Heparin-binding Epidermal Growth Factor-like Growth Factor Links Hepatocyte Priming with Cell Cycle Progression during Liver Regeneration*

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The mechanisms that regulate the transition between the initial priming phase and DNA replication in liver regeneration are poorly understood. To study this transition, we compared events occurring after standard two-thirds partial hepatectomy, which elicits full regeneration, with response to a reduced hepatectomy, one-third partial hepatectomy (1/3PH), which leads to little DNA replication. Although the initial response to partial hepatectomy at the priming phase appeared to be similar between the two procedures, cell cycle progression was significantly delayed in 1/3PH mice. Among the main defects observed in 1/3PH mice were an almost complete deficiency in retinoblastoma phosphorylation and the lack of increase in kinase activity associated with cyclin E. We report that, in two-thirds partial hepatectomy mice, the expression of heparin-binding epidermal growth factor-like growth factor (HB-EGF) preceded the start of DNA replication and was not detectable in 1/3PH animals. Injection of HB-EGF into 1/3PH mice resulted in a >15-fold increase in DNA replication. Moreover, we show that hepatocyte DNA replication was delayed in HB-EGF knock-out mice. In summary, we show that HB-EGF is a key factor for hepatocyte progression through G1/S transition during liver regeneration.

Adult hepatocytes, while highly differentiated, retain a remarkable ability to proliferate in response to liver injury or reduction in hepatic mass. The surgical removal of ~70% of the liver, two-thirds partial hepatectomy (2/3PH), is the most studied model of liver regeneration. This procedure induces a synchronized growth response involving almost all hepatocytes, leading to the restoration of liver mass in 7–10 days in rodents (1).

Liver regeneration is a complex process involving the activation of multiple pathways. The entry of quiescent hepatocytes into the cell cycle, corresponding to the G1/S transition, is largely regulated by cytokines. This phase, often referred to as priming, is characterized by the increase in cytokines such as tumor necrosis factor-α and IL-6 and the activation of immediate early genes that include c-Jun, c-Fos, and c-Myc (2). Although this phase is essential for the hepatocyte response to growth factors, the priming stage is reversible. Without the involvement of growth factors, hepatocytes do not progress through cell cycle and they return to quiescence (3).

Hepatocyte growth factor (HGF) and transforming growth factor-α (TGF-α) are two of the most studied growth factors in liver regeneration. It has been demonstrated that the mRNA levels of both growth factors are elevated after 2/3PH (4, 5). HGF stimulates hepatocyte replication by paracrine or endocrine mechanisms (6, 7). Recent studies using conditional knock-out mice for the HGF receptor, c-Met, showed that c-Met signaling is essential for liver regeneration and may primarily affect hepatocyte survival and tissue remodeling (8, 9). By contrast, TGF-α is an autocrine factor whose effects are primarily proliferative (5). However, TGF-α knock-out mice have no defects in liver regeneration, an observation that might be explained by the redundancy of ligands of the EGF family (10). Indeed, heparin-binding EGF-like growth factor (HB-EGF) has been reported to participate in liver regeneration (11), but its role has not been well characterized. Nevertheless, transgenic mice expressing HB-EGF appear to have an accelerated liver growth response after partial hepatectomy (12).

The interaction between the early events of liver regeneration and growth factor availability is crucial for the regenerative process. However, the events linking these two phases have not been characterized. Bucher and Swafield (13) show that the extent of hepatocyte replication in the regenerating liver of adult rats is proportional to the amount of tissue respected for resections involving 40–70% of the liver (13). Removal of 30% of the liver lies below this threshold and does not elicit a clear wave of DNA replication. Moreover, we have previously demonstrated that continuous infusion of TGF-α or HGF for 24 h into the portal vein of rats with 30% hepatectomies or one-third partial hepatectomy (1/3PH) produced a vigorous replicative response to the growth factors (14). Together, these data indicated that 1/3PH, in contrast to the standard 2/3PH, may induce hepatocyte priming that does not progress to DNA replication. We reasoned that the analysis of events occurring after 1/3PH may uncover linkages between priming

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¶ The abbreviations used are: 2/3PH, two-thirds partial hepatectomy; 1/3PH, one-third partial hepatectomy; EGF, epidermal growth factor; HB, heparin-binding; IL, interleukin; HGF, hepatocyte growth factor; TGF-α, transforming growth factor; BrdUrd, bromodeoxyuridine; Rb, retinoblastoma; Tricine, N-[2-hydroxy-1,1-bis(hydroxymethyl)glycine; RPA, ribonuclease protection assays Cdk, cyclin-dependent kinase; SOCS, suppressor of cytokine signaling.
and cell cycle progression that are decisive for liver regeneration. Here we show that HB-EGF is a key factor for the progression of hepatocytes through the G1/S phases.

MATERIALS AND METHODS

Animals and Surgical Procedures—8–10-week-old male wild-type C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were kept on a 12-h light/dark cycle with free access to food and water. HB-EGF-null male mice were from a hybrid C57BL/6 × 129/Sv background (15). In experiments using HB-EGF+/− mice, the wild-type controls were from the same hybrid background. Partial hepatectomies were performed under general anesthesia with inhaled isoflurane. One-third hepatectomy consisted of ligating the pedicle of the left lateral lobe before excising it. Two-thirds hepatectomy was performed as described by Higgins and Anderson (16). Sham surgery consisted of a midline laparotomy with gentle manipulation of the liver. Surgeries were performed between 8 a.m. and 4 p.m., and mice were killed at different time points as described in the legends of the figures. All of the animal work was done in accordance with the animal care committees of the University of Washington and the University of North Carolina at Chapel Hill.

Growth Factor Injections—For the growth factor experiment, male wild-type C57BL/6 mice received a bolus injection of 0.1 mg/kg HB-EGF (R&D Systems, Minneapolis, MN; dissolved in 0.9% NaCl), HGF (a gift from Genentech, San Francisco, CA; dissolved in 0.5 x NaCl and 20 mM Tris, pH 7.6), or TGF-α (R&D Systems; dissolved in 0.9% NaCl) through the tail vein 24 h after a one-third partial hepatectomy. Mice were killed 36 h after hepatectomy and 12 h after growth factor injection.

BrdUrd Immunohistochemistry—Mice received an intraperitoneal injection of BrdUrd (50 mg/kg) (Roche Applied Science) 2 h before killing. Livers were fixed in methacarn (60% methanol, 30% chloroform, and 10% acetic acid) overnight at room temperature and then embedded in paraffin. BrdUrd incorporation was measured using a mouse anti-BrdUrd antibody (Dako, Carpinteria, CA) and the Elite Vectastain ABC kit (Vector laboratories, Burlingame, CA) as described previously (17). For each liver sample, ~3,000 hepatocytes were counted.

Western Blot Analyses—Total liver protein was isolated from snap-frozen tissue by homogenization in immunoprecipitation lysis buffer described previously and briefly sonicated (17). Nuclear extracts were prepared by the method described by Struhl (18). Proteins (30 μg for total liver protein and 10 μg for nuclear extracts) were separated on 12% SDS-PAGE (29.1 (v/v) acrylamide:Bi) gels with the exception of phospho-retinoblastoma (Rb) blots in which 10% (30.0:4 (v/v) acrylamide:Bi) SDS-PAGE gels were used and TGF-α blot in which Tris-Tricine 10–20% gels (Bio-Rad) were used. Proteins were transferred onto nitrocellulose membranes (Hybond ECL, Amersham Biosciences) and blocked in 5% milk TBST (Tris-buffered saline with 0.1% Tween 20) prior to incubation with primary antibody. The following antibodies were used: cyclin A (sc-596, Santa Cruz Biotechnology, Santa Cruz, CA); p21 (556431, BD Biosciences); phos-Rb (Ser-807/811, Cell Signaling, Beverly, MA); cyclin D1 (AHF 082, Biotechnology, Santa Cruz, CA); p21 (556193) and two custom probe sets, A and B. The custom probe set A included the following mouse DNA templates: c-jun; HGF; p53; c-fos; HB-EGF; TGF-β1; fatty-acid synthase; L32; and glyceraldehyde-3-phosphate dehydrogenase. The custom probe set B included the following templates: tumor necrosis factor-α; IL-1; SOCS-3; KC (a cytokine-induced neutrophil chemoattractant); ICAM (intercellular adhesion molecule); SOCS-1, IL-6; interferon-γ; IL-12; L32; and glyceraldehyde-3-phosphate dehydrogenase. Samples were loaded on a 6% Tris borate-EDTA/urea gel (Invitrogen) at 150 V for 1.5 h. Gels were subsequently dried, and signals were quantified using a PhosphoImager. To control for equal loading between samples, the level of each mRNA species was normalized against the level of the housekeeping gene transcript, L32.

Real-time Reverse Transcriptase-PCR—One microgram of total RNA from livers was used for the Reverse Transcriptase reaction using Applied Biosystems TaqMan reverse transcription kit, and then one-tenth of the reaction was used for the real-time PCR analysis. Assay kits for mouse TGF-α and amphiregulin from Applied Biosystems (Foster City, CA) were used for the quantification of the expression of these genes in an Applied Biosystems 7900HT SDS instrument. The housekeeping gene mouse β-glucuronidase (Applied Biosystems) was used to normalize the measurements using the ΔΔ Ct method. The PCR conditions were the standard when using TaqMan hydrolysis probes.

Statistical Analysis—Statistical calculations were performed using the software Statview 4.5 (SAS Institute, Cary, NC). The Mann-Whitney test and the ANOVA Student’s t test were used. p values lower than 0.05 were accepted as significant. Error bars indicate the mean ± S.E.
RESULTS

A Lack of Synchronized DNA Replication after 1/3PH in Mice—In rats, the removal of 30% of the liver results in little DNA replication (13, 19). To determine whether 1/3PH also fails to elicit a wave of hepatocyte replication in mice, we analyzed DNA replication of hepatocytes after 1/3PH at different times after surgery and compared with DNA replication after 2/3PH. We observed a striking difference in the proportion of hepatocytes that incorporated BrdUrd from 30 to 72 h after partial hepatectomy between these procedures (Fig. 1 A). At 36 h, which corresponds to the peak of DNA replication after 2/3PH, the livers of mice with 2/3PH had almost 10-fold higher levels of DNA replication compared with animals with 1/3PH. The mitotic index determined 48 h after hepatectomy was 5 times higher in 2/3PH mice compared with 1/3PH animals (Fig. 1 B). These data demonstrated that, after a 1/3PH, there is lack of a robust synchronous wave of DNA replication and that this procedure can serve as a model for the analysis of incomplete regeneration.

Priming Phase Present after 1/3PH—To identify factors that may be responsible for the incomplete regenerative response after 1/3PH, we first examined the expression of a few representative genes that are known to be highly expressed during the priming phase that occurs during the first few hours after partial hepatectomy. It is well established that c-jun, c-fos, and c-myc are transiently expressed between 1 and 4 h after 2/3PH as part of the immediate early gene response (20–22). RPA analysis revealed that these three genes were similarly expressed in 1/3PH and 2/3PH from 30 to 72 h after partial hepatectomy (Fig. 2 A and data not shown). We also found that the expression of genes that participate in the acute phase response, such as IL-6 and SOCS-3, are similarly expressed after 1/3PH and 2/3PH (Fig. 2, B and C). These findings are in agreement with and greatly extend a previous report that suggested that 1/3PH can trigger a priming response (14), and it is consistent with data from DNA microarray gene expression analyses in progress in the laboratory.2

Deficient G1/S Progression after 1/3PH—Cell cycle progression is regulated by the activity of complexes consisting of cyclins, Cdns, and cyclin-dependent kinase inhibitors (23). It is well established that Cdk-2 complexed with either cyclin E or A cooperates with cyclin D-Cdk-4/6 to phosphorylate the Rb and related p107 and p130 proteins. The phosphorylated proteins release bound E2F transcription factor, which stimulates the expression of genes required for S-phase (24). Therefore, we analyzed the expression and activity of key regulators of the G1/S transition from 24 to 48 h after 1/3PH compared with 2/3PH mice. First, we analyzed the expression of the Rb and of p107, another member of the Rb family. In 2/3PH mice, the phosphorylation of Rb was detected at 30 h after hepatectomy and remained throughout the period of time studied (Fig. 3 A). In marked contrast, we could not detect phosphorylated Rb after 1/3PH during the same period of time. The expression of p107 was detectable but greatly diminished in 1/3PH mice (Fig. 3 A). We also analyzed the expression of p21, cyclin A, and cyclin D1

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and cyclin E complexes, proteins associated with the G_{1}/S transition. In 2/3PH, we detected cyclin A and p21 expression from 24/30 to 48 h (the last time point sampled in Fig. 3A). However, in 1/3PH mice, the expression of these proteins was delayed, diminished, and of shorter duration (Fig. 3A). The expression of the Cdk-4/cyclin D1 complex was more robust and longer lasting in 2/3PH than in 1/3PH, even though the total levels of cyclin D1 did not vary after either procedure (Fig. 3B). Finally, the kinase activity associated with cyclin E increased only in 2/3PH mice (Fig. 3C). Altogether, these results showed that there are well-defined differences between 1/3PH and 2/3PH regarding the expression of various cell cycle proteins. Whereas 2/3PH hepatocytes are clearly committed to proliferation between 24 and 48 h after the operation, at identical time points, 1/3PH hepatocytes do not exhibit protein expression patterns characteristic of the G_{1}/S transition.

**HB-EGF Expression Increases prior to the G_{1}/S Transition in 2/3PH but is Not Changed in 1/3PH**—Growth factors drive cell cycle progression from early to late G_{1}, at which time replication becomes growth factor-independent (25). Therefore, we examined the expression of growth factors from 12 to 36 h after 1/3PH and 2/3PH. The 12–24-h time period corresponds to a phase that precedes the G_{1}/S transition (see Fig. 1). We first examined, by RPA and real-time PCR, the liver mRNA levels of the two main growth factors implicated in liver regeneration, TGF-α and HGF. TGF-α mRNA levels increased at 36 h only in 2/3PH mice (Fig. 4A), but there were no obvious differences in HGF mRNA levels between 1/3PH and 2/3PH at the time points examined (Fig. 4B). Given that the expression of HGF and TGF-α mRNA at 12–24 h after hepatectomy (a period of time that precedes the G_{1}/S transition) was similar in 1/3PH and 2/3PH, we determined whether HB-EGF might be differentially expressed in these two procedures. In 2/3PH, HB-EGF mRNA expression approximately doubled between 12 and 24 h after 2/3PH and
HB-EGF at a Low Dosage Stimulates DNA Replication in 1/3PH Mice—We compared the effects of small dosages of HB-EGF, TGF-α, and HGF in stimulating DNA synthesis in animals subjected to 30% hepatectomies. We gave a single injection of 0.1 mg/kg of each of these growth factors to 1/3PH mice compared with 1/3PH. Thus, the elevated HB-EGF levels are correlated with liver regeneration and precede the activation of cell cycle proteins. We conclude from these experiments that HB-EGF might be a key factor in determining cell cycle progression in regenerating liver and that its deficiency could be associated with incomplete regeneration.

Liver Regeneration Is Delayed in HB-EGF Knock-out Mice—Because of the large differential sensitivity to HB-EGF and TGF-α effects demonstrated in 1/3PH mice (Fig. 5) and the earlier timing of the expression of HB-EGF during liver regeneration (Fig. 4C), we investigated whether HB-EGF knock-out mice would have defects in liver regeneration. These knock-out mice are viable and do not present abnormalities during liver development or in non-injured livers. We performed 2/3PH in HB-EGF knock-out mice and found that hepatocyte DNA replication in these animals was delayed and significantly lower at 30 and 36 h after partial hepatectomy compared with wild-type mice (Fig. 6A). Despite its delayed onset, the levels of DNA hepatocyte DNA replication in HB-EGF knock-out mice at 42 and 48 h after partial hepatectomy did not differ from the levels in wild-type mice. To investigate whether other ligands of the EGF family may compensate in part for the lack of HB-EGF in the knock-out animals, we analyzed the expression of TGF-α and amphiregulin mRNAs in these animals. TGF-α mRNA was significantly increased at 24 h after 2/3PH in the knock-out mice compared with wild-type animals (Fig. 6B), but there was no difference in the expression of amphiregulin between wild-type and knock-out animals after 2/3PH (data not shown). In agreement with these findings, we detected a higher TGF-α protein expression at 36 h post-hepatectomy in the HB-EGF knockouts compared with the wild-type mice (Fig. 6C). These data indicate that the lack of HB-EGF does affect the kinetics of liver regeneration and that increases in TGF-α expression may compensate for the absence of HB-EGF.

DISCUSSION

In the regeneration of the liver after partial hepatectomy, hepatocytes that are normally quiescent cells enter the cell cycle, replicate once or twice, and then return to quiescence. Information obtained primarily in studies using genetically modified mice support the view that regeneration is initiated by a priming phase largely regulated by cytokines in which hepatocytes undergo the G0/G1 cell cycle transition. During this phase, which lasts approximately 4–6 h in regenerating mouse liver, multiple genes are activated including several proto-oncogenes. It is also well established that hepatocyte DNA replication in the regenerating mouse liver does not start until ~30 h after partial hepatectomy. Cell-cycle progression through the G1 phase is driven primarily by two growth factors, HGF and TGF-α. In addition to its proliferative effects, HGF is important for cell survival and motility, whereas TGF-α is an autocrine growth factor for hepatocytes and has mostly proliferative effects. Despite the vast amount of information on the role of cytokines and growth factors in liver regeneration, the mechanisms that connect hepatocyte priming with cell cycle progression are largely unknown.

To investigate these mechanisms, we compared some aspects...
of liver regeneration after 2/3PH, the standard procedure used to elicit full synchronized liver regeneration, with 1/3PH, which causes a delayed and asynchronous regenerative process (13, 19, 26). Using this approach, we established that the expression of HB-EGF, which occurs between 12 and 30 h after 2/3PH, is critical for cell cycle progression and the G1/S transition in the regenerating liver. Compared with 2/3PH mice, 1/3PH animals had a very small replicative and mitotic response and had defects in the expression of Rb and p107 and deficiencies in the formation of cyclin/Cdk complexes. In these animals, the expression of HB-EGF between 12 and 24 h after partial hepatectomy was >10-fold lower than that of 2/3PH mice.

Previous reports have shown that HB-EGF is expressed in the regenerating liver before the hepatic expression of HGF and TGF-α, but it is not known whether HB-EGF is a crucial player for the G1/S transition (11, 12). Injection of HB-EGF into 1/3PH mice 24 h post-PH resulted in a >15-fold increase in DNA replication measured 12 h after the injection. In contrast, the injection of HGF or TGF-α at the same dosages failed to elicit significant hepatocyte DNA replication. We have previously demonstrated that the continuous infusion of HGF and TGF-α for 24 h increases DNA replication in 1/3PH rats (14). However, in this study, we gave a single injection of growth factors at a specific time during liver regeneration and used a lower dose of growth factors. The results indicate that, at 24 h after partial hepatectomy, a period that precedes the G1/S transition in 2/3PH mice, hepatocytes of 1/3PH mice are highly sensitive to the proliferative effects of HB-EGF in comparison with TGF-α or HGF. The fact that an injection of TGF-α did not stimulate proliferation suggests that the mechanisms of induction of cell proliferation and the times at which hepatocytes are particularly sensitive to a specific factor are not necessarily the same for various ligands of the EGF family, even though HB-EGF and TGF-α share the same receptor (27). The differential activity of these ligands may reflect differences in affinity or prolonged binding for each ligand or be a consequence of changes in the constitution of the EGF receptor dimer. However, no difference in the expression of ErbB4 could be seen between 1/3PH and 2/3PH animals at 24 h after surgery (data not shown).

The importance of HB-EGF for liver regeneration is further highlighted by the delay in DNA replication observed in HB-EGF knock-out mice after 2/3PH. This result is particularly significant because TGF-α knock-out mice have no defects in liver regeneration, an observation that may be due to redundancy between the ligands of the EGF family. In HB-EGF knock-out mice, there is an early increase in the expression of TGF-α, presumably as a compensation for the lack of HB-EGF. Nevertheless, the early expression of TGF-α is not sufficient to overcome the defect caused by the lack of HB-EGF.

FIG. 6. Liver regeneration after 2/3PH in HB-EGF knock-out mice. A, DNA synthesis was analyzed by BrdUrd incorporation at different times after two-thirds partial hepatectomy in HB-EGF knock-out (KO) or wild-type (WT) mice (4–7 animals/group were analyzed). B, the mRNA levels of TGF-α were analyzed at different time points post-surgery in these animals, and the relative mRNA levels were obtained by normalizing each sample against non-operated control mice. *, p < 0.05; **, p < 0.01. C, Western blot analysis of TGF-α (6-kDa form) and β-actin at 36 h after 2/3PH in wild-type and HB-EGF knock-out animals.
In summary, to uncover mechanisms that link the priming phase of liver regeneration with hepatocyte DNA replication, we used the model of \( \frac{1}{3}\text{PH} \), which differs from the standard \( \frac{2}{3}\text{PH} \) by the lack of a clear wave of replication. These animals have a defect in the expression of cell cycle genes that may be attributed to the lack of expression of HB-EGF, a growth factor that appears to play a key role in the induction of the G1/S transition in the regenerating liver. The differential expression of HB-EGF between \( \frac{2}{3}\text{PH} \) and \( \frac{1}{3}\text{PH} \) is consistent with data showing that HB-EGF is not detectable in the serum of patients who underwent minor hepatectomies (subsegmentectomy) but is present in the serum of patients with larger hepatectomies (lobectomy or segmentectomy) (28).

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