NF-κB activation in Kupffer cells after partial hepatectomy

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Hepatocytes in the normal adult liver are mitotically quiescent; however, they can reenter the cell cycle from the quiescent G₀ phase to the G₁ phase after liver injury (25). After partial hepatectomy (PH), hepatocytes proliferate until the liver regeneration after partial hepatectomy. However, the physiological role and cellular localization of NF-κB activation are unresolved. In this study, we used an adenoviral vector expressing a mutated form of IκBα to inhibit NF-κB activity during liver regeneration. After partial hepatectomy in mice, introduction of Ad5IκB, but not a control virus (Ad5SGFP), resulted in increased liver injury and decreased hepatocyte proliferation. Hepatocyte apoptosis was not observed. To investigate the kinetics and cellular localization of NF-κB-induced transcription during liver regeneration, we generated a transgenic mouse expressing enhanced green fluorescent protein (EGFP) under the transcriptional control of NF-κB cis elements (cis-NF-κB-EGFP). During liver regeneration, EGFP expression was detected within 12 h and was primarily located in Kupffer cells. Our data demonstrate that activation of NF-κB initially occurs in Kupffer cells after partial hepatectomy in mice.

Liver regeneration; nuclear factor-κB; NF-κB-1; Kupffer cell

MATERIALS AND METHODS

Adenoviral Purification, In Vivo Infection, PH, and Bromodeoxyuridine Labeling

The adenoviral vector (Ad5IκB) encoding a mutated form of IκBα, a strong inhibitor of NF-κB activity, was amplified and purified as previously described (17). The virus was dialyzed two times against PBS for 8 h and one time overnight in 5% sucrose (in PBS). Male C57BL/6 mice (22–25 g) were injected via the tail vein with 200 μl PBS (2 × 10⁹ plaque-forming units of Ad5IκB or Ad5SGFP) used as a control virus. After viral injection (24 h), mice were anesthetized with 100–200 mg/kg ketamine (ip) and two-thirds PH was performed according to the methods of Higgins and Anderson (14). Animals received humane care in compliance with the guidelines for the use of experimental animals from the University of North Carolina at Chapel Hill Institutional Animal Care and Use Committee. Animals were injected with 10 mg/kg bromodeoxyuridine (BrDU; BD Bioscience, San Diego, CA) 12, 22, 34, or 46 h after PH, and animals were killed 2 h later (n = 3–4 animals/time point). To assess cell proliferation before PH, animals (n = 4) were injected with BrDU 22 h after viral injection and killed 2 h later. Positive, dark-stained hepatocyte nuclei were counted in 10 different ×400 fields/tissue section. Blood samples were collected by puncture of inferior vena cava, and serum was stored at −80°C. Liver tissue was snap-frozen in liquid nitrogen or fixed in 10% buffered formalin for subsequent histological analysis.

cis-NF-κB-EGFP mice

The cis-NF-κB-EGFP mice were generated as previously described (20). For all experiments, EGFP-positive heterozygotes were crossed to inhibit NF-κB induction during liver regeneration in mice. After PH, administration of Ad5IκB, but not a control virus (Ad5SGFP), resulted in increased liver injury, decreased hepatocyte proliferation, and little hepatocyte apoptosis. To investigate the kinetics and cellular localization of NF-κB-induced transcription during liver regeneration, we created a transgenic mouse expressing enhanced green fluorescent protein (EGFP) under the transcriptional control of NF-κB cis elements (cis-NF-κB-EGFP). During liver regeneration, EGFP expression was induced 12 h after PH and was primarily located in Kupffer cells.

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to C57B6 mice. Wild-type littermates were used as control animals for all experiments. F1, cis-NF-κB-EGFP mice were genotyped by collecting blood (~5 µl) from a tail vein nick (using heparin-coated capillary tubes), placing the blood on a glass microscope slide with a glass cover slip, and using fluorescence microscopy to identify EGF positive mononuclear cells. This genotyping method demonstrated that the cis-NF-κB-EGFP transgene was inherited as a Mendelian sex-linked trait.

**Evaluation of Liver Regeneration**

Hepatocyte mitotic activity. To evaluate hepatocyte replication, mitotic figures in hepatocytes were counted in 10 different ~400 fields from 4 mice/group at each time point.

Liver mass regeneration. Presurgical liver weight was estimated from the weight of the 70% of the liver removed during hepatectomy. Harvested liver weight was ascertained directly at indicated times posthepatectomy. Percentage of liver regeneration was calculated by comparing harvested liver weight to the estimated presurgical weight.

**Hepatic Stellate Cell Isolation**

Hepatic stellate cells (HSCs) were isolated from mice 24 h after PH, as previously described (34).

**mRNA Quantification by Real-Time RT-PCR**

mRNAs were quantified by a real-time RT-PCR per the manufacturers’ specifications (Mx3000P Real-Time PCR; Stratagene). The sequences of the primers for 18S, TNF-α, and interleukin (IL)-6 are as follows: 18S sense, 5'-TTGACGGAAGGGCACCACCA-3', and antisense, 5'-GCACCCACACCCGAACTCG-3', product size 130 bp; TNF-α sense, 5'-TCGAGCACAACCAAGGT-3', and antisense, 5'-AGATACGAAATCGGCTGAC-3', product size 207 bp; IL-6 sense, 5'-GAGCCCCACAAAGCAGATG-3', and antisense, 5'-TCACGATTTCCGAGAAC-3', product size 229 bp.

Total RNA was extracted from whole livers using TRIzol (Invitrogen, Carlsbad, CA). RNA (1 µg) was reverse transcribed using random primer (Promega, Madison, WI) and Superscript RNase H-RT (Invitrogen). Samples were incubated at 25°C for 10 min and 42°C for 60 min; RT was inactivated by heating at 99°C for 5 min and cooling at 5°C for 5 min. Amplification reactions were performed using a SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA). Diluted cDNA samples (5 µl) were used for quantitative two-step PCR (a 10-min step at 95°C, followed by 50 cycles of 15 s at 95°C and 1 min at 65°C) in the presence of 400 nM specific forward and reverse primers, 5 mM MgCl2, 50 mM KCl, 10 mM Tris buffer (pH 8.3), 200 µM dATP, dCTP, and dGTP, and 400 µM dUTP and 1.25 units of AmpliTaq Gold DNA polymerase (Perkin-Elmer Applied Biosystems). Each sample was analyzed in triplicate.

**Nuclear Extract Preparation and Mobility Shift Assay**

Nuclear proteins were prepared from liver tissues as previously described (12). Binding reactions were carried out for 20 min on ice using 8 µg nuclear extract and 10 pg [32P]DNA probe containing a NF-κB consensus binding site (3) with or without 1 ng (100-fold) unlabeled competitor probe. Complexes were separated by electrophoresis on nondenaturing 5% acrylamide gels and analyzed by autoradiography and PhosphorImager analysis (Molecular Dynamics, Sunnyvale, CA).

**Immunohistochemistry**

To assess cell proliferation in the liver, formalin-fixed liver tissue sections (5 µm) were immunostained using an antibody against BrDU (DAKO, Carpinteria, CA), as previously described (31). Immunohistochemical staining for platelet endothelial cell adhesion molecule-1 (PECAM-1), an endothelial cell marker, was performed using a PECAM-1 antibody (BD Biosciences), diluted 1:300 in 1% BSA albumin in PBS. The tissue was incubated with CyTM3-conjugated donkey anti-rat IgG (Jackson ImmunoResearch, West Grove, PA), diluted 1:200 in PBS, for 30 min. Control slides were incubated with 1% BSA instead of the primary antibody and did not show any positive staining.

**Terminal Deoxynucleotidyl Transferase-Mediated dUDP Nick-End Labeling Assay**

Formalin-fixed and paraffin-embedded liver sections (5 µm thickness) were deparaffinized in xylene and rehydrated through graded ethanol. Terminal deoxynucleotidyl transferase-mediated dUDP nick-end labeling (TUNEL) assay was performed using the In Situ Cell Death Detection Kit, AP (Boehringer Mannheim, Mannheim, Germany). DNA ends were tagged in situ with dUTP using terminal deoxynucleotidyl transferase by incubating the tissue sections in a
humidified chamber for 60 min at 37°C. Apoptotic cells were detected using an anti-fluorescein antibody conjugated with alkaline phosphatase (AP) for 30 min at 37°C. Slides were incubated with NBT/BCIP (Boehringer Mannheim) for 10 min at 25°C to visualize AP-positive cells and subsequently counterstained with hematoxylin. The percentage of AP-positive cells was counted in five high-power fields on each slide compared with the total number of hepatocytes.

**Microscopy Analysis**

Epifluorescence microscopy was used to detect EGFP in live cells and tissue sections from the cis-NF-κB-EGFP mice. To label Kupffer cells, mice were injected with 1 × 10^9 red fluorescent beads (Fluospheres polystyrene microspheres, 1.0 μm; Molecular Probes, Eugene, OR), precoated with rabbit serum, via tail vein injection 2 h before death. Tissue samples were fixed in 4% paraformaldehyde for 24 h, washed two times with PBS, and transferred to vials containing 30% sucrose (made in PBS) for 24 h. Sections (5 μm) were cut, and the EGFP expression of the sections was imaged using an Olympus IX70 (Olympus, Melville, NY) fitted with EGFP-specific filters (XF116-2; Omega Optical, Brattleboro, VT). Images were captured using a digital SPOT camera (Diagnostic Instruments, McHenry, IL). Identical exposure times were used for each data point within an individual experiment. EGFP-positive cells were counted in 10 different ×400 fields from 4 mice/group at each time point.

**Statistical Analysis**

Results are expressed as means ± SD. Statistical significance was assessed using Students t-test and ANOVA when appropriate. Data were considered significant at P < 0.05.

**RESULTS**

*IκB Superrepressor Prevents NF-κB Activation in Mice After PH*

To confirm the functionality of the IκB superrepressor adenovirus in mice, 2 × 10^9 plaque-forming units of Ad5GFP or Ad5IκB were administered via tail vein injections. After 24 h, partial hepatectomies were performed, and then the mice were killed 1 h later. Electrophoretic mobility shift assays demonstrated early induction of NF-κB binding activity after PH in the mice administered control Ad5GFP. Administration of Ad5IκB in mice effectively prevented induction of NF-κB binding activity, as previously described in rats (Fig. 1B; see Ref. 15).

![Fig. 2. Inhibiting NF-κB activation with Ad5IκB does not increase apoptosis in the liver after PH.](http://ajpgi.physiology.org) Ad5GFP-infected (A and C) and Ad5IκB-infected (B and D) livers were stained by terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay to detect apoptotic cells. A: Ad5GFP-infected liver 0 h after PH showed occasional apoptosis. B: Ad5IκB-infected liver 0 h after PH shows increased apoptotic cells. C and D: Ad5GFP-infected and Ad5IκB-infected liver 24 h after PH show similar apoptosis in hepatocytes. Quantitative analysis of TUNEL experiments is depicted in E. Positive stain nuclei were counted as described in MATERIALS AND METHODS, shown as apoptotic cell number/1,000 hepatocytes. *P < 0.05 for Ad5IκB compared with Ad5GFP, n = 4.
IκB Superrepressor Does Not Induce Apoptosis After PH in Mice

Because the Ad5IκB superrepressor adenovirus induces apoptosis in rats (15), we examined this effect when Ad5IκB was administered to mice. Increased apoptosis was observed in the livers of mice administered Ad5IκB 24 h after injection compared with mice administered Ad5GFP before PH (20.25 ± 3.86 vs. 4.05 ± 2.16 apoptotic cells/1,000 hepatocytes; Fig. 2, B vs. A). However, there was no significant difference between the number of apoptotic cells between the Ad5IκB and Ad5GFP animals 24 h after PH (27.75 ± 9.11 vs. 19 ± 4.32 apoptotic cells/1,000 hepatocytes; Fig. 2, C and D, and graphically shown in E). Thus the combined stresses of PH, adenoviral infection, and inhibition of NF-κB do not increase the apoptosis in hepatocytes. To verify the effect of NF-κB inhibition on cytokine expression, we next measured TNF-α and IL-6 mRNA expressions in the liver after PH using real-time PCR. As previously reported (15), adenoviral infection with either Ad5GFP or Ad5IκB led to increased levels of TNF-α before PH (Fig. 3A). These TNF-α levels were maintained after PH, and there was no significant difference between Ad5GFP- and Ad5IκB-infected mice. For the IL-6 mRNA level, we also saw IL-6 mRNA induction caused by adenoviral infection before PH (Fig. 3B). After PH (12 and 24 h), IL-6 mRNA levels in Ad5IκB-treated mice were significantly decreased compared with the Ad5GFP control group. Thus IκB superrepressor inhibited IL-6 expression in the liver after PH.

Fig. 3. IκB superrepressor inhibits IL-6 mRNA expression in liver after PH. Ad5IκB (2 × 10⁹ plaque-forming units/mouse) was injected via the tail vein; Ad5GFP used as a control virus. Later (24 h), mice underwent PH and were killed at 0, 12, and 24 h after surgery. Livers were harvested, and total RNA was extracted. Real-time PCR was performed to detect TNF-α (A) and IL-6 (B) mRNA. *P < 0.05 for Ad5IκB compared with Ad5GFP, n = 4.

Fig. 4. Inhibition of NF-κB activation inhibits murine hepatocyte proliferation after PH. Mitosis and DNA synthesis in the livers of mice administered Ad5GFP (A and C) or mice administered Ad5IκB (B and D) 48 h after PH. Liver sections were examined with hematoxylin and eosin staining (A and B) and bromodeoxyuridine (BrDU) incorporation (C and D). Mitotic figures and BrDU-positive cells were counted as described in MATERIALS AND METHODS. Quantitative data are represented in E and F. *P < 0.05 for Ad5IκB compared with Ad5GFP, n = 4.
Inhibition of NF-κB Activation Inhibits Murine Hepatocyte Proliferation After PH

To assess the effect of inhibiting NF-κB activation on hepatocyte cell proliferation after PH, mice were administered either the Ad5IκB superrepressor adenovirus or Ad5GFP as a control virus. Typically, after PH, hepatocytes exit the G0 phase of the cell cycle and begin to proliferate (25). After PH (48 h), the number of mitotic hepatocytes in the Ad5GFP group was significantly higher than that in the Ad5IκB group (Fig. 4, A vs. B). Quantitation of the number of mitotic bodies per 1,000 hepatocytes at 48 h after PH was 11.75 ± 3.4 vs. 5.75 ± 1.5 (Fig. 4E). DNA synthesis after PH was assessed by BrDU incorporation and expressed as percentage of positive hepatocytes. After PH (48 h), the number of BrDU-positive cells in the animals administered Ad5GFP (67.6 ± 16%) was significantly higher than that in the Ad5IκB group (11.7 ± 4%; Fig. 4, C, D, and F).

Inhibition of NF-κB ACTIVATION IN KUPFFER CELLS AFTER PARTIAL HEPATECTOMY

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Liver Injury and Liver Mass Restoration During Liver Regeneration

To assess liver injury after PH in mice, serum enzyme levels of alanine aminotransferase (ALT) were measured. ALT levels at time 0 h and time 24 h in the Ad5IκB group were significantly higher than in mice administered Ad5GFP compared with the mice administered Ad5IκB (2,419 ± 1,938 vs. 80 ± 45 U/l at 0 h and 5,570 ± 1,199 vs. 2,931 ± 2,026 U/l at 24 h). ALT levels were found to return to normal levels after 48 h (Fig. 5). Liver mass was fully restored in animals receiving Ad5GFP ~7 days after PH, with 70% of the liver mass restored after 72 h. However, in the animals receiving Ad5IκB superrepressor, there was a consistent delay in the restoration of liver mass compared with the control Ad5GFP group at 48 h (47.25 ± 8.66 vs. 61.5 ± 5.45) and 72 h (56 ± 9.42 vs. 74.5 ± 8.35; Fig. 5B).

EGFP Expression in cis-NF-κB-EGFP Mouse Liver After PH

To assess which cells are expressing active NF-κB in the liver before and after PH, we utilized a novel reporter gene mouse in which NF-κB transcriptional activity produces the reporter protein EGFP. Before PH, a very small amount of EGFP-positive cells can be found in the liver of the cis-NF-κB-EGFP transgenic mice (Fig. 6A), but the intensity of EGFP florescence in some of these cells is high. After PH (12 h), EGFP-positive cell numbers were significantly increased in the cis-NF-κB-EGFP transgenic mice; however, the intensity of the EGFP fluorescence was low in most of cells expressing EGFP (Fig. 6B). After PH (24 h), the total number of EGFP-positive cells was not significantly increased compared with the number observed after 12 h of PH, but the intensity of EGFP fluorescence was significantly increased (Fig. 6C).
Morphologically, EGFP-positive cells appeared to be non-parenchymal cells. There was no increase in either EGFP-positive cell numbers or in the intensity of fluorescence 48 h after PH (data not shown). Thus, after PH, NF-κB is activated in a select subset of hepatic cells.

**NF-κB Activation Was Determined to be Primarily in Kupffer Cells After PH in Mice**

To identify which cell type was expressing EGFP in the cis-NF-κB-EGFP transgenic mice after PH, mice were injected with 1 × 10⁹ red fluorescent beads (as described in MATERIALS AND METHODS) via tail vein injection 2 h before death. These beads are specifically phagocytosed by the resident macrophage in the liver, the Kupffer cells. Before PH, few cells were found to colabel with the red fluorescent beads and EGFP expression (yellow cells; Fig. 7, A, C, and E). However, 24 h after PH, the percentage of colabeled cells in EGFP-positive cells was greatly increased from 6.4 ± 1.64% (0 h) to 44.75 ± 6.02% (24 h; Fig. 7, B, D, F, and G). After PH (24 h), ~40% of EGFP-positive cells were definitely Kupffer cells that con-

![Image](https://via.placeholder.com/150)

**Fig. 7.** Kupffer cells express EGFP 24 h after PH. Uptake by red fluorescence beads labels Kupffer cells, and green fluorescence by EGFP identifies cells expressing NF-κB transcriptional activity in mouse liver at 0 h (A, C, and E) and 24 h (B, D, and F) following PH. E and F: overlay images (magnification, ×400). Colabeled (yellow) cells and EGFP-positive cells were counted as in MATERIALS AND METHODS. The percentage of Kupffer cells in total EGFP-positive cells is depicted in G. *P < 0.01 compared with 0 h after PH, n = 4.
tained red fluorescent beads (Fig. 7F). HSCs were isolated 24 h after PH and analyzed for EGFP expression by fluorescence activated cell sorter analysis. No significant difference in EGFP expression was observed between 0 and 24 h after PH, suggesting that NF-kB was not activated in HSCs during liver regeneration in the cis-NF-kB-EGFP transgenic mice (data not shown). To assess EGFP expression in endothelial cells, PECAM-1 expression was assessed as an endothelial cell-specific marker. Immunohistochemistry (red fluorescence for PECAM-1) demonstrated very rare colabeled cells in endothelial cells at 24 h after PH in the treated animals (Fig. 8, A-C). Only a small increase in the percentage of colabeled cells were observed at 0 h (2.36 ± 0.47) compared with 24 h (5.53 ± 1.86) after PH (Fig 7D). Together, these data indicate that the majority of EGFP-positive cells, after PH in the liver of the cis-NF-kB-EGFP transgenic mouse, represent Kupffer cells. Early activation of NF-kB primarily occurs in Kupffer cells and a small percentage of endothelial cells, but not in HSCs.

**DISCUSSION**

After PH, TNF receptor I (TNFRI) knockout mice show reduced DNA replication and significant mortality 24–40 h after PH (33). In TNFRI knockout mice, activation of NF-kB and signal transducer and activator of transcription (STAT)3 is inhibited (33). In normal animals, TNF-α and IL-6 expression increase in the blood very quickly after PH (1, 29). In TNFRI knockout mice, TNF-α also increases, but only a slight change in IL-6 is observed. Normal liver regeneration and STAT3 activation can be restored with the administration of exogenous IL-6 (33). IL-6 knockout mice showed impaired liver regeneration, and IL-6 injection can correct the deficits in DNA replication and STAT3 activation after PH (6). After PH, TNF-α signals from the TNFRI to activate NF-kB, which translocates into the nucleus to induce IL-6 gene expression and cytokine production (18, 32, 33). IL-6 binds to its receptor and activates STAT3 (6). IL-6 has been shown to exert both mitogenic and antiapoptotic effects on hepatocytes (28).

NF-kB is rapidly activated after PH (7, 10, 30). NF-kB is represented by p50/p65 heterodimers, p50 homodimers, and PHF, a complex composed of p50 and p35 (a truncated form of p65; see Refs. 2, 8, and 30). NF-kB associates with the cytoplasmic inhibitor, IκBα, which prevents NF-kB from translocating to the nucleus and effectively inhibits transcriptional activity. Activation of NF-kB involves the phosphorylation of IκBα, ubiquitination, and degradation by a proteasome-mediated pathway, phosphorylation of the trans-activation domain of p65, and subsequent translocation of the active form of NF-kB in the nucleus (4). Blocking NF-kB activation in vivo using an adenoviral vector expressing a mutated form of IκBα has been shown to induce hepatocyte apoptosis and liver dysfunction after PH in rats (15). Mice deficient in the p65 subunit die during gestation from hepatocyte apoptosis (2). Mice deficient in p50 are viable after PH; the livers of these mice show a loss of NF-kB binding activity and decreased STAT3 activation, but normal liver regeneration and repair. Presumably this is because of a compensatory effect of increased nuclear levels of p65 in the absence of the p50 subunit (9). In this study, we first investigated if there exists a species difference between rats and mice with respect to NF-kB DNA binding activity and transcriptional activity after liver regeneration. Mice administered an adenoviral vector expressing a mutated form of IκBα that prevents NF-kB activation resulted in significant liver injury and decreased hepatocyte proliferation after PH compared with mice receiving a control Ad5GFP virus. However, no increased hepatocyte apoptosis was observed after PH, unlike that which we reported in rats (15). On the other hand, mild apoptosis was observed at 0 h after PH. This may reflect the combination of increased inflammatory cytokine expression after adenoviral vector injection (19) accompanied by inhibition of NF-kB activation in hepatocytes.
Thus there is a distinct species difference in liver regeneration between rats and mice with respect to the effect of blocking NF-κB. Other differences in liver regeneration include a prolonged G1 phase of the cell cycle in mice. Further comparisons between mice and rats are limited by the lack of rat genetics.

To investigate the kinetics and cellular localization of NF-κB-induced transcripational activation during liver regeneration, we generated a transgenic mouse expressing the EGFP under the transcriptional control of NF-κB cis-regulatory elements (cis-NF-κB-EGFP). During liver regeneration, EGFP expression was observed after 12 h, and expression was primarily located in Kupffer cells. Kupffer cells are generally presumed to be an important source of hepatic TNF-α during an inflammatory response (23). After PH, depletion of Kupffer cells using CI2MDP-liposomes abolishes hepatic-derived IL-6 and hepatic growth factor mRNA synthesis, well-known stimulators for hepatic regeneration process (6, 16, 21), and depletion of Kupffer cells using CI2MDP-liposomes abolishes hepatic-derived IL-6 and hepatic growth factor mRNA synthesis, well-known stimulators for hepatic regeneration process (6, 16, 21), and depletes NF-κB-regulated cytokines, and growth factors. These data are consistent with the result that hepatocyte-specific inhibition of NF-κB does not prevent normal liver regeneration after PH (5).

Previous studies (7, 26) emphasized that NF-κB activation primarily occurs in hepatocytes after PH. However, these studies may have incorrectly interpreted the cellular source of increased NF-κB binding activity since whole liver extracts were used, or possibly the hepatocyte preparations were contaminated with nonparenchyma cells. In addition to nuclear translocation, p65 itself requires phosphorylation to induce transcriptional activity of NF-κB-responsive genes (24, 35) so that NF-κB translocation by itself does not necessarily reflect NF-κB transcriptional activity. Previous methods to detect NF-κB activation failed to capture the dynamic aspect of NF-κB activity and provided only limited physiological information on this complex signaling pathway. Using the cis-NF-κB-EGFP mouse allows us for the first time to visualize NF-κB transcriptional activation in the whole animal after PH and demonstrate that NF-κB activation in the liver after PH is almost exclusively found in Kupffer cells.

In summary, inhibition of NF-κB activation using a super-repressor IkBα results in liver dysfunction after PH in mice with minimal hepatocyte apoptosis. NF-κB-induced transcriptional activity was shown to occur primarily in Kupffer cells, which in turn results in the production of NF-κB-regulated cytokines that are critical for liver regeneration.

GRANTS

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REFERENCES


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