TNFR2-mediated apoptosis and necrosis in cisplatin-induced acute renal failure

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Ramesh, Ganesan, and W. Brian Reeves. TNFR2-mediated apoptosis and necrosis in cisplatin-induced acute renal failure. Am J Physiol Renal Physiol 285: F610–F618, 2003.—Cisplatin produces acute renal failure in humans and mice. Previous studies have shown that cisplatin upregulates the expression of TNF-α in mouse kidney and that inhibition of either the release or action of TNF-α protects the kidney from cisplatin-induced nephrotoxicity. In this study, we examined the effect of cisplatin on the expression of TNF receptors TNFR1 and TNFR2 in the kidney and the role of each receptor in mediating cisplatin nephrotoxicity. Injection of cisplatin into C57BL/6 mice led to an upregulation of TNFR1 and TNFR2 mRNA levels in the kidney. The upregulation of TNFR2 but not TNFR1 was blunted in TNF-α-deficient mice, indicating ligand-dependent upregulation of TNFR2. To study the roles of each receptor, we administered cisplatin to TNFR1- or TNFR2-deficient mice. TNFR2-deficient mice developed less severe renal dysfunction and showed reduced necrosis and apoptosis and leukocyte infiltration into the kidney compared with either TNFR1-deficient or wild-type mice. Moreover, renal TNF-α expression, ICAM-1 expression, and serum TNF-α levels were lower in TNFR2-deficient mice compared with wild-type or TNFR1-deficient mice treated with cisplatin. These results indicate that TNFR2 participates in cisplatin-induced renal injury in mice and may play an important role in TNF-α-mediated inflammation in the kidney in response to cisplatin.

cisplatin-induced structural damage (44). However, the pathway through which TNF-α mediates its toxicity in cisplatin injury is not known.

TNF-α is a potent proinflammatory cytokine that plays important roles in chronic inflammation and autoimmune diseases, such as rheumatoid arthritis, autoimmune diabetes, and multiple sclerosis (2, 10). The biological activities of TNF-α are mediated by two functionally distinct receptors, TNFR1 (p55) and TNFR2 (p75). Many of the cytotoxic and proinflammatory actions of TNF-α are mediated by TNFR1 (7, 32). TNFR1-deficient mice are resistant to endotoxic shock and show abrogated induction of adhesion molecules by TNF-α (38, 46). In contrast, TNFR2-deficient mice exhibit only subtle defects (18), and the role of TNFR2 in disease is unclear (9, 11). TNFR2 is thought to cooperate with TNFR1 by passing ligands to TNFR1 (53) or forming heterocomplexes with TNFR1 (40). However, the engagement of TNFR2 by TNF-α also leads to TNFR1-independent cellular events, including apoptosis of activated T cells (39, 57), thymocyte proliferation (52), and inhibition of early hematopoiesis (55). In this study, we have used TNFR1-, TNFR2-, and TNF-α-deficient mice to examine the TNF-α receptor subtype that mediates cisplatin-induced renal injury and the regulation of their expression in response to cisplatin. Our results indicate that TNFR2 expression in the kidney is regulated in a ligand-dependent manner and participates in both necrosis and apoptosis of renal epithelial cells in cisplatin nephrotoxicity.

MATERIALS AND METHODS

Animals and drug administration. Experiments were performed on 10- to 12-wk-old male C57BL/6, TNFR1 (C57BL/6-Tnfr1tm1Gkl)−/−, TNFR2 (C57BL/6-Tnfr2tm1Gkl)−/−, or TNF-α (B6;129-Tnfα1tm1Gkl)−/− deficient mice weighing ~30 g. Mice were obtained from Jackson Laboratory (Bar Harbor, ME) and maintained on a standard diet, and water was freely available. PCR genotyping was performed on selected animals from each strain to confirm the correct genotype. Cisplatin (Sigma-Aldrich, St. Louis, MO) was dissolved in saline at a concentration of 1 mg/ml. Mice were given a single intraperitoneal injection of either vehicle (saline) or cisplatin (20 mg/kg body wt). This dose of cisplatin produces severe renal failure in mice (44). Animals were killed 72 h after...
cisplatin injection, and blood and kidney tissues were collected.

Renal function. Renal function was assessed by measurement of urea nitrogen in the serum using a commercially available kit.

Quantitation of mRNA by real-time RT-PCR. Total RNA was isolated from kidneys using the TRIzol reagent. Real-time RT-PCR was performed using the Applied Biosystems 7700 Sequence Detection System. Total RNA (5 μg) was reverse transcribed in a reaction volume of 20 μl using Superscript II reverse transcriptase and random primers. The product was diluted to a volume of 500 μl, and either 2 (actin)- or 10-μl (all others) aliquots were used as templates for amplification using the SYBR green PCR amplification reagent (PE Biosystems, Foster City, CA) and gene-specific primers. The primer sets used were actin (forward: CATGGTACGATATCGCT; reverse: CATAGGTTAGTCTGTG-CAGGT), TNF-α (forward: GCAATCGCCGACCTGGAA; reverse: AGATCCATGCGGTG GCCACAG), TNFRI (forward: CGGGCCACCTGGTCCG; reverse: CAAGTAGGTTCCCTTGTG), TNFR2 (forward: GTGGCCGGTCTTGGCAACTC; reverse: GTGATACATGCTTGGCCTCAACGTC), and ICAM-1 (forward: AGATCACATTACGGTGGCTG; reverse: TTCTCA-GAAGCGAGAAACACG).

TNF-α and soluble TNFR2 quantitation by ELISA. Levels of TNF-α and soluble TNFR2 in serum were determined using an ELISA assay (Quantikine Mouse TNF-α and Quantikine Mouse sTNFRII kits, R&D Systems, Minneapolis, MN) according to the manufacturer’s instructions.

Western blot analysis. Kidneys were homogenized in PBS, and the protein concentration was quantitated (BCA protein assay reagent, Pierce, Rockford, IL). Samples of protein (100 μg) were separated by 10% SDS-PAGE and then transferred onto a polyvinylidene fluoride membrane. Western blot analysis was performed with an anti-TNFR2 antibody (1:1,000 dilution, Santa Cruz Biotechnology, Santa Cruz, CA).

Histology and immunohistochemistry. Kidney tissue was fixed in buffered formalin for 12 h and then embedded in paraffin wax. Sections (5 μm) were stained with periodic acid-Schiff (PAS) or naphthol AS-D chloroacetate esterase (Sigma kit 91A). The esterase stain identifies infiltrating neutrophils and monocytes. Thirty ×40 fields of esterase-stained sections of kidney cortex were examined for quantitation of leukocytes. Tubular injury was assessed in PAS-stained sections using a semiquantitative scale (23, 26, 43) in which the percentage of cortical tubules showing epithelial necrosis was assigned a score: 0 = normal; 1 = <10%; 2 = 10–25%; 3 = 26–75%; and 4 = >75%. Apoptosis was scored by counting the number of apoptotic cells, as defined by chromatin condensation or nuclear fragmentation (apoptotic bodies), on PAS-stained sections of cortex. The individual scoring the slides was blinded to the treatment and strain of the animal.

Statistical methods. All assays were performed in duplicate. The data are reported as means ± SE. Statistical significance was assessed by an unpaired, two-tailed Student t-test for single comparison or ANOVA for multiple comparisons.

RESULTS

Cisplatin upregulates TNFR2 in a ligand-dependent manner. TNFR1 is widely expressed relative to the more restricted distribution of TNFR2 (17). The expression of TNFR1 and, in particular, TNFR2, which has NF-κB and other transcription factor binding sites in its promoter (47), can be altered in disease states. Therefore, we studied the expression of TNFR1 and TNFR2 mRNA in response to cisplatin injection. As shown in Fig. 1, cisplatin increased the expression of TNFR1 about threefold and increased TNFR2 expression six- to ninefold over saline-treated controls in either C57BL/6 or B6;129J mice. To examine whether the upregulation of either TNFR1 or TNFR2 is TNF-α dependent, receptor mRNA was quantified in cisplatin-treated TNF-α-deficient mice. The expression of TNFR1 was unaltered between the wild-type mice treated with cisplatin and TNF-α-deficient mice (Fig. 1). However, the upregulation of TNFR2 mRNA was blunted in TNF-α-deficient mice. We also examined the effect of cisplatin on kidney TNFR2 protein levels (Fig. 2). As shown in Fig. 2 (top), kidney TNFR2 protein levels were increased by cisplatin, and this increase was blunted in TNF-α-deficient mice. These results indicate ligand-dependent regulation of TNFR2 in cisplatin nephrotoxicity. As shown in Fig. 2 (bottom), TNFR2 protein was measured in C57BL/6 and TNFR1-deficient and TNFR2-deficient mice. Little or no TNFR2 was detectable in kidneys of saline-treated mice. Consistent with the above results, cisplatin produced a marked increase in TNFR2 content in C57BL/6 mice. Moreover, a similar increase occurred in TNFR1-deficient mice. As expected, no TNFR2 protein was present in the TNFR2-deficient kidneys. These results confirm that TNFR2 expression is increased in cisplatin-treated kidneys and indicate that the upregulation is not mediated via TNFR1.

Serum levels of soluble TNFR2 were measured in wild-type mice and in mice deficient in either TNF-α,
TNFR1, or TNFR2 (Fig. 3). Treatment of mice with cisplatin increased soluble TNFR2 levels in wild-type mice (either B6;129J or C57BL/6 strains) and TNFR1-deficient mice. TNF-α-deficient mice had lower levels of soluble TNFR2 in the presence or absence of cisplatin. As expected, TNFR2-deficient mice had undetectable levels of soluble TNFR2. These results are also consistent with TNF-α-dependent regulation of TNFR2 expression.

Cisplatin upregulates TNF-α in TNFR1-deficient but not in TNFR2-deficient mice. Cisplatin increases kidney TNF-α expression and serum TNF-α levels (15, 23, 44). To determine whether this upregulation is mediated through TNF-α receptors, we measured TNF-α mRNA in kidney and TNF-α protein in the serum of TNFR1- or TNFR2-deficient mice after cisplatin injection. As shown in Fig. 4A, TNFR1-deficient mice showed a similar increase in kidney TNF-α mRNA as seen in wild-type mice treated with cisplatin. However, the increase was blunted significantly in TNFR2-deficient mice. Similarly, serum TNF-α protein levels (Fig. 4B) were also significantly lower in TNFR2-deficient mice than in wild-type or TNFR1-deficient mice, suggesting TNFR2-dependent regulation of TNF-α production in the kidney in response to cisplatin.

TNFR2-deficient mice are resistant to cisplatin nephrotoxicity. To address the role of TNFR1 and TNFR2 in the pathogenesis of cisplatin-induced acute renal failure, we examined cisplatin nephrotoxicity in mice with targeted deletions of either TNFR1 or TNFR2. As shown in Fig. 5, wild-type and TNFR1-deficient mice developed severe renal failure after injection with cisplatin (135 ± 14 mg/dl for 72-h urea).

Fig. 2. Regulation of TNFR2 expression by cisplatin. Mice from each indicated strain were injected with saline or cisplatin and killed after 72 h. The content of TNFR2 in kidneys was determined by Western blot analysis. Top: cisplatin treatment increased the TNFR2 protein content in B6;129 mice. This increase was blunted in TNF-KO mice. Bottom: cisplatin increased TNFR2 protein content in both C57BL/6 and TNFR1-deficient (TNFR1-KO) mice.

Fig. 3. Effect of cisplatin injection on soluble TNFR2 in serum. Mice from each indicated strain were injected with either saline or cisplatin (20 mg/kg). Serum was obtained 72 h after injection for measurement of soluble TNFR2 protein, ND, not detectable. Cisplatin increased soluble TNFR2 levels in both B6;129J and C57BL/6 mice (*P < 0.001 vs. saline; n = 3–8). Soluble TNFR2 levels were lower in TNF-KO mice than in B6;129J wild-type mice (*P < 0.001; n = 4).

Fig. 4. Effect of cisplatin on renal TNF-α mRNA and serum TNF-α protein levels. Mice from the indicated strains were injected with either saline (open bars) or cisplatin (filled bars). Kidney and blood were obtained 72 h after injection for measurement of TNF-α mRNA (A) and TNF-α protein (B). Cisplatin caused marked elevations in renal TNF-α mRNA and serum TNF-α levels in C57BL/6 and TNFR1-KO mice. The levels were significantly lower in TNFR2-deficient (TNFR2-KO) mice. TNF-α mRNA levels are expressed relative to the levels in saline-injected mice. *P < 0.05 vs. cisplatin-treated C57BL/6 (n = 3 for mRNA and n = 8 for protein measurements).
wild-type (n = 17) and TNFR1-deficient mice (n = 15), respectively, P = not significant (NS)]. In contrast, TNFR2-deficient mice had better preservation of function (72-h urea = 88 ± 8 mg/dl, n = 16, P = 0.015 vs. wild-type). The histological findings also revealed less severe damage in the TNFR2-deficient mice. As shown in Fig. 6, cisplatin treatment of wild-type and TNFR1-deficient mice resulted in severe tubular injury as reflected by cast formation, loss of brush-border membranes, sloughing of tubular epithelial cells, and dilation of tubules. This injury was present throughout the cortex and outer medulla. These changes were minimal in kidneys from TNFR2-deficient mice treated with cisplatin.

**TNFR2 induces apoptosis and necrosis in cisplatin nephrotoxicity.** Cisplatin produces both necrosis and apoptosis of renal epithelial cells in vitro (31, 37). The contribution of necrosis and apoptosis to cisplatin injury in vivo is less clear. Moreover, the contribution of TNFR2 signaling to apoptosis in vivo is not well established. Therefore, we quantitated the extent of cisplatin-induced necrosis and apoptosis in vivo and determined the role of TNF-α and TNFR1 and TNFR2 in both processes. The results in Fig. 7 show that cisplatin treatment resulted in both necrosis and apoptosis in vivo. Deletion of TNF-α resulted in a decrease in both...
necrosis and apoptosis. Deletion of TNFR2 also reduced apoptosis and necrosis, although to a lesser extent than did TNF-α deletion. Deletion of TNFR1 resulted in a slight reduction in histological necrosis but no decrease in apoptosis.

TNFR2 induces leukocyte infiltration and ICAM-1 expression. Cisplatin nephrotoxicity is associated with the infiltration of leukocytes into the kidney and up-regulation of ICAM-1 (15, 23, 44). Inhibition of TNF-α (44) or ICAM-1 (23) reduces leukocyte infiltration and also lessens cisplatin nephrotoxicity. Accordingly, we examined the dependence of leukocyte infiltration and ICAM-1 expression on the presence of TNFR1 and TNFR2. Leukocyte infiltration was measured using the naphthol AS-D chloroacetate esterase stain. As shown in Fig. 8, in either C57BL/6 or TNFR1-deficient mice, cisplatin injection produced a large increase in leukocytes within the kidney cortex. In contrast, TNFR2 knockout mice had little or no increase in leukocytes.

A similar pattern was observed for ICAM-1 expression (Fig. 9). Namely, cisplatin increased ICAM-1 expression in wild-type and TNFR1-deficient mice six- to ninefold over saline-treated control mice. In contrast, ICAM-1 expression was significantly blunted in TNFR2-deficient mice compared with wild-type mice ($n = 4$, $P < 0.05$).

**DISCUSSION**

TNF-α is a highly pleiotropic cytokine that plays a role in immune inflammatory response. Intracellular signaling through TNF receptors may lead to apoptosis, cell activation, and/or cell proliferation. Whereas TNFR1 signaling is clearly involved in a number of pathological states (41), the role of TNFR2 in organ pathology is not widely established. Recently, a role for

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**Fig. 7.** Role of TNFR2 in cisplatin-induced necrosis and apoptosis. Mice from each indicated strain were injected with either saline or cisplatin and killed 72 h later. Kidneys were harvested and processed for light microscopy. Tubular necrosis (A) and apoptosis (B) were measured using a semiquantitative scoring method. Cisplatin injection produced a large increase in necrosis and apoptosis in C57BL/6 and TNFR1-KO mice. TNF-KO and TNFR2-KO mice sustained less tubular necrosis and less apoptosis than the corresponding wild-type mice. TNFR1-KO mice had less tubular necrosis than but apoptosis equivalent to that in C57BL/6 mice. $^*P < 0.01$ vs. wild-type mice. $^{+}P < 0.05$ vs. C57BL/6.

**Fig. 8.** Role of TNFR1 and TNFR2 in renal neutrophil infiltration. Neutrophils and monocytes were counted in sections of kidney cortex stained with naphthol AS-D chloroacetate esterase. Cisplatin-treated C57BL/6 and TNFR1-KO mice had a large number of infiltrating leukocytes. Kidneys from TNFR2-KO mice had fewer infiltrating leukocytes. $^{*}P < 0.05$ vs. cisplatin-treated C57BL/6 mice ($n = 5$).
TNF-α in toxic and ischemic acute renal failure has been recognized (14, 16, 26, 44, 51). The mechanisms whereby TNF-α mediates acute renal failure are not clear. We used a clinically relevant model of acute renal failure, cisplatin nephrotoxicity, to investigate the TNF-α signaling pathways during acute renal injury. Several results are noteworthy.

First, we found that the expressions of both TNFR1 and TNFR2 are upregulated after cisplatin injection. This upregulation may serve to sensitize the kidney to the effects of TNF-α. In this regard, serum levels of TNF-α in cisplatin nephrotoxicity, although increased (44), are lower than those that occur in some other disorders mediated by TNF-α, such as sepsis. A dissociation between serum TNF-α levels and TNFR2 expression has been noted in other settings (1), possibly reflecting a need for high levels of TNFR2 expression to mediate biological actions. In addition, elegant studies by Douni and Kollias (17) and Akassoglou et al. (3) demonstrated that high levels of TNFR2 expression can mediate inflammation in a ligand-independent fashion. We did not directly test for ligand-independent actions of TNFR2 in cisplatin nephrotoxicity. However, the observation that deletion of either TNF-α (44) or TNFR2 (Fig. 5) results in similar degrees of protection suggests that ligand-independent actions of TNFR2 do not play a major role. Upregulation of kidney TNF receptors has also been reported in kidney transplant rejection (4). Al-Lamki et al. (4) found relatively little expression of TNFR1 and TNFR2 in normal human kidney allografts. During acute transplant rejection, however, the expression of TNFR1 and TNFR2 was increased in areas of lymphocytic infiltration. TNFR2 expression and/or serum levels of soluble TNFR2 are also elevated in a number of inflammatory conditions, including inflammatory bowel diseases (35), sepsis (48), acute respiratory distress syndrome (33), and cerebral malaria (33).

We determined that the upregulation of TNFR2 was dependent, in part, on TNF-α. TNF-α, via receptor-interacting protein (RIP), activates IκB kinase and subsequent NF-κB transcriptional activity (22). Because the promoter of TNFR2 contains NF-κB binding sites (47), this pathway is a plausible mechanism to account for the observed TNF-α-dependent upregulation of TNFR2. Similarly, the expression of TNF-α was dependent on TNFR2. TNFR2 activation can result in NF-κB activation (34). The presence of NF-κB binding sites within the TNF-α promoter (56), then, provides a mechanism whereby TNF-α can stimulate its own production via TNFR2. The mechanism for the TNF-α-independent upregulation of both TNFR1 and TNFR2 is unknown. We have found that cisplatin activates multiple signaling pathways in the kidney, including ERK, JNK, and p38 (preliminary data). It is possible that one or more of these pathways may influence TNF receptor expression. Finally, the actions of TNF-α in a heterogenous organ like the kidney are likely determined by both the quantity and spatial distribution of TNF receptors. Accordingly, it will be informative to determine the specific sites of TNFR1 and TNFR2 expression in cisplatin nephrotoxicity.

Second, cisplatin-induced tissue injury is mediated, at least in part, via TNFR2. In many pathological states, including some kidney diseases (see below), the actions of TNF-α are mediated through TNFR1. In other settings, TNFR2 may contribute to tissue injury by enhancing TNFR1-mediated toxicity (40, 53, 55). In contrast, we found that TNFR2, independently of TNFR1, was responsible for cisplatin nephrotoxicity. There was a tendency, although not statistically significant, for renal function to be worse in TNFR1-deficient mice than in wild-type mice, raising the possibility that TNFR1 activation may oppose the cytotoxicity of TNFR2 in this model. Further studies with TNFR1/TNFR2-deficient mice will be needed to examine the interactions between these receptors.

Our finding that TNFR2 mediates acute renal injury expands a small but growing list of disorders in which TNFR2 has been shown to play an important role. For example, TNFR2 is upregulated in intestinal inflammation and TNFR2-deficient mice develop less severe intestinal inflammation (35). TNFR2 also participates in intestinal graft vs. host disease (10) and accelerates the early phase of collagen-induced arthritis (50). The recent report by Akassoglou et al. (3) demonstrated that overexpression of TNFR2, in the absence of...
TNFR1 and even TNF-α, induces vascular inflammation and ischemic necrosis in the central nervous system (CNS). Few studies have assigned the actions of TNF-α to a specific receptor in the kidney. In a model of obstructive uropathy, Guo et al. (21) found that both TNFR1 and TNFR2 contributed to interstitial fibrosis, NF-κB activation, and TNF-α expression. Cunningham et al. (13) determined that endotoxin-induced acute renal injury was dependent on intrarenal TNFR1, consistent with the known role of TNFR1 in mediating endotoxic shock (38). There are a number of possible explanations for the differences between our results and the results of Cunningham et al. (13). Injection of endotoxin causes rapid and massive release of TNF-α, the prime mediator of endotoxic shock. In comparison, TNF-α secretion in cisplatin nephrotoxicity is much slower and more modest (44). TNFR2 may be more important in cell death induced by low levels of TNF-α (18). The TNF-α-dependent induction of TNFR2 expression may also affect the relative importance of TNFR1 and TNFR2 in this model. Moreover, soluble TNF-α is a more efficient agonist of TNFR1 (20), whereas membrane-bound TNF-α preferentially activates TNFR2 (19). Accordingly, with endotoxin injection, the high levels of secreted TNF-α might be expected to act primarily via TNFR1, which has a broader constitutive level of expression than TNFR2, whereas, in cisplatin nephrotoxicity, upregulation of TNFR2 along with local production of TNF-α may favor TNFR2 pathways.

Third, cisplatin produces both necrotic and apoptotic cell death in vivo, and TNF-α/TNFR2 signaling contributes to both processes (Fig. 7). Apoptotic signaling has been clearly demonstrated to occur through TNFR1 (6). However, the role of TNFR2, which lacks an intracellular death domain, in apoptosis and inflammation is less clear. TNFR2 can potentiate the proapoptotic effects of TNFR1 activation (55, 57). TNFR2-mediated ubiquitination and degradation of TNF receptor-associated factor 2 may account for this phenomenon (30). TNFR2 may also mediate apoptosis and inflammation independently of TNFR1 (3, 39, 57). In T cells, the ability of TNFR2 to initiate apoptosis in vitro was dependent on high levels of RIP expression (39). However, in vivo demonstrations of TNFR2-dependent apoptosis are lacking. Overexpression of TNFR2 in the CNS, for example, produced vasculitis and necrosis but not apoptosis, whereas TNFR1 expression resulted in apoptosis of oligodendrocytes (3). In cisplatin-induced acute renal failure, we found that TNFR2 mediates, either directly or indirectly, both apoptotic and necrotic death of renal epithelial cells. The relative roles of apoptosis and necrosis in the pathogenesis of renal dysfunction after cisplatin injection are not known. In ischemic injury, recent evidence points to an important role for apoptosis rather than necrosis (24, 25). However, because both necrosis and apoptosis were reduced in TNFR2-deficient mice, our results do not allow any conclusions regarding their relative importance in cisplatin toxicity. Further studies are required to determine whether the cells expressing TNFR2 are the cells that subsequently undergo necrotic or apoptotic death. Similarly, we do not understand the factors that determine whether renal epithelial cells die by necrosis or apoptosis.

In summary, we demonstrated, using TNF-α- and TNF receptor-deficient mice, that cisplatin-induced renal inflammation, cell death, and organ dysfunction were mediated, in part, through TNFR2. Moreover, the induction of TNF-α and TNFR2 expression is interdependent. We also demonstrated that both apoptosis and necrosis of renal epithelial cells were dependent on TNFR2. We conclude that TNFR2 may play a greater role in ischemic and toxic organ injury than had been previously appreciated. Antagonism of TNF-α production or action may have a therapeutic benefit in these settings.

DISCLOSURES

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TNFR2-MEDIATED ACUTE RENAL FAILURE

F617


