Role of p55 tumor necrosis factor receptor 1 in acetaminophen-induced antioxidant defense

Hawjyh Chiu, Carol R. Gardner, Donna M. Dambach, Jennie A. Brittingham, Stephen K. Durham, Jeffrey D. Laskin, and Debra L. Laskin. Role of p55 tumor necrosis factor receptor 1 (TNFR1) in acetaminophen-induced antioxidant defense. Am J Physiol Gastrointest Liver Physiol 285: G959–G966, 2003. First published July 3, 2003; 10.1152/ajpgi.00219.2003.—Tumor necrosis factor (TNF)-α is a macrophage-derived proinflammatory cytokine implicated in hepatotoxicity. In the present studies, p55 TNF receptor 1 (TNFR1) mice were used to assess the role of TNF-α in acetaminophen-induced antioxidant defense. Treatment of wild-type (WT) mice with acetaminophen (300 mg/kg) resulted in centrilobular hepatic necrosis and increased serum alanine transaminases. This was correlated with a rapid depletion of hepatic glutathione (GSH). Whereas in WT mice GSH levels returned to control after 6–12 h, in TNFR1 mice recovery was delayed for 48 h. Delayed induction of heme oxygenase-1 and reduced expression of CuZn superoxide dismutase were also observed in TNFR1 mice compared with WT mice. This was associated with exaggerated hepatotoxicity. In WT mice, acetaminophen caused a time-dependent increase in activator protein-1 nuclear binding activity and in c-Jun expression. This response was significantly attenuated in TNFR1 mice. Constitutive NF-κB binding activity was detectable in livers of both WT and TNFR1 mice. A transient decrease in this activity was observed 3 h after acetaminophen in WT mice, followed by an increase that was maximal after 6–12 h. In contrast, in TNFR1 mice, acetaminophen-induced decreases in NF-κB activity were prolonged and did not return to control levels for 24 h. These data indicate that TNF-α signaling through TNFR1 plays an important role in regulating the expression of antioxidants in this model. Reduced generation of antioxidants may contribute to the increased sensitivity of TNFR1 mice to acetaminophen.

ACETAMINOPHEN IS A COMMONLY used over-the-counter analgesic and antipyretic agent. When ingested in excess quantities, acetaminophen is metabolized by cytochrome P-450 to N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive and toxic metabolite. Concomitant binding of NAPQI to proteins leads to centrilobular hepatic necrosis and fulminant liver failure (26). Other factors contributing to the hepatotoxicity of acetaminophen include proinflammatory and cytotoxic mediators, such as tumor necrosis factor-α (TNF-α), as well as reactive oxygen and nitrogen species (2, 4–7, 10, 12, 13, 19, 20, 22a). These mediators are generated in large quantities by hepatic nonparenchymal cells.

The biological activities of TNF-α are mediated by two distinct cell surface receptors: TNF receptor 1 (TNFR1 or p55) and TNF receptor 2 (TNFR2 or p75). TNFR1 is expressed on most mammalian cell types, whereas TNFR2 is predominantly localized on cells of the immune system (16). Binding of TNF-α to its receptor causes recruitment of cytoplasmic adaptor proteins important in initiating signal transduction. This can lead to activation of various transcription factors, including nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), which are known to be important in regulating genes controlling proinflammatory mediator and antioxidant production, apoptosis, cellular proliferation, and tissue repair (17, 35). The present studies were aimed at evaluating the role of TNF-α in acetaminophen-induced antioxidant defense. For these studies we used mice with a targeted disruption of TNFR1, which has been shown to be primarily involved in TNF-α-induced inflammatory responses (32). We found that these mice exhibited increased sensitivity to acetaminophen-induced hepatotoxicity. This was correlated with decreased activation of NF-κB and AP-1, delayed regeneration of glutathione (GSH) and induction of heme oxygenase-1 (HO-1), and reduced expression of CuZn superoxide dismutase (SOD). These findings suggest that cellular antioxidants may be important in regulating the susceptibility of TNFR1 mice to acetaminophen-induced hepatotoxicity.

MATERIALS AND METHODS

Animals and treatments. C57BL/6 mice with a targeted disruption of the p55 TNFR1 gene were obtained from Immunex (Seattle, WA). Wild-type C57BL/6 mice were from Jackson Labs (Bar Harbor, ME). Male mice were used for all experiments.
experiments. The animals were maintained on food and water ad libitum and housed in groups of six in microisolator cages. Mice were fasted overnight before treatment. All animals received humane care in compliance with the institution’s guidelines, as outlined in the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences. Animals were administered a single intraperitoneal dose of acetaminophen (300 mg/kg) or PBS control. Blood samples were collected from the inferior vena cava, Serum alanine transaminase (ALT) was quantified by using a diagnostic assay kit (Sigma, St. Louis, MO).

**Reagents.** Acetaminophen was purchased from Sigma. Rabbit anti-rat HO-1 and CuZn SOD antibodies were obtained from Stressgen (Victoria, BC, Canada). Rabbit anti-human catalase antibody was from Roche (Indianapolis, IN), and rabbit anti-human c-Jun, phospho-c-Jun (Ser63) and phospho-c-Jun (Ser73) antibodies were from Cell Signaling (Beverly, MA). Rabbit anti-mouse p65 and p50 antibodies and goat anti-rabbit horseradish peroxidase-conjugated secondary antibody were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Horse anti-rabbit biotinylated secondary antibody was from Vector Laboratories (Burlingame, CA).

**Measurement of GSH.** Whole liver GSH was quantified by using the method of Gualilqui et al. (15). Briefly, samples of freshly isolated liver were homogenized in 5% trichloroacetic acid (1:5 wt/vol) on ice. Homogenates were centrifuged at 3,000 g for 10 min at 4°C, and supernatants were collected and frozen at −70°C.

**Preparation of liver extracts.** To prepare whole liver extracts, samples (200–600 mg) were homogenized and then lysed in buffer (50 mM Tris·HCl, pH 7.5, 0.5% Igepal CA-630, 10 mM PMSF, 1.5 mM aprotinin, and 20 mM leupeptin) on ice. The samples were then centrifuged (4°C, 15,000 g, 20 min), and supernatants were collected and frozen at −70°C. To prepare nuclear extracts, livers were homogenized in buffer (in mM: 10 HEPES, pH 7.4, 10 KCl, 2 MgCl2, and 2 EDTA, with 10% Igepal CA-630) on ice. After 5 min on ice, the homogenates were centrifuged (4°C, 16,000 g, 5 min) and the pellets were resuspended in extraction buffer (in mM: 50 HEPES, pH 7.4, 50 KCl, 300 NaCl, and 0.1 EDTA, with 10% glycerol) and incubated on ice for 20 min with periodic mixing. The samples were then centrifuged (4°C, 16,000 g, 5 min), and supernatants containing nuclear extracts were collected and frozen at −70°C until analysis. Protein concentrations were determined by using the BCA protein assay (Pierce Biotechnology, Rockford, IL) with bovine serum albumin as the standard.

**Western blotting analysis.** Equal amounts of proteins were fractionated on 10 or 12% SDS polyacrylamide gels and transferred to Immun-Blot PVDF membranes (Bio-Rad Laboratories, Hercules, CA). Membranes were incubated with rabbit polyclonal antibody against HO-1 (1:2,000), CuZn SOD (1:40,000), catalase (1:2,000), c-Jun (1:2,000), p65 (1:2,000), or p50 (1:2,000) for 2 h at 25°C followed by horseradish peroxidase-labeled IgG (1:5,000) for 1 h at 25°C. Antibody binding was visualized by autoradiography using enhanced chemiluminescence Western blotting detection reagents (Amersham Life Science, Arlington Heights, IL). Blots were quantified by using One-Decan software (Scanalytics, Fairfax, VA).

**Histology and immunohistochemistry.** Livers were removed, fixed in 3% paraformaldehyde in PBS at 4°C, transferred to 50% ethanol, and paraffin-embedded. Tissue sections (6 μm) were prepared and stained with hematoxylin and eosin (Goode Histolabs, New Brunswick, NJ). For immunohistochemical analysis, sections were incubated overnight at 4°C with a 1:250 dilution of rabbit polyclonal antibody against c-Jun or phospho-c-Jun (Ser63) followed by a 30-min incubation with biotinylated secondary antibody (1:2,000). Antibody binding was visualized by using a Vectastain Elite ABC Kit (Vector Laboratories, Burlingame, CA).

**Measurement of catalase activity.** Catalase activity was measured by the decomposition of hydrogen peroxide (22). Briefly, 333 μl of liver homogenate was diluted in 1 volume of phosphate buffer (50 mM K2HPO4 and 50 mM KH2PO4, pH 7.0) and transferred immediately to a cuvette containing 1 volume of 30 mM hydrogen peroxide. The change in absorbance at 240 nm was recorded for 1 min. One unit of catalase activity is defined as 1 μmol of hydrogen peroxide consumed per minute per milligram of protein.

**Electrophoretic mobility gel shift assay.** Binding reactions were performed at room temperature for 30 min in a total volume of 15 μl containing 2–5 μg of nuclear extracts; 5 μl of 5× gel shift binding buffer [20% glycerol with (in mM) 5 MgCl2, 2.5 EDTA, 2.5 dithiothreitol, 250 NaCl, and 50 Tris·HCl, pH 7.5]; 2 μg poly(dI·dC); and 3 × 104 counts·min·ml−1·μl−1 [γ-32P]ATP (3,000 Ci/mmol at 10 μCi/ml)-labeled probe containing NF-κB (AGTTGAGGGGACTT-CGCCAGGC) or AP-1 (GATCTTCGTGACTCAGCGG-GATCTTTTGACTCAGCGG) consensus oligonucleotides (Gel Shift Assay System; Promega, Madison, WI). Protein-DNA complexes were separated on 5% non-denaturing polyacrylamide gels run at 250 V in 0.5× TBE (45 mM Tris-borate and 1 mM EDTA, pH 8.0) and visualized after the gels were dried and autoradiographed. For supershift assays, the reaction mixtures were preincubated on ice for 15 min with 1 μg of antibody to NF-κB (p65 or p50) or AP-1 (c-Jun, phospho-c-Jun Ser63 or Ser73) subunits before the addition of labeled oligonucleotide. For competition reactions, 40-fold excess of the respective unlabeled oligonucleotide was added to the mixture 15 min before the addition of the labeled probe.

**Statistics.** All experiments used 3–10 animals per treatment group and were repeated 3–4 times. Data were analyzed by using Student’s t-test or ANOVA followed by Tukey’s post hoc test. Results were considered statistically significant at P < 0.05.

**RESULTS**

Acetaminophen-induced hepatotoxicity in TNFR1+/− mice. Treatment of wild-type mice with acetaminophen resulted in a time-dependent increase in serum ALT, which reached maximal levels at 18 h (Fig. 1, top). Subsequently, ALT levels returned toward control. A generally similar temporal pattern of serum ALT was observed in TNFR1−/− mice after acetaminophen administration; however, the response of these mice was significantly greater 6–18 h after treatment. Hepatic injury assessed morphologically was also greater in TNFR1−/− mice compared with wild-type mice (Fig. 1, bottom).

**Effects of acetaminophen on hepatic GSH levels.** GSH plays an important role in detoxification of the acetaminophen metabolite NAPQI (27). We found that acetaminophen administration resulted in rapid depletion of hepatic GSH (Fig. 2). This was evident within...
1 h in both wild-type and TNFR1−/− mice. Whereas in wild-type mice GSH levels returned toward control levels by 6 h, in TNFR1−/− mice GSH depletion was prolonged and did not return to control levels until 48 h after acetaminophen administration. At this time GSH levels were approximately twofold greater in TNFR1−/− mice than in wild-type mice.

**Effects of acetaminophen on hepatic expression of antioxidants.** We next analyzed expression of other antioxidants known to protect against acetaminophen-induced tissue injury. HO-1, or heat shock protein 32, is upregulated during oxidant-induced injury (11) and has previously been shown to be important in acetaminophen-induced hepatotoxicity (9). Treatment of wild-type mice with acetaminophen resulted in a rapid induction of HO-1, which reached a maximum within 6 h (Fig. 3A). Although HO-1 was also induced by acetaminophen in TNFR1−/− mice, maximal expression was delayed for 24 h. HO-1 expression was markedly higher at this time in TNFR1−/− mice compared with wild-type mice. SOD and catalase are antioxidant enzymes also reported to protect against acetaminophen-induced hepatotoxicity (12, 25, 29). Both of these proteins were constitutively expressed in livers of wild-type and TNFR1−/− mice (Fig. 3, B and C). Whereas acetaminophen administration had no effect on expression of CuZn SOD in wild-type mice, a time-dependent decrease in expression of this antioxidant was observed in TNFR1−/− mice beginning 6 h after treatment (Fig. 3B). In contrast, acetaminophen had no significant effects on Mn SOD protein expression in either mouse strain (data not shown). No major changes in catalase levels or activity were detected in livers of either wild-type or TNFR1−/− mice following acetaminophen administration (Fig. 3C and Fig. 4). However, the activity of this antioxidant was significantly lower in TNFR1−/− mice compared with wild-type mice 24 h after acetaminophen treatment (Fig. 4). No differences in catalase activity were noted between wild-type and TNFR1−/− mice 3–12 h after acetaminophen administration (data not shown).

**Effects of acetaminophen on AP-1 and NF-κB.** The transcription factors AP-1 and NF-κB are downstream...
effectors of TNFR1 signaling (8, 32). They are known to regulate expression of many inducible genes involved in hepatotoxicity, including antioxidants (20, 31, 33).

In further studies, we compared acetaminophen-induced AP-1 and NF-κB nuclear binding activity in livers of wild-type and TNFR1−/− mice. Treatment of wild-type mice with acetaminophen resulted in an increase in AP-1 nuclear binding activity (Fig. 5) that was maximal at 12 h. By 24 h, AP-1 nuclear binding activity returned to control levels. Acetaminophen administration also resulted in an increase in nuclear expression of total c-Jun and phospho-c-Jun proteins in the liver within 3 h, which persisted for at least 24 h (Figs. 6 and 7). In contrast, AP-1 nuclear binding activity was not detected in the livers of TNFR1−/− mice until 6 h after acetaminophen. Furthermore, this activity, as well as expression of c-Jun and phospho-c-Jun, was reduced in TNFR1−/− mice compared with wild-type mice (Figs. 5–7). AP-1 nuclear binding was blocked by excess unlabeled oligonucleotide, demonstrating the specificity of the probe (Fig. 5). Antibodies to c-Jun, phospho-c-Jun (Ser63), and phospho-c-Jun

Fig. 3. Effects of acetaminophen on hepatic antioxidant expression. Liver samples were collected 3–24 h after treatment of WT or TNFR1−/− mice with PBS control or acetaminophen. Heme oxygenase-1 (A; HO-1; 20 μg/lane), CuZn SOD (B; 5 μg/lane), and catalase (C; 10 μg/lane) protein expressions were analyzed by Western blotting. One representative blot is shown. Blots were scanned by densitometry, and the data are presented as relative intensity units. Values are means ± SE (n = 3 animals). Open bars, WT; closed bars, TNFR1−/−. aSignificantly different (P < 0.05) from control. bSignificantly different (P < 0.05) from WT.

Fig. 4. Effects of acetaminophen on hepatic catalase activity. Liver samples were collected 24 h after treatment of WT or TNFR1−/− mice with PBS control or acetaminophen. Values are means ± SE (n = 3 animals). bSignificantly different (P < 0.05) from WT mice.

Fig. 5. Effects of acetaminophen on activator protein-1 (AP-1) nuclear binding activity. Liver samples were collected 1–24 h after treatment of WT or TNFR1−/− mice with PBS control or acetaminophen. Nuclear extracts were analyzed for AP-1 binding activity by EMSA. Extracts from WT mice prepared 12 h after acetaminophen administration were incubated on ice for 20 min with antibodies to c-Jun, phospho-c-Jun (Ser63), phospho-c-Jun (Ser73), or 40-fold excess of unlabeled cold competitor (cc) before the labeled probe. One representative of three experiments is shown.
(Ser\textsuperscript{73}) caused a supershift of the AP-1 complex, suggesting the presence of c-Jun phosphorylated on serines 63 and 73.

Constitutive NF-\kappaB nuclear binding activity was detected in livers of both wild-type and TNFR1\textsuperscript{−/−} mice (Fig. 8). Acetaminophen administration to wild-type mice resulted in a transient decrease in NF-\kappaB nuclear binding activity, which was observed at 3 h. This was followed by an increase in NF-\kappaB activity at 6 and 12 h and a secondary decrease at 24 h. Decreased NF-\kappaB nuclear binding activity was also observed in TNFR1\textsuperscript{−/−} mice following acetaminophen administration; however, this was more rapid, occurring within 1 h, and was prolonged. NF-\kappaB nuclear binding was blocked by excess unlabeled oligonucleotide, demonstrating the specificity of the probe. Furthermore, the addition of antibody specific for the p50 subunit of NF-\kappaB resulted in a supershift of the NF-\kappaB complex in the gel. Reduced NF-\kappaB binding activity was observed in the presence of anti-p65 NF-\kappaB antibody. We also analyzed expression of NF-\kappaB p50 and p65 in wild-type and TNFR1\textsuperscript{−/−} mice (Fig. 9). Acetaminophen had no significant effect on expression of these proteins in either genotype.

**DISCUSSION**

In the present studies, mice lacking TNFR1 were used to evaluate the role of TNF-\alpha in the generation of antioxidants known to be important in limiting acetaminophen-induced hepatotoxicity. TNFR1\textsuperscript{−/−} mice were found to be more sensitive to the toxic effects of...
acacetaminophen than wild-type mice, which was evident in histologic sections and by increases in serum transaminase levels. This was correlated with delayed regeneration of GSH and induction of HO-1 as well as reduced expression of CuZn SOD. Nuclear binding activity of the transcription factors NF-κB and AP-1, which regulate the production of antioxidants, was also reduced. These findings suggest a potential mechanism contributing to exaggerated hepatotoxicity of acetaminophen.

TNF-α is a macrophage-derived proinflammatory mediator that has been implicated in tissue injury induced by a number of hepatotoxicants, including acetaminophen (19). However, the precise role of TNF-α in acetaminophen-induced hepatitis is controversial. Whereas some studies have suggested that TNF-α contributes to toxicity, others indicate that it has no effect. This may be related to multiple capabilities of TNF-α in the liver. Thrus Blazka et al. (2, 5) showed that administration of polyclonal antisera to TNF-α immediately before acetaminophen delayed hepatic necrosis, indicating a cytotoxic action of TNF-α in this model. In contrast, Simpson et al. (36) reported no effect of anti-TNF-α antibody on acetaminophen-induced hepatotoxicity. Similarly, Boess et al. (6) found no significant differences in the susceptibility of wild-type and TNF-α/lymphotoxin-α double-knockout mice to acetaminophen. In our studies, TNFR1−/− mice treated with acetaminophen exhibited exaggerated hepatic injury compared with wild-type mice. This did not appear to be due to changes in the activity of reactive acetaminophen metabolites (14). These findings suggest that TNF-α signaling through TNFR1 plays a protective role in this model. Our results are consistent with previous reports that TNFR1−/− mice are more susceptible to bacterial infection and to liver injury induced by partial hepatectomy or carbon tetrachloride (32, 34, 37). Differences between our findings and previous studies may be due to differences in the genotypes of the animals used and/or the doses of acetaminophen administered. The fact that different approaches were used to manipulate TNF-α activity may also be a contributing factor.

Oxidative stress is an important step in the pathogenesis of acetaminophen-induced hepatotoxicity. GSH, a scavenger of reactive oxygen species, is normally present at relatively high levels in hepatocytes and is the major thiol responsible for detoxification of the reactive acetaminophen metabolite NAPQI (27). Consistent with previous studies (6), we found that acetaminophen-induced hepatotoxicity was associated with a rapid depletion of liver GSH in wild-type mice as well as in TNFR1−/− mice. Whereas in wild-type mice GSH levels returned to control levels by 6 h, recovery of cellular GSH was extended for at least 24 h in TNFR1−/− mice. These findings indicate that TNF-α plays a role in regulating GSH levels in the liver during acetaminophen-induced tissue injury. In this regard, previous studies have shown that γ-glutamylcysteine synthase, the enzyme catalyzing the rate-limiting step in the de novo synthesis of GSH, is upregulated in hepatocytes treated with TNF-α (28). Decreased activation of γ-glutamylcysteine synthase may account for the delay in GSH regeneration in TNFR1−/− mice treated with acetaminophen. Interestingly, GSH levels rebounded at 48 h and were greater in TNFR1−/− mice compared with wild-type mice. This may reflect an attempt to overcome excessive accumulation of cytotoxic oxidants in the liver.

HO-1 is the inducible form of the rate-limiting enzyme responsible for degrading heme into biliverdin, carbon monoxide, and iron (23). It functions to down-regulate the inflammatory response by either attenuating the expression of adhesion molecules and thus inhibiting leukocyte recruitment or by repressing the induction of cytokines and chemokines (38). In previous studies, we reported that acetaminophen treatment of animals resulted in a time-dependent increase in HO-1 expression in hepatocytes and Kupffer cells (9). Furthermore, pretreatment of the animals with hemin, a substrate and inducer of HO-1, or biliverdin, a product of heme metabolism, significantly attenuated acetaminophen-induced hepatotoxicity (9). The present studies show that induction of HO-1 by acetaminophen was significantly delayed in TNFR1−/− mice compared with wild-type mice. These results are
in accord with previous findings demonstrating a critical role of TNF-α in regulating HO-1 expression (30). The increase in HO-1 expression that we observed in TNFR1−/− mice 12 and 24 h after acetaminophen may be due to compensatory increases in other inflammatory mediators that induce HO-1 in these mice.

Exaggerated hepatotoxicity of acetaminophen in TNFR1−/− mice was also correlated with decreased CuZn SOD expression as well as catalase activity in the liver. SOD and catalase are responsible for reducing cellular levels of superoxide anion and hydrogen peroxide, respectively (24). Treatment of hepatocytes with SOD and catalase has been reported to prevent acetaminophen-induced toxicity (18). Moreover, transgenic mice overexpressing CuZn SOD or mice pretreated with a liposome-encapsulated SOD or a SOD mimetic were protected from acetaminophen-induced tissue injury (12, 25, 29). These findings demonstrate the importance of SOD and catalase in protecting against acetaminophen-induced injury. Decreased levels of SOD and catalase in TNFR1−/− mice may lead to increased susceptibility of the liver to oxidative stress, contributing to exaggerated tissue injury following acetaminophen administration. This is supported by our findings that expression of inducible nitric oxide synthase and peroxynitrite-mediated injury occur more rapidly in the livers of TNFR1−/− mice compared with wild-type mice (14).

Many inducible genes involved in the antioxidant response are transcriptionally regulated by NF-κB and AP-1. These include glutathione-S-transferase, γ-glutamylcysteine synthase, catalase, SOD, and HO-1 (17, 21, 31, 33, 35). In accord with previous reports in rats (1), we found that AP-1 nuclear binding activity and c-Jun expression were increased in wild-type mice following acetaminophen administration. Although increased AP-1 nuclear binding activity was also observed in TNFR1−/− mice after acetaminophen, this response was significantly attenuated. Expression of c-Jun was also reduced. These results suggest a key role of TNF-α in regulating c-Jun expression and AP-1 nuclear binding activity in this model of hepatotoxicity.

Constitutive NF-κB nuclear binding activity was observed in both wild-type and TNFR1−/− mice. These findings are consistent with previous reports (3) and most likely reflect activation of liver cells by continuous exposure to endotoxin from the portal circulation. Acetaminophen administration to wild-type mice resulted in a transient decrease in NF-κB binding activity, followed by an increase that was maximal after 6–12 h. In contrast, acetaminophen administration to TNFR1−/− mice resulted in a more rapid and more prolonged decrease in NF-κB nuclear binding activity, which did not recover until 24 h after treatment. This timing correlated with the delayed regeneration of GSH and upregulation of HO-1. These data indicate that TNFR1 is important in activation of both AP-1 and NF-κB during acetaminophen-induced hepatotoxicity. We speculate that reduced activity of these transcription factors in TNFR1−/− mice treated with acetaminophen may contribute to decreases in GSH and HO-1, which would be expected to exacerbate tissue injury. NF-κB has recently been shown to be involved in the regulation of anti-inflammatory genes implicated in the resolution of tissue injury (21). This action may also be important in tissue injury induced by acetaminophen.

In summary, the present studies demonstrate that exaggerated hepatotoxicity of acetaminophen in TNFR1−/− mice is associated with decreased hepatic antioxidant response. Additional studies are required to determine if signaling through TNFR1 leading to activation of redox-sensitive transcription factors are important in protecting the liver against acetaminophen-induced tissue injury.

DISCLOSURES

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REFERENCES


