediating the vasodilator response to TNF-α in the absence of TNFαR1 in those mice. On the other hand, the hemodynamic responses to TNF-α administration in TNFαR2 KO mice seem to play a more regulatory role in maintaining the basal MAP in TNFαR1 KO mice.
mice were comparable to those in WT mice, indicating that the renal vasoconstrictor response to TNF-α was largely dependent on the activation of TNFαR1.

In the present study, TNF-α administration resulted in increases in V and \(U_{\text{NaV}}\) in WT mice, as reported earlier (32). These diuretic and natriuretic responses to TNF-α were completely absent in TNFαR1 KO, but not TNFαR2 KO, mice. The responses to TNF-α in TNFαR2 KO mice were qualitatively identical to those in WT mice. It was reported in previous in vitro studies that TNF-α exerts direct inhibitory action on \(\text{Na}^+\text{K}^+\text{ATPase}, \text{Na}^+\text{K}^+-2\text{Cl}^-\) cotransporter (25), and epithelial sodium channel activity (2) in the renal tubule. As shown in our earlier experiments (27, 32), this diuretic and natriuretic response to TNF-α was prevented in mice pretreated with amiloride, indicating that this natriuretic response was mediated by inhibitory action of TNF-α on tubular epithelial sodium channel activity. The finding in the present study that TNFαR1 is localized in the collecting ducts also supports this action of TNF-α. Moreover, TNFαR1 is also localized in the proximal tubular cells. Collectively, these results indicate that the natriuretic response to TNF-α is mediated by its activation of TNFαR1 in the renal tubules.

The findings in the present study clearly emphasize an interactive role for these TNF-α receptors in regulating the renal hemodynamic and tubular transport in conditions of acute episodes of inflammatory insult that are marked with an increase in the plasma level of TNF-α. Although TNFαR1 and TNFαR2 seem to play opposing roles in renal vascular function, it is not clear how these receptors interact with each other in regulating tubular transport function. As it was observed in the present study that the sodium excretion response to TNF-α infuision remains unaltered in TNFαR2 KO mice, it seems that there is no role or a minimal role of TNFαR2 in this natriuretic response, although this receptor is abundantly located in proximal and distal tubular segments. The exact functional role of TNFαR2 in regulating renal tubular function, which may be important in chronic inflammatory conditions, is not clearly understood. More comprehensive studies using in vitro and in vivo models are required to examine further the mechanistic insight or in-depth evaluation of the interactions of TNF-α and its receptors in regulating renal tubular function.

The physiological or pathophysiological significance of these acute renal responses to TNF-α is not clearly understood. Although an involvement of TNF-α has been implicated recently in the development of salt sensitivity (10, 11, 17, 33) and hypertension (16, 18, 38), the present finding that TNF-α administration induces the diuretic and natriuretic responses does not support a direct role of TNF-α in the mediation of salt-sensitive hypertension. However, it was demonstrated that ANG II infuision failed to induce hypertensive responses in mice lacking the genes for TNF-α (33) or T lymphocytes (18) that are activated to increase the production of TNF-α in response to ANG II administration. Future studies to delineate the differences between acute and chronic renal effects of TNF-α and other proinflammatory molecules would provide more in-depth understanding of the pathophysiology of the disease conditions that are marked with inflammatory processes due to many biological and environmental threats.

In conclusion, the present investigation describes the localizations of TNFαR1 and TNFαR2 in the mouse kidney and evaluates the renal functional phenotype in mice that are lacking either of these receptors. These data demonstrate that activation of TNFαR1, not TNFαR2, is mainly involved in mediating the acute renal vasoconstrictor and natriuretic actions of TNF-α.

**REFERENCES**


DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.C. and M.T.I. performed the experiments; A.C., M.T.I., M.C.P., and D.S.A.M. analyzed the data; A.C., M.T.I., M.C.P., and D.S.A.M. prepared the figures; A.C., M.T.I., M.C.P., and D.S.A.M. approved the final version of the manuscript; M.C.P. and D.S.A.M. interpreted the results of the experiments; M.C.P. and D.S.A.M. edited and revised the manuscript; D.S.A.M. are responsible for conception and design of the research; D.S.A.M. drafted the manuscript.

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