Tumor necrosis factor (TNF) has multiple biological effects such as participating in inflammation, apoptosis, and cell proliferation, but the mechanisms of its effects on epithelial cell proliferation have not been examined in detail. At the early stages of liver regeneration, TNF functions as a priming agent for hepatocyte replication and enhances the sensitivity of hepatocytes to growth factors such as transforming growth factor α (TGFα); however, the mechanisms by which TNF interacts with growth factors and enhances hepatocyte replication are not known. Using the AML-12 hepatocyte cell line, we show that TNF stimulates proliferation of these cells through transactivation of the epidermal growth factor receptor (EGFR). The transactivation mechanism involves the release of TGFα into the medium through activation of the metalloproteinase TNFα-converting enzyme (also known as ADAM 17). Binding of the ligand to EGFR initiates a mitogenic cascade through extracellular signal-regulated kinases 1 and 2 and the partial involvement of protein kinase B. TNF-induced release of TGFα and activation of EGFR signaling were inhibited by TNFα protease inhibitor-1, an agent that interferes with TNFα-converting enzyme activity. We suggest that TNF-induced transactivation of EGFR may provide an early signal for the entry of hepatocytes into the cell cycle and may integrate proliferative and survival pathways at the start of liver regeneration.

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The abbreviations used are: TNF, tumor necrosis factor; TNFα, TNF receptor; TRADD, TNFR1-associated death domain protein; TRAF2, TNFR-associated factor; FADD, Fas-associated death domain; TGFα, transforming growth factor-α; EGFR, epidermal growth factor receptor; ADAM, a disintegrin and metalloproteinase; TACE, TNFα-converting enzyme; TAPI-1, TNFα protease inhibitor-1; DMEM, Dulbecco’s modified Eagle’s medium; MP, metalloproteinase; MMP, matrix MP; BrdUrd, bromodeoxyuridine; PBS, phosphate-buffered saline; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase/ERK kinase; HB-EGF, heparin-binding EGF-like growth factor; F3K, phosphoinositide 3-kinase; PKB, protein kinase B (also known as Akt).

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Epidermal Growth Factor Receptor Transactivation Mediates Tumor Necrosis Factor-induced Hepatocyte Replication*

Epidermal Growth Factor Receptor Transactivation Mediates Tumor Necrosis Factor-induced Hepatocyte Replication*
Vector; EK1/2 antibody as described previously (16); γ[32P]ATP (3000 Ci/mmol) and Renaissance chemiluminescent reagent from PerkinElmer Life Sciences; Triton X-100, 3,3-diaminobenzidine tablets, phosphoamino acid standards, and protein A-Sepharose from Sigma; Immobilon P polyvinylidene difluoride membrane from Millipore; blotting grade dry milk from Bio-Rad; EGFR (immunoprecipitation) antibody from UBI, EGFR (Western blot) and F299 antibodies from Santa Cruz Biotechnology; and TGFα-neutralizing antibody from R & D Systems. All other antibodies were purchased from Cell Signaling Technologies.

Buffers—The buffers used were Triton lysis buffer (25 mM HEPES, pH 7.4, 5 mM EDTA, 5 mM EGTA, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 50 mM NaF, 4 μg/ml aprotinin, 10 μg/ml benzamidine, 1 mM Na3VO4, 0.1% SDS polyacrylamide, 1 mM Na3VO4, 1 mM Na2VO4), an assay buffer (20 mM HEPES, pH 7.4, 20 mM MgCl2, 0.1% β-mercaptoethanol), and an assay buffer plus ATP (100 μM cold ATP, 20 μM CTP, ATP). Cells were plated in 6- or 12-well plates, serum-starved overnight in complete medium containing the insulin:transferrin:selenium mixture, dexamethasone, and gentamicin. The medium was changed to phosphate-free DMEM/hi glucose medium, and cultures were pretreated for 30 min prior to stimulation with the indicated concentration of inhibitor, which remained in the medium for the remainder of the experiment. The final concentration of Me2SO, the diluent for the inhibitor, was present in the culture medium at 0.1%. When using the TGFα-neutralizing antibody, cultures were preincubated with 3 μg/ml antibody for 2 h prior to stimulation. Aliquots of TNF and TGFα used for stimulation were also preincubated with antibody (3 μg/ml) for 2 h at room temperature.

[3H]Thymidine Incorporation Assay—AML-12 cells were plated at 40,000 cells/well in 24-well tissue culture plates and allowed to grow overnight in 10% fetal bovine serum. The following day, the cells were rinsed twice with Hanks’ buffered saline solution, and complete medium containing no fetal bovine serum was added to the cells. The cells were stimulated the following day for 24 h unless otherwise noted. [3H]Thymidine (1 μCi/ml final concentration) was added to the medium for 4 h before harvesting cells. The trichloroacetic acid non-precipitable fraction was removed from the cells, and the precipitable fraction was solubilized in NaOH and quantified using a scintillation counter. Each treatment was measured in triplicate, and the data are represented as the average, with the error bars representing the mean ± S.E.

BrdUrd Labeling—Cells were plated in 6- or 12-well plates, serum-starved, and stimulated as described previously in the [3H]thymidine incorporation assay. For the last 3 h of stimulation, the cultures were incubated with BrdUrd labeling reagent at 1:1000 dilution. Cells were rinsed and fixed for 30 min at room temperature with acetic alcohol (90% ethanol, 5% acetic acid, 5% distilled H2O). Endogenous peroxidase was blocked by incubation in 1% H2O2 in methanol for 20 min at room temperature. Cells were washed in PBS and incubated in 1.5 M HCl at 37 °C for 15 min followed by extensive washing in PBS. Cells were then incubated in anti-BrdUrd antibody at 1:40 dilution in PBS containing 1% bovine serum albumin for 1 h at 37 °C and washed in PBS. Cells were incubated in anti-mouse secondary antibody at 1:100 dilution in PBS, 1% bovine serum albumin for 30 min at room temperature followed by washing. Cells were incubated in ABC solutions for 30 min at room temperature, washed, and incubated in 50 mM Tris, pH 7.6, for 5 min, and then the 3,3-diaminobenzidine solution was added. Three areas in each well were counted for a total of ~1000 cells. Proliferation is indicated as a percentage of labeled nuclei.

Transforming Growth Factor α Enzyme-linked Immunosorbent Assay—Cells were cultured and stimulated according to [3H]thymidine incorporation protocol. Cell culture medium was collected 21 h after stimulation and frozen in aliquots at ~80 °C for analysis. Human TGFα was quantified by enzyme-linked immunosorbent assay (Oncogene Research Products, San Diego, CA) according to the manufacturer’s protocol.

Preparation of Lysates—To harvest for whole cell protein after the indicated stimulation, cells in 10-cm plates were washed twice with ice-cold PBS and harvested by scraping into 0.5 ml of Triton X-100 lysis buffer. Lysates were sonicated twice for 1–2 s on the lowest setting and then clarified by centrifugation at 16,000 × g for 10 min at 4 °C. Supernatants were frozen in aliquots at −80 °C. Western blots were performed following standard protocols. Briefly, lysates (20 μg) were resolved on SDS polyacrylamide gels and electrotransferred to Immobilon P polyvinylidene difluoride membranes. Anti-EGFR Western blots, 50 μg of lysate was resolved on low bisacrylamide (0.4%) gels (18) that were transferred overnight at 4 °C. Membranes were blocked in Tris-buffered saline, 0.1% Tween-20 (TBST) containing 4% milk or bovine serum albumin (anti-phosphotyrosine blots) prior to incubation with primary antibodies. Membranes were then washed well with TBST, incubated with secondary antibody (anti-rabbit horseradish peroxidase at 1:10,000, anti-mouse horseradish peroxidase at 1:5000) for 1 h, washed extensively in TBST, and developed with a chemiluminescent reagent.

Epithelial Growth Factor Receptor Immunoprecipitation—AML-12 cells were harvested in Triton X-100 lysis buffer containing no reducing agent (β-mercaptoethanol). Lysate (25 μg) was incubated overnight at 4 °C with 1 μg of antibody and 20 μl of a 50% protein A-Sepharose slurry. The beads were washed once with lysis buffer and once with kinase buffer. The beads were then boiled in 2× Laemmli sample buffer and run on SDS-polyacrylamide gels. Gels were transferred to polyvinylidene difluoride membranes overnight at 4 °C and then immunoblotted as described previously.

32P Labeling and Phosphoamino Acid Analysis—10-cm dishes of AML-12 cells were serum-starved overnight in DMEM/hi glucose medium containing the insulin:transferrin:selenium mixture, dexamethasone, and gentamicin. The medium was changed to phosphate-free DMEM/hi glucose, and 1 MCI of [32P]orthophosphate (PerkinElmer Life Sciences) was added to each plate (5 ml). Cells were labeled for 6 h and then stimulated as indicated. Whole cell lysates were prepared as described previously. EGFR was immunoprecipitated overnight (500 μg of lysate, 2 μl of antibody, and protein A-Sepharose). Immunoprecipitates were run on SDS polyacrylamide gels, dried, and exposed to film to visualize [32P]incorporation into the receptor. The labeled bands were excised from the gel and quantified by Cerenkov counting. Protein was extracted from the gel and analyzed for phosphoamino acid as described previously (18). For phosphoamino acid analysis, dried pellets were resuspended in 5 μl of distilled H2O. 1 μl of the phosphoserine, -threonine, and -tyrosine standard and 2 μl of sample were loaded onto the origin of a 10 × 10-cm cellulose TLC plate. First dimension separation was run in ethanol:glacial acetic acid:distilled H2O (1:1:1) for 90 min at room temperature. Second dimension separation was run in butanol:formic acid:distilled H2O (8:3.4:4, v/v/v) for 40 min. Plates were dried and sprayed with 0.5% ninhydrin in 0.5% acetic acid and heated to 80 °C for 5 min to visualize standards. Plates were then exposed to film for visualization of [32P]incorporation.

**RESULTS**

**Induction of Cell Proliferation by Tumor Necrosis Factor—**To study the effects of TNF on cell replication, AML-12 cells were maintained in serum-free medium for 24 h, a procedure that reduced DNA replication as determined by BrdUrd labeling to a basal level of less than 10%. Subconfluent serum-starved cells were exposed to 20 ng/ml TNF for 24–72 h (Fig. 1a). Cell labeling by BrdUrd increased to 53% at 24 h and progressively decreased to the same level as non-stimulated cultures by 72 h. In repeated experiments, TNF increased BrdUrd labeling by 2–5-fold at 24 h and also increased the cell number by 2.5-fold at 48 h (data not shown). AML-12 hepatocytes produce membrane-bound pro-TGFα (17). Nevertheless, addition of TGFα to the culture medium enhances DNA replication (Fig. 1b). At the doses used, TGFα increased BrdUrd labeling between 5- and 10-fold 24 h after exposure and increased cell numbers at 48 h. These data indicate that the EGFR is not saturated with endogenous ligand and is receptive to additional ligand stimulation. Consistent with this notion, we found that EGF and HB-EGF also stimulate DNA replication in AML-12 cells at levels comparable with those obtained with TGFα. In contrast, interleukin-6 and oncostatin M had little to no effect (data not shown).

**Tumor Necrosis Factor-induced Cell Replication Requires Transforming Growth Factor α/Epithelial Growth Factor Receptor Signaling—**We have previously shown that TNF functions as a mitogen for intrahepatic stem cells (oval cells) and for primary hepatocytes in serum-containing cultures but is without effect in serum-free cultures (4). The finding that TNF functions as a complete mitogen for AML-12 hepatocytes maintained in serum-free medium indicated that in these cells a second proliferative signal may be generated by TNF. We hy-
We next examined whether exposure to TNF causes phosphorylation of EGFR (Fig. 3). Whole cell lysates from cultures treated with either TNF or TGFα were immunoprecipitated with EGFR antibody and immunoblotted to detect phosphoryrosine. Fig. 3a shows that EGFR is phosphorylated on tyrosine in unstimulated AML-12 cells maintained in serum-free medium as determined by using the anti-phosphotyrosine antibody PY99. As expected, stimulation with TGFα caused increased phosphotyrosine reactivity. The addition of TNF did not cause a detectable increase in phosphotyrosine reactivity over the high basal signal, but it did cause an apparent shift in mobility, suggesting that the receptor might be modified by phosphorylation after TNF stimulation. To analyze the specific residues in the EGFR that may be phosphorylated after exposure to TNF or TGFα, we labeled serum-starved cells with [32P]orthophosphate. Cells were exposed to TNF or TGFα for 15 min and processed for phosphoamino acid analysis of EGFR. Both TNFα and TGFα increased EGFR phosphorylation by 2–4-fold. EGFR protein was then extracted from the gel to determine which residues were phosphorylated after TNF and TGFα stimulation. Both agents caused an increase in serine and tyrosine phosphorylation of the receptor but did not appreciably enhance threonine phosphorylation (Fig. 3b).

Tumor Necrosis Factor-induced DNA Replication Requires EGFR Transactivation—The MEK1/2-ERK1/2 signaling pathway is activated by multiple tyrosine kinase receptors and is generally involved in cell proliferation. To test whether ERK1/2 is required for TNF-induced DNA replication in AML-12 cells, we inhibited the ERK1/2 pathway by blocking its upstream activator MEK1/2 with U0126 (Fig. 4a). This compound almost entirely blocked DNA replication induced by either TNF or TGFα.

Growth factors and cytokines can also activate the phosphoinositide 3-kinase (PI3K) pathway. To determine whether this pathway participates in TNF-induced DNA replication, we blocked PI3K with the specific inhibitor LY294002 (Fig. 4b). DNA replication induced by either TNF or TGFα was blocked by this agent. Inhibition of ERK1/2 and PI3K in TNF-stimu-
lated cells prevented the increase in DNA replication but did not affect cell survival.

The MEK/ERK, PI3K, and NFκB pathways are all required for survival and/or proliferation after TNF exposure to AML-12 cells. To determine whether EGFR signaling is required for the activation of these pathways, we blocked EGFR kinase activity with AG1478 and assayed for phosphorylation of ERK1/2, PKB, and IκBα after TNF and TGFα stimulation. In preliminary experiments, we determined that the peak activation of ERK1/2, PKB, and IκBα occurred respectively at 15, 10, and 5 min after TNF exposure (data not shown). Fig. 5 shows that inhibition of EGFR activity during TNF stimulation completely blocked the phosphorylation of ERK1/2 at Thr-202 and Tyr-204

![Graphs and diagrams illustrating TNF-induced phosphorylation/activation of EGFR, MEK/ERK and PI3K/PKB signaling, and EGFR kinase activity, with corresponding experimental results and data tables.]
TNF-induced Proliferation Requires EGFR Transactivation

...the amounts of TGFα released in the culture medium (Fig. 6a). The broad specificity MP inhibitor GM6001 prevented this increase at concentrations of 10 and 50 μM, whereas an inactive form of GM6001 (negative control) had no effect (Fig. 6a). The inhibitor also blocked TNF-induced DNA replication by more than 50% (Fig. 6b) but had no effect on DNA synthesis induced by TGFα. This suggests that MPs act in TNF-mediated cell proliferation but do not participate in EGFR activation by exogenous TGFα. To determine what types of MPs may be involved in this process, we tested the effect of MP inhibitors with more defined specificity. TACE is a metalloproteinase disintegrin that cleaves proteins anchored in the cell membrane (20, 21). TNF, TGFα, and other ligands of the EGF family can serve as substrates for this enzyme (22, 23). TAPI-1, a specific inhibitor of TACE, blocked TNF-induced DNA replication and the release of TGFα into the medium (Fig. 7, a and b). In marked contrast, inhibitors of matrix metalloproteinases 2, 3, 8, 9, and 13 had no effect on TNF-induced DNA replication (Fig. 7c).

We next determined whether TACE blockage, shown to inhibit TNF-induced DNA replication, would interfere with EGFR signaling. Cells treated with TAPI-1 or MeSO (as control) were stimulated with TNF or TGFα. Immunoblot analysis (Fig. 8) showed that TAPI-1 completely blocked the phosphorylation of ERK1/2 induced by TNF (Fig. 8a) and partially prevented the phosphorylation of PKB by TNF (Fig. 8b). The TACE inhibitor had no effect on ERK1/2 or PKB phosphorylation induced by exogenous TGFα. These experiments suggest that TNF stimulates cell proliferation in AML-12 hepatocytes through the activation of TACE, which cleaves membrane-bound TGFα. This ligand in turn binds to EGFR to initiate a mitogenic cascade that involves ERK1/2 and PKB.

**DISCUSSION**

TNF induces multiple responses in the liver, including cytokine activation, cell death, and cell proliferation (24). Although the mechanisms by which TNF causes cytokine stimulation and apoptosis have been well studied, much less is known about the mechanisms by which TNF stimulates hepatocyte replication. Activation of NFκB and signal transducer and activator 3 and increases in interleukin-6 are associated with hepatocyte proliferation in the regenerating liver in vivo and in cell cultures, but it is still unresolved whether these agents function to maintain cell survival or are direct participants in signaling events that culminate in DNA replication. We have shown that TNF acts in conjunction with growth factors to stimulate hepatocyte replication (10). This conclusion is based on the following observations: 1) TNF injections cause little stimulation of hepatocyte replication in mouse liver; 2) in primary cell cultures, TNF stimulates hepatocyte DNA replication in serum-containing cultures but has little activity in cultures maintained in serum-free medium, suggesting that it is not a complete mitogen; and 3) a single injection of 10 μg of TNF enhances the proliferative activity of TGFα and hepatocyte growth factor in normal livers. To investigate the relationship between TNF and mitogenic growth factors for hepatocytes, we examined the proliferative effects of TNF on AML-12 cells, a differentiated, non-transformed hepatocyte cell line developed in this laboratory. These cells produce precursor TGFα, which is anchored in the cell membrane. We show that in these cells TNF stimulates DNA replication by causing release of TGFα into the culture medium through the metalloproteinase disintegrin TACE. TGFα then activates EGFR and multiple downstream intracellular signaling cascades that are required for DNA replication.

...the EGFR ligands TGFα and HB-EGF are synthesized as transmembrane precursor molecules (20). Cleavage of these...
molecules by limited proteolysis releases soluble growth factors, a process known as ectodomain shedding (25, 26). The soluble factors cleaved from the precursor molecules bind to and activate EGFR signaling. Examples of this type of mechanism include HB-EGF-mediated EGFR transactivation by stimulation of G-protein-coupled receptors (27–29) and TGFβ-mediated EGFR transactivation in colonic and gastric mucosal cells (30, 31). Although the mechanisms of EGFR signaling triggered by ligand binding are well described, much less is known about the source and generation of these ligands. Several lines of evidence suggest that the cell surface proteinases known as ADAM (a disintegrin and metalloproteinase), which contain a zinc-dependent catalytic domain, play an important role in ectodomain shedding of adhesion molecules and EGFR ligands (22, 32–34). In particular, TACE has been implicated in TGFβ-mediated EGFR activation (22, 23). In the work described here, we show that TACE activity is involved in TNF-induced TGFβ shedding and EGFR transactivation in AML-12 hepatocytes. The TACE inhibitor TAPI-1 interferes with TGFβ release into the culture medium and subsequent EGFR signaling through ERK1/2 and PKB, thereby blocking DNA replication. Cleavage of membrane proteins by TACE generally occurs at very low levels in unstimulated cells but is greatly enhanced by exposure of cells to various agents such as phorbol 12-myristate 13-acetate (35). We demonstrate that in AML-12 hepatocytes TGFβ is released into the culture medium after TNF treatment and that this release is blocked by TAPI-1, suggesting that TACE is activated by TNF. We do not know how TNF activates TACE, but our data suggest that ERK1/2 may not be involved in ligand shedding as has been proposed in other systems (22, 36). Transactivation of EGFR by TNF has been described in the human endometrium (37), mammary epithelial cells (38), and squamous carcinoma cells (39), but in squamous carcinoma cells, EGFR transactivation involves the up-regulation of EGFR, a mechanism that does not occur in hepatocytes (data not shown). At another level of regulation, it has also been shown that in the liver TNF may enhance TGFβ transcription (11).

Our results identify an important mode of interaction between cytokines and growth factors in hepatocytes. We suggest that in the regenerating liver, TNF provides the conditions for cell survival through NFκB activation and also triggers an
initial stage for cell replication that involves the rapid transactivation of EGFR through metalloproteinase-mediated ligand release. At later times during liver regeneration, sustained production of these ligands is mediated by transcriptional mechanisms (24).

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