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Cascades of transcription regulation during liver regeneration

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Abstract

An increasing demand for new strategies in cancer prevention and regenerative medicine requires a better understanding of molecular mechanisms that control cell proliferation in tissue-specific manner. Regenerating liver is a unique model allowing use of biochemical, genetic, and engineering tools to uncover molecular mechanisms and improve treatment of hepatic cancers, liver failure, and fibrotic disease. Molecular mechanisms of liver regeneration involve extra- and intracellular factors to activate transcription of genes normally silenced in quiescent liver. While many upstream signaling pathways of the regenerating liver have been extensively studied, our knowledge of the downstream effectors, transcription factors (TFs), remains limited. This review describes consecutive engagement of pre-existing and de novo synthesized TFs, as cascades that regulate expression of growth-related and metabolic genes during liver regeneration after partial hepatectomy in mice. Several previously recognized regulators of regenerating liver are described in the light of recently identified co-activator and co-repressor complexes that interact with primary DNA-binding TFs. Published results of gene expression and chromatin immunoprecipitation analyses, as well as studies of transgenic mouse models, are used to emphasize new potential regulators of transcription during liver regeneration. Finally, a more detailed description of newly identified transcriptional regulators of liver regeneration illustrates the tightly regulated balance of proliferative and metabolic responses to partial hepatectomy.

Keywords

transcription; regeneration; hepatectomy; gene expression

INTRODUCTION

Models of liver regeneration

Liver regeneration (LR) after partial hepatectomy (PH), or after toxic injury induced by specific chemicals, offers a unique and robust model to study initiation, progression, and termination of tissue growth *in vivo*. A major goal is to understand this process in humans, in order to apply this knowledge in regenerative medicine or to oppose dysregulated proliferation and growth in tumorigenesis. Monitoring patients with liver disease, as well as healthy liver donors, provides invaluable, but limited, information about regulation of liver regeneration in humans (Haga et al., 2008, de Jonge et al., 2009). To fill this gap, research

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turns to animal models, and several exist for the study of LR (Martins et al., 2008, Michalopoulos, 2007). Among these, the mouse LR model allows more mechanistic insights, as knock-out (KO) and knock-in mutations of selected genes are more readily created in this species. Interestingly, LR in zebrafish has gained in use during the past few years; small-scale PH performed in this animal triggers a regenerative response similar to that of rodents and humans (Kan et al., 2009, Sadler et al., 2007). In this review, we primarily focus on the mouse model, and present an overview of the progressive activation of transcription factors in response to inductive signals of PH, which exert their influence through networks of targeted gene regulation that promote and precisely terminate the remarkable process of tissue regeneration.

The classical mouse model of PH requires ~65–70% removal of liver, to initiate LR via hepatic cell proliferation. This initial phase of LR is often termed the priming phase, and is required for the G₀-G₁ transition of hepatocytes and non-parenchymal liver cells. The responsive phase includes proliferation (G₁-S-G₂-M transitions) and cessation of growth (exit back to G₀). Unless hepatocytes are inhibited or greatly delayed in replication by extensive disease or injury, response of these differentiated cells is the primary means by which liver mass is restored.

PH-induced regeneration is initiated by hemodynamic changes due to two-thirds removal of liver mass, which triples the portal load per unit of tissue (Marubashi et al., 2004). Proliferation occurs in all populations of cells within the liver: mature normal hepatocytes of the liver parenchyma, as well as induction and proliferation of non-parenchymal, hepatic cell types: stellate cells, endothelial cells of sinusoid, biliary epithelium, and hepatic macrophage-like Küpffer cells (Figure). Cellular proliferation begins in the periportal region, *i.e.* around the portal triad consisting of portal vein, hepatic artery and bile duct, and proceeds toward the central vein. An increase of gut-derived factors, such as lipopolysaccharide (LPS), inflammatory mediators of the innate immune response complement factors C3a and C5a, and immunoglobulin superfamily proteins intercellular adhesion molecules (ICAMs) in portal blood and, subsequently, in liver sinusoids, activate Küpffer cells (Fausto, 2006, Strey et al., 2003)

Küpffer cells come in close contact with parenchymal hepatocytes and induce replication of hepatocytes through their release of tumor necrosis factor (TNF α) and interleukin 6 (Il6) cytokines in a paracrine manner. Experiments performed with mice mutant for *Il6* (Cressman et al., 1996) and *Tnfa receptor 1 (Tnfrsf1)* (Yamada et al., 1997) demonstrated that these factors are essential for initiation of liver regeneration. Il6 release from Küpffer cells can be also activated by neuromediator acetylcholine, as shown by surgical removal of the hepatic branch of *nervus vagus*, followed by PH in mice (Ikeda et al., 2009). Importantly, LR is impaired in vagotomized mice, emphasizing the engagement of extra-hepatic stimuli during the priming phase of LR.

The mechanisms responsible for priming of non-parenchymal liver cells during regeneration are less clear, compared to the parenchymal cells, and may include regulation by hypoxia-induced vascular endothelial growth factor (VEGF) (discussed in more detail below). Primed endothelial cells of the sinusoid activate the release of pro-HGF from stellate cells. Pro-HGF is cleaved by uPA and plasminogen proteases, producing an active HGF, which binds the Met receptor on hepatocytes (Borowiak et al., 2004). Other blood-borne factors (*e.g.*, insulin, norepinephrine) also contribute to the initiation of liver regeneration, as reviewed in (Taub, 2004, Fausto et al., 2006).

Endocrine and paracrine signals activate pre-existing TFs to induce early response genes

Paracrine and endocrine signals from non-parenchymal hepatic cells initiate the first cascade of transcriptional activity in hepatocytes (priming phase). During this phase, pre-existing TFs are activated by post-translational modifications without *de novo* protein synthesis. This allows rapid expression of genes that promote hepatocytes to leave their quiescent G₀ state and enter the cell cycle (G₀-G₁ transition).

The first TFs are activated within 30 minutes and continue over approximately 4h after PH, and these include **NFκB**, **Stat3**, and **AP-1** (Wuestefeld et al., 2003, Yamada et al., 1997, Cressman et al., 1996). The transcriptional activity of these factors is critical for initiation of LR, as their target genes encode many proteins, which are not expressed in quiescent hepatocytes and must be synthesized *de novo* for the G₀-G₁ and later transitions.

Multiple studies clearly point to cytokine-mediated upstream signaling, as a major activator of NFκB-, Stat3-, and AP-1-mediated transcription in hepatocytes. DNA-binding of NFκB, Stat3, and AP-1, as assayed *in vitro*, is activated shortly after PH. However, in mice with mutated *Tnfrsf1* or *Il6/glycoprotein 130 (gp130) receptor*, this ability to bind DNA-consensus sites is impaired (Cressman et al., 1996, Wuestefeld et al., 2003, Yamada et al., 1997).

Regulation by NFκB: TNFα, LPS, complement factors C3a and C5a, and ICAMs activate NFκB-mediated transcription in Küpffer cells (Fausto, 2006, Fausto et al., 2006). Mice with mutated *Tnfrsf1* have almost complete inhibition of nuclear NFκB binding due to cytoplasmic relocation after PH that is not corrected by administration of Il6 (Yamada et al., 1997). Binding of TNFα to *Tnfrsf1* leads to an activation of NFκB-dependent transcription in Küpffer cells, which produce Il6, thereby activating Stat3-dependent transcription in hepatocytes (Fausto et al., 2006). A study of the conditional *gp130* KO mice showed that both NFκB and *Tnfrsf1* gene expression is, in turn, regulated by Il6 (Wuestefeld et al., 2003). However, in contrast to *Tnfrsf1* KO mice, regenerating livers from *gp130* KO mice displayed only minor effects on cell cycle and DNA synthesis after PH (Wuestefeld et al., 2003, Yamada et al., 1997). Importantly, LPS stimulation in *gp130*-deleted and also *Il6*^{-/-} animals after PH leads to a significant reduction in survival and DNA synthesis (Wuestefeld et al., 2003), suggesting that the initial activation of NFκB transcription in Küpffer cells is critical for the subsequent activation of cytokine-mediated transcription in hepatocytes.

The crucial role of inflammation in NFκB-mediated transcription during the priming phase of LR is emphasized by deletion of *Inhibitor of Kappa B Kinase β (Ikkβ)*. IKKβ mediates signaling from the *Tnfrsf1* by opposing an inhibitor of NFκB transcriptional activity. IKKβ-mediated phosphorylation of IκB releases NFκB (p65) protein, which translocates to the nucleus to activate expression of target genes. Liver-specific *Ikkβ* deletion triggered a more rapid and pronounced inflammatory response in non-parenchymal liver cells, leading to earlier hepatocyte proliferation (Malato et al., 2008).

The roles of Stat3: Within the first two hours following PH, Il6 binding to the Il6/gp130 receptor leads to phosphorylation of Stat3 and direct DNA-binding, to activate early-response genes (Seidel et al., 1995, Li et al., 2002). Among the genes activated by Stat3, during this time period, are important players in early regenerative response: *Myc*, *Gadd45*, *Fos*, *Junb*, and *Egr1*. Liver-specific deletion of *Stat3* caused lower expression of *cyclin D1* and *cyclin E*, required for G₁-S transition of the cell cycle (Li et al., 2002). Overall, expression of at least 100 genes is up-regulated in this phase of LR, leading to *de novo* synthesis of proteins required for G₀-G₁ and G₁-S transitions (Li et al., 2002, Fausto et al., 2006).

Hepatocyte Growth Factor (HGF) acts alongside Il6 signaling to induce early response genes by binding to the Met receptor of hepatocytes, which leads to activation of ERK1/2 and Akt – mediated signaling (Fausto et al., 2006, Borowiak et al., 2004). Liver-specific *Met* mutant mice displayed a decrease in *cyclin D1* levels and an increase in *Cdkn1a* (*p21*) cell cycle inhibitor, resulting in defective exit from G₀, stalled G₁-S transition, and impaired liver regeneration (Borowiak et al., 2004, Huh et al., 2004). Inhibition of Met-signaling with shRNA against the Met receptor in partially hepatectomized rats altered expression of many cell cycle and apoptosis-related genes. Microarray analysis detected a decrease in expression of *cyclin E* (associated with G₁-S transition); whereas expression of *cyclin B* (associated with progression of mitosis) increased during liver regeneration in Met shRNA-treated rats, compared to scrambled shRNA-treated and to Sham-operated groups. BrdU incorporation was decreased and apoptosis increased at 24h after PH (Paranjpe et al., 2007). This study suggests that HGF/Met signaling is important not only for G₀-G₁ transition, but also for the S-phase entry and protection of hepatocytes from apoptosis.

Function of AP-1: Similar to Stat3, PH-induced binding activity of the dimeric Fos/Jun transcription factor, AP-1, is decreased in *Tnfrsf1* KO and *Il6* KO mice, and restored after injection of Il6 (Yamada et al., 1997, Cressman et al., 1996). Jun, Fos, and JunB bind to the AP-1 DNA-binding site of the early-response genes within 1–5 hours after PH (reviewed in (Hsu et al., 1992)). Conditional inactivation of *Jun* in the perinatal liver causes high morbidity and severe impairment of LR after PH, which correlates with increased protein levels of cell cycle inhibitor p21 and increased activity of the stress kinase p38 α (Behrens et al., 2002, Stepniak et al., 2006). Simultaneous deletion of *p38 α* and *Jun* in the liver decreases p21 protein levels and fully restores hepatocyte proliferation after PH (Stepniak et al., 2006). These data demonstrate that Jun/AP-1 regulates liver regeneration through p21 and p38 α , suggesting a role for AP-1 both in G₀-G₁ and G₁-S transitions.

More recently, a family of TFs, nuclear factor of activated T-cells (**NFAT**), that is normally associated with late response, has also been implicated in early response to PH (Pierre et al., 2009). Immediate early gene *Fos* was elevated in NFAT4 KO mice at 1 hour and 24 hours after PH, as compared to WT mice, whereas *Jun* showed late increase in expression (7–10 days after PH). Overall, NFAT4 KO mice had approximately 20% reduction in regenerating liver mass at day 10 following PH, as compared to a normally complete restoration of initial liver mass in WT mice by this time point. Functions of NFATs are implicated in Myc-induced proliferation, VEGF-mediated angiogenesis, and cellular migration during carcinogenesis (Buchholz and Ellenrieder, 2007). Further studies are needed to determine potential functions of this TF-family during LR.

Mechanisms of transcription regulation by the Notch signaling pathway are shared among hepatocytes and non-parenchymal liver cells in response to PH (Wang et al., 2009, Kohler et al., 2004). Notch receptor and its ligand Jagged-1 are expressed in quiescent hepatocytes, bile duct cells and endothelial cells of sinusoid at low levels (Kohler et al., 2004). Upon ligand binding, cleavage of the receptor releases intracellular cytoplasmic domain of Notch (**NICD**), which translocates to the nucleus within 15 min following PH (Kohler et al., 2004). In the nucleus, NICD binds to the transcription factor recombination signal-binding protein J (**RBP-J**) and converts it from a transcriptional repressor to a transcriptional activator. One of the target genes activated by NICD/RBP-J within 30–60 minutes after PH is a transcriptional repressor hairy and enhancer of split 1 **Hes-1** (Kohler et al., 2004). Importantly, RBP-J KO mice have impaired LR as evidenced by a decreased number of nuclei and abnormal arrangement of liver sinusoids (Wang et al., 2009). Disruption of RBP-J also leads to changes in *Vegf*, *Il6* and *Hgf* expression and defective LR due to damage of endothelial cells and a decrease in microcirculation in sinusoids (Wang et al., 2009). Thus, Notch-mediated signaling is necessary for successful regeneration of hepatocytes and

endothelial cells; however, more studies are needed to define functions of Notch-regulated TFs NICD/RBP-J and HES-1 during LR.

Wnt-signaling controls development and tissue regeneration by stabilizing β -catenin and activating expression of its target genes. During LR in rats, Wnt signaling is activated by 5 min after PH, resulting in translocation of β -catenin to the nucleus (Monga et al., 2001). In zebrafish and mice, stable β -catenin also accumulates in hepatic nuclei, particularly, in the periportal area of the murine liver, and LR is significantly enhanced (Goessling et al., 2008). In addition, prostaglandin E2 (PGE2) increases β -catenin protein stability through cAMP/PKA-mediated phosphorylation (Goessling et al., 2009). Inhibitors of PGE2 production dramatically decrease nuclear β -catenin, hepatocyte proliferation, and LR in zebra fish and mice after PH (Goessling et al., 2009). Therapeutic manipulation of PGE2 levels using anti-inflammatory cyclooxygenase inhibitors may be beneficial for the controlled regulation of both liver regeneration and cancer treatment in patients. The role of Wnt-signaling in liver is covered in more detail elsewhere in this issue.

Hypoxic response contributes to liver regeneration

Ligation of the left lateral and median lobes during PH surgery leads to a diminished blood supply in the remaining right and caudate lobes, and imposes oxidative stress in liver tissue (Maeno et al., 2005, Mitchell and Willenbring, 2008). Angiogenesis is required to restore an adequate oxygen supply to the newly formed liver mass (Drixler et al., 2002). Despite numerous studies of hypoxia-mediated gene expression in rapidly growing tissue during tumor development and normal tissue repair (Scheid et al., 2000, Elson et al., 2000, Tsuzuki et al., 2000), mechanisms of hypoxia-induced transcriptional cascades in liver regeneration remain elusive. Hypoxia-induced factor 1 α (**HIF1 α**) is post-translationally modified and stabilized under low oxygen conditions, to regulate transcription of HIF1 α -target genes during organ development and regeneration (Iyer et al., 1998, Elson et al., 2000). HIF1 α mRNA and protein levels increase at 12–48 hours following PH, followed by up-regulation of HIF1 α -target gene *Vegf* (Maeno et al., 2005). Importantly, VEGF induces proliferation of sinusoidal endothelial cells during regeneration after PH and mediates angiogenesis (Shimizu et al., 2001). Restoration of small vessels (resinusoidalization) is essential for normal liver function and may contribute to termination of regeneration, as we will discuss later.

Recently created conditional hepatic *Hif1a* KO mice (Tajima et al., 2009) have delayed onset of DNA replication at 60h post-PH, compared to onset of DNA replication following PH in WT controls at 36h post-PH (Tajima et al., 2009). Hepatic *Hif1a* KO mice develop severe hypoglycemia and accumulate more glycogen in regenerated liver compared to WT animals. Previous studies describe direct binding of HIF1 α to the promoter region of *phosphoenolpyruvate carboxykinase* (*Pepck*), recruitment of CREB-binding protein (**CBP**) and activation of *Pepck* expression in hepatocytes under hypoxic stress (Choi et al., 2005). *Phosphoglycerate kinase 1* (*Pgk1*), another gluconeogenic enzyme and direct transcriptional target of HIF1 α (Semenza et al., 1994), is decreased in *Hif1a*-null liver compared to WT controls after PH surgery. At the same time, *Hif1a* KO mice have a higher level of phosphorylated Akt and GSK-3 β kinases, leading to accelerated glycogen synthesis in regenerating *Hif1a* KO liver. Thus, the activity of HIF1 α in transcription regulation may provide a critical mechanism to accelerate glucose production and prevent deposition of glycogen in the remaining liver after surgery, in response to hypoxia and increased metabolic demand imposed by PH.

De novo synthesized TFs regulate mitosis, termination of proliferation and size adjustment in regenerating liver

Expression of immediate-early and delayed-early response genes initiated during the priming phase of LR leads to *de novo* synthesis of TFs, thus starting the next cascade of transcriptional activity during the G₁-S and S-G₂ transitions. The newly synthesized TFs include **Myc**, **C/EBPs**, **FoxM1**, and others previously reviewed in (Costa et al., 2003). However, the number of TFs necessary for successful initiation and completion of mitosis may be significantly higher. At least 185 genes change expression during the first 4 hours after PH, as revealed by high-density microarray analysis (Su et al., 2002). Among these, 19 genes encoding TFs were identified. Some of these TFs are well studied (Taub, 2004, Fausto et al., 2006, Michalopoulos, 2007); however, several TF-encoding genes, not previously described in the context of LR, showed significant up-regulation that continued over the first 4 hours following PH, including **Zif268/early growth response 1 (Egr1)**, **Ets2** and **Atf3** (Su et al., 2002).

Egr1 is a hypoxia-inducible, zinc-finger TF and an immediate early gene in other cell types (Inuzuka et al., 1999, Yan et al., 2000). Egr1 gene expression increases 12-fold during the first 30 min after PH, compared to sham-operated mice (Su et al., 2002). This TF is implicated in expression of the cell division cycle 20 (*Cdc20*) gene, a key regulator of the anaphase-promoting complex during mitosis (Liao et al., 2004). *Cdc20* expression was induced within 48 h following PH in mouse liver. LR in *Egr1*^{-/-} mice proceeds normally through the priming phase, but shows impaired metaphase to anaphase transition during mitosis (Liao et al., 2004). This result suggests that Egr1 transcriptional activity is specific for mitotic progression, and not for other phases of LR.

Ets2 is another TF encoded by an immediate early gene, which may be important for normal LR. In primary mouse hepatocytes, Ets2 interacts with leucine-zipper CCAAT enhancer-binding proteins C/EBP α and C/EBP β and regulates *p21* promoter activity in response to mitogen stimulation (Park et al., 2000). Two independent studies show strong induction of Ets2 (and not Ets1) at 4 h post-PH, compared to sham-operated mice (Bhat et al., 1987, Su et al., 2002). LR-specific transcriptional activity of Ets2 might have direct downstream effects on cell cycle progression; however, studies of an *Ets2* KO mouse are needed to provide further insight into functions of this TF in regenerating hepatocytes.

Atf3 is a leucine zipper DNA binding protein, which can act as an activator and as a repressor, and is a member of the ATF/cAMP-responsive element binding protein (CREB) TF family. Atf3 expression stimulates proliferation of mouse hepatoma cells, and this effect is mediated, at least in part, by the Atf3-dependent activation of *cyclin D1* transcription (Allan et al., 2001). Atf3 is highly up-regulated (up to 50 fold) during the first 4 h following PH, compared to sham-operated mice (Su et al., 2002). Expression of Atf3 can be induced by transforming growth factor β 1 (TGF β 1) (Chen et al., 1996). A nuclear effector of TGF β 1-induced signaling **Smad3** activates expression *Atf3* gene and then recruits Atf3 protein to repress inhibitors of differentiation (*Id1*, *Id2*, and *Id3*) genes (Kang et al., 2003). Interestingly, chromatin immunoprecipitation experiments demonstrated that **Id2** forms a co-repressor complex with **mSin3A** at the *Myc* promoter in quiescent hepatocytes (Rodriguez et al., 2006). *Id2*/mSin3A dissociates from the *Myc* promoter during the first 6 hours after PH, allowing *Myc* expression (Rodriguez et al., 2006). It is tempting to speculate that Smad3/Atf3-mediated repression of *Id2* gene is an important mechanism leading to a decrease of *Id2* levels and release of *Id2*-mediated *Myc* repression during hepatocyte priming. However, transcriptional activity of Smad3/Atf3 during LR requires further investigation.

Studies of cultured epithelial cells showed that Atf3 is also recruited by **NF-E2-related factor 2 (Nrf2)** resulting in transcriptional repression of Nrf2 target genes (Brown et al., 2008). *Nrf2* KO mice have a lower liver/body weight ratio compared to WT, suggesting a role for Nrf2-mediated transcriptional activity in liver growth and homeostasis (Beyer et al., 2008). Indeed, Nrf2 deficiency causes considerable delay in DNA synthesis and enhances hepatocyte apoptosis following PH in mice, due to loss of expression of many Nrf2 target genes, increased oxidative stress, and reduced insulin responsiveness (Beyer et al., 2008). Nrf2 regulates transcription by recruiting CBP histone acetyl transferase to antioxidant response elements (AREs) located in the promoter regions of target genes (Beyer and Werner, 2008). Atf3 represses Nrf2-mediated expression by direct binding of Atf3 to Nrf2, which displaces CBP from the ARE (Brown et al., 2008). These results suggest that Atf3- and Nrf2-mediated transcriptional activity and repression are important in the G₁-S and S-G₂ transitions and engage multiple pathways activating DNA synthesis and suppressing apoptosis in regenerating liver (Beyer and Werner, 2008).

Late response TFs control mitotic entry and progression during LR

Mitotic entry (G₂-M transition) occurs during the second day after PH in mice, and requires expression of *cyclin A*, *cyclin B*, cyclin-mediated kinases *Cdk2*, *Cdk1*, and the *Cdc25* family of protein phosphatases. Some of these genes are induced by FoxM1, a TF activated during the early response phase of LR. FoxM1 regulates the G₁-S transition by activating expression of *cyclin D1* and *Cdc25b* and repressing cell cycle inhibitors *p21* and *Cdkn1b* (*p27*) (Wang et al., 2002a, Wang et al., 2002b). Regulation of *Cdc25a*, *Cdc25b*, *cyclin B1*, *p21* and *p27* by FoxM1 is critical for hepatocyte proliferation, as shown by studies of LR in mice with hepatocyte-specific KO of *Foxm1* (Krupczak-Hollis et al., 2003). Transcriptional activity of FoxM1 is important for timely mitotic entry and accurate chromosome segregation (Laoukili et al., 2005) and is associated with increased cyclin F and p55cdc, which are involved in completion of mitosis during LR, reviewed in (Mackey et al., 2003).

Similar to FoxM1, late-response TF **C/EBP β** protein is induced during the priming phase of LR. The transcriptional activity of C/EBP β is maintained throughout G₁-S-G₂-M transition, as previously described in several reviews (Diehl, 1998, Schrem et al., 2004, Timchenko, 2009)). C/EBP α is expressed in hepatocytes of quiescent livers and, unlike C/EBP β , is down-regulated through G₁-S-G₂-M after PH. Upon mitotic exit, C/EBP α levels increase, whereas C/EBP β decreases, re-establishing the G₀ balance of C/EBPs (Greenbaum et al., 1995, Mischoulon et al., 1992). The significance of the C/EBP isoform balance during termination of liver regeneration is described in more detail below; here, we briefly describe recently added details of C/EBP β -mediated transcription during the G₂-M transition in regenerating liver.

C/EBP β acts in the G₂-M transition by regulating transcription of E2F target genes, responsible for cell cycle progression. A comprehensive list of these genes is found in a recent microarray analysis of E2F-regulated genes in quiescent and 40h post-PH liver of *Cebp β* KO and WT mice (Wang et al., 2007). C/EBP β occupancy on the promoters of 2 out of 4 analyzed pro-proliferative E2F-regulated genes (*Cdc6*, *Mcm3*) increased at 40 h after PH in WT mice. Using LR in *Cebp β* KO mice, the authors identified the histone acetyl transferase p300/CBP complex as a transcriptional co-activator of E2F-C/EBP β -regulated genes (Wang et al., 2007). The same group later showed that C/EBP β binds to the **PPAR γ coactivator-1 α (Pgc1 α)** gene and activates its expression during LR (Wang et al., 2008b). Pgc1 α , in turn coordinates expression of genes involved in gluconeogenesis and ketogenesis: two metabolic functions supported by regenerating liver. Expression of two Pgc1 α target genes, *Cpt1a*, encoding the rate-limiting enzyme in fatty acid beta-oxidation, and *Acadl*, encoding an enzyme for beta-oxidation of long chain fatty acids, was significantly reduced in C/EBP β KO livers after PH (Wang et al., 2008b). These two findings demonstrate how

one TF (C/EBP β) can couple both proliferative and metabolic functions at the level of regulation of gene expression during LR.

In contrast with C/EBP β , the transcriptional activity of **C/EBP α** must be decreased to allow hepatocyte mitosis (Johnson, 2005). Several studies demonstrated a complex mechanism regulating C/EBP α and C/EBP β activity during LR (recently reviewed in (Timchenko, 2009). C/EBP α forms a multi-protein complex with histone deacetylase 1 (**HDAC1**), **cyclin D3**, and **Brm**, silencing E2F depending promoters to decrease hepatocyte proliferation (Wang et al., 2008a). GSK-3 β was shown to promote proliferation of hepatocytes during LR by targeting cyclin D3 for degradation, thus inactivating C/EBP α /HDAC1/Brm/cyclin D3 complex (Jin et al., 2009). Importantly, HDAC1 deacetylates histones present at the E2F-dependent promoters of *Myc* and *Foxm1* genes, leading to decreased expression of these TFs (Wang et al., 2008a). These results suggest an intricate regulation of the transcriptional activity of Myc, FoxM1, and C/EBP isoforms during LR. Although the reciprocal regulation of C/EBPs during liver regeneration has been known for some time (Mischoulon et al., 1992, Greenbaum et al., 1995), additional experiments are needed to find mechanisms that initiate the increase in C/EBP β levels during mitotic entry and the up-regulation of C/EBP α during termination of LR. These mechanisms will provide valuable clues for designing therapies to enhance regeneration in patients with liver failure or liver resection, while at the same time preventing abnormal hepatic growth and tumorigenesis.

Hepatocytes enter mitosis as a synchronized population at approximately 48 h after PH, followed by non-parenchymal liver cells. At approximately 72h after liver resection, a subset of hepatocytes exits cell cycle, returning back to G₀, while the remainder continues to divide through one more round of mitosis prior to exit to G₀ at approximately 96 h after PH (Taub, 2004). Mitotic progression is controlled by Polo-like kinases Aurora A and Aurora B, which phosphorylate regulatory proteins of the mitotic machinery and mediate prophase-to-metaphase transition, chromosome alignment, mitotic spindle assembly, and cytokinesis (Carmena and Earnshaw, 2003, Marumoto et al., 2005). Expression of Aurora A is initiated in late S phase and peaks at the G₂-M transition, rapidly returning to basal levels after the last phase of mitosis in different cell types, including regenerating hepatocytes (Marumoto et al., 2005, Li et al., 2009). FoxM1 is essential for expression of the Aurora B gene and normal proliferation of liver cells during development, as demonstrated by defects in hepatoblast mitosis of *Foxm1* KO embryos (Krupczak-Hollis et al., 2003). This result suggests that transcriptional activity during G₁-S and S-G₂ transitions in LR controls expression of genes responsible for mitotic progression. The intriguing question remains about mechanisms that promote some hepatocytes “to decide” to return to G₀ after the 1st round of replication, or go through G₁-S-G₂-M transitions one more time.

To elucidate factors that regulate mitosis during LR, Li *et al.* over expressed Aurora A in mouse liver under the control of the *Pepck* promoter (Li et al., 2009). Aurora A transgenic mice exhibit early S-phase and increased DNA synthesis in regenerating liver, followed by a premitotic arrest and an increase in the number of binuclear hepatocytes compared to regenerating WT liver. An earlier induction, higher and persistent expression of G₂-M genes, as well as a significantly lower number of mitotic hepatocytes, suggest that over expression of Aurora A in regenerating liver: 1) accelerated S-G₂ transition, but 2) caused a stall during G₂-M transition and a pre-mitotic arrest. Moreover, aging Aurora A transgenic mice have an incidence of benign liver tumors (Liu et al., 2004). While the first finding is rather expected, but not completely understood, the second requires an additional regulator of mitotic entry to explain activation of a G₂-M checkpoint.

The G₂-M checkpoint may be activated by mitogenic stimuli and/or signaling induced by DNA replication-induced damage (Bartek and Lukas, 2007, Astuti et al., 2009). Expression

and post-translational modifications of the major checkpoint regulator and tumor suppressor **p53** have been previously linked to Aurora A function (Katayama et al., 2004, Liu et al., 2004). In contrast to what was observed in cultured cells, where Aurora A destabilized p53 (Katayama et al., 2004), p53 protein was significantly increased in Aurora A transgenic liver at 2 and 4 days post-PH, indicating that p53 expression and/or protein stability is regulated by the G₂-M checkpoint during LR (Li et al., 2009). Importantly, KO of *Trp53* rescues impaired G₂-M transition and premitotic arrest in Aurora A-transgenic liver during regeneration (Li et al., 2009), suggesting a role for p53 in G₂-M transition in normal proliferating cells. Further experiments addressing Aurora A and p53 function during mitosis in the LR model could provide important insights into p53 functions relevant to liver tumorigenesis.

While much effort is spent on characterization of PH-induced TFs that activate expression of genes required for LR, surprisingly little is known about TFs that either repress their target genes or transiently lose transcriptional activity during LR. Two related, transcriptional repressors **SnoN** and **Ski**, which bind phosphorylated, DNA-bound Smad proteins to antagonize TGF β -signaling, are induced during LR and likely oppose the anti-proliferative functions of TGF β (Macias-Silva et al., 2002). In quiescent liver, DNA-bound p53 and Smad proteins anchor a repressive complex of SnoN, corepressor mSin3A and HDAC1 (Wilkinson et al., 2008), and further recruit **histone H3K4 demethylase LSD1**, leading to a loss of active epigenetic marks and repression of *Afp*. In response to PH, p53 and LSD1 are displaced and expression of *Afp* is reactivated (Tsai et al., 2008).

Loss of p53-mediated regulation of transcription may be necessary for G₂-M transition during LR, an observation supported by enhanced mitosis in regenerating livers of p53 KO mice ectopically expressing Aurora A (Li et al., 2009). Cyclin B1 is repressed by p53 but must be expressed for mitotic progression; whereas, genes that inhibit mitotic entry and are activated by p53, *e.g.* *p21*, *Gadd45*, and *14-3-3 σ* , must be repressed for successful G₂-M transition (Taylor and Stark, 2001). However, LR in *Trp53* KO mice proceeds without major complications. One possibility is that **p73**, a p53 family member and itself a tumor suppressor, partially compensates for loss of p53 transcriptional activity during LR, as it does during liver development of *Trp53* KO mice (Cui et al., 2005). *Trp73* KO mice have profound developmental abnormalities and do not live to adulthood (Yang et al., 2000); therefore, p73-mediated transcription has not been studied in the context of LR. While *Trp53*^{+/-} mice do not develop liver tumors, depletion of p73 in a *Trp53*^{+/-} background leads to hepatocellular carcinoma (HCC), suggesting that both p53 and p73 act as tumor suppressors in normal liver (Flores et al., 2005). Patients with HCC have high expression of a truncated isoform of p73 DNp73, which blocks pro-apoptotic activity of p73 and correlates with decreased survival (Muller et al., 2005, Stiewe et al., 2004, Putzer et al., 2003). DNp73 acts as a dominant-negative competitor for DNA binding with p53 and full-length p73, thereby counteracting their growth-suppressive properties (Stiewe et al., 2002). Transgenic mice with liver-specific over expression of DNp73 exhibit hepatic histological abnormalities, including increased hepatocyte proliferation resulting in hepatic carcinoma in 83% of mice (Tannapfel et al., 2008). In light of these findings, it would be beneficial to decipher functions of p53, full-length p73, and DNp73 during LR in tissue-specific KO mice, as it could provide insights into mechanisms that control proliferation in normal and tumor cells.

“Hidden” nuclear receptor-mediated cascades control LR

During LR, hepatocytes and non-parenchymal liver cells demonstrate an amazing ability to exit quiescence and progress through the cell cycle in a highly synchronous fashion, along the way performing all metabolic functions of the quiescent uninjured liver. In an elegant study, combining molecular and computational pathway analyses, the Greenbaum laboratory

outlined the shifts in transcriptional programs that occur during LR (White et al., 2005). In this study, microarray analysis of RNA isolated from regenerating livers was followed by Ingenuity Pathway Analysis, which identified networks of differentially expressed genes at 0, 2, 16 and 40 h after PH, which correspond, respectively, to G₀, G₀-G₁, G₁-S, and S phases of LR. Expression of genes involved in lipid and hormone metabolism in quiescent liver is rapidly overrun by increased expression of genes contributing to cytoskeleton formation, followed by a large cluster of genes responsible for mitotic spindle assembly and DNA synthesis. Importantly, metabolic genes maintain low expression during the first 40 hours of LR, as compared to quiescent liver, suggesting a temporary loss of transcriptional activators of lipid and hormone metabolism in regenerating liver (White et al., 2005).

Patterns of gene expression in regenerating liver must be realigned toward the end of mitosis, to reverse the shift from proliferative activities during LR back to metabolic functions of quiescent liver. Microarray analysis of genes, associated with the response of regenerating liver to nutrients and xenobiotics, showed an increase in expression of these genes toward the end of mitosis in rat LR (Qin et al., 2006). These results suggest the presence of a “hidden” and temporarily suppressed transcriptional cascade, controlling response to metabolic demands in regenerating liver by physiologically variable blood glucose, hormone, and toxin levels. Although difficult to discern amid dramatic changes in gene expression induced by inflammatory and growth factors during the priming phase of LR, transcriptional mechanisms controlling normal liver lipid metabolism, hormone synthesis, and drug detoxification must maintain expression of target genes at the lowest sufficient level.

Two recent studies shed light on this hidden metabolic transcriptional activity. The first one shows that *Tnfrsf1a* and *Tnfrsf1b* double KO mice, which are non-responsive to induction of hepatocyte proliferation by PH due to the loss of TNF α -mediated Il6 signaling, actually initiate hepatocyte proliferation after activation of constitutive androstane receptor (CAR), responsible for xenobiotic signaling in liver (Columbano et al., 2005). Interestingly, this proliferation occurs without activation of NF κ B- and Stat3-mediated transcription, but involves activation of an early response gene *Gadd45* by CAR-mediated transcription, independently of TNF-activated NF κ B (Columbano et al., 2005). Based on these results, the authors suggest that negative cross-talk exists between CAR and TNF/NF κ B in regulation of hepatocyte proliferation (reviewed in more detail in (Costa et al., 2005).

Further studies by the Moore laboratory further emphasize the importance of liver-specific transcription focused on metabolism during regeneration. By supplementing the diet with bile acids, during a time course of LR, liver growth is significantly augmented after PH in mice (Huang et al., 2006). This increase is completely abolished by withdrawal of bile acids from the diet, as well as in mice lacking expression of the primary bile acid receptor FXR, suggesting bile acid-induced transcription is necessary for normal LR. During regeneration, hepatic bile acid levels decrease while bile flow from the liver increases to meet metabolic demands imposed on the remaining 1/3 of the original liver mass. In FXR KO mice, hepatic bile acid levels significantly increased on the first day after PH, and slowly declined toward the end of LR. The authors suggest that an FXR-dependent pathway in WT mice prevents an increase in bile acids during LR. In WT mice, high levels of bile acids promote an earlier increase in FoxM1 transcription, and induced expression of FoxM1 target *Cdc25b*. FoxM1 is a key regulator of gene expression in G1-S transition (Wang et al., 2002a, Wang et al., 2002b). Expression of FoxM1 is strongly down-regulated in FXR KO mice, and significantly decreased in CAR KO mice, indicating that both bile acid and xenobiotic receptors contribute to regulation at the G1-S transition during LR. Importantly, growth factor- and cytokine-mediated response is not lost in regenerating FXR KO livers and can contribute to eventual regrowth of the liver (Huang et al., 2006).

Taken together, these studies support the existence of nuclear receptor-dependent transcriptional mechanisms that respond to increased metabolic demands after PH, in parallel with more evident mitogenic transcriptional cascades initiated by cytokines and growth factors during induction of LR. Both mitogenic and metabolic transcriptional cascades are required for normal liver regeneration and provide insight into an amazing ability of liver cells to undergo mitotic divisions without loss of major metabolic functions.

Termination of regeneration and liver size adjustment

The liver index (ratio of liver weight/body weight) is tightly regulated and depends on metabolic demands of the organism. Liver regeneration after PH stops precisely when a pre-operative liver index is restored, within 7–14 days in mice. Liver cells therefore possess highly effective mechanisms that control mitotic exit of hepatocytes and non-parenchymal cells and return to G₀. A deeper understanding of these mechanisms will provide valuable information about regulation of proliferation and quiescence in normal cells, critical for treatment of cancer, wound repair, and many other medical conditions associated with abnormalities in tissue growth.

As a result of significant research efforts in this area, several molecules are noted as potential terminators of hepatocyte proliferation, among them suppressors of cytokine signaling Socs proteins, plasminogen activator inhibitor PAI-1 protein, as well as TGF β - and activin-ligands (reviewed in (Taub, 2004, Michalopoulos, 2007)). The latter ligands of TGF β receptor were longtime favorites, as regulators of termination signaling, since TGF β activates PAI-1 expression and suppresses DNA synthesis in regenerating hepatocytes (reviewed in more detail in (Michalopoulos, 2007)). However, hepatic-specific, TGF β receptor KO mice, which were treated with activin-signaling inhibitor follistatin, exhibit normal termination of liver regeneration (Oe et al., 2004).

New insights into LR termination come from studies of extracellular matrix (ECM) proteins in regenerating livers. Cultured hepatocytes and *ex vivo* liver reconstruction experiments show that ECM-signaling is very important for maintenance of hepatocyte-specific gene expression (Zimmermann, 2002). It is suggested that rapid proliferation of hepatocytes, during the first three days following PH, is accompanied by degradation of ECM, resulting in formation of transient clusters of newly formed hepatocytes with limited access to endocrine and paracrine factors that inhibit proliferation of liver cells during quiescence (Zimmermann, 2002). Hepatocyte clusters are oversized and require termination and remodeling mechanisms in order to achieve a pre-operative liver index.

Recent work from the Michalopoulos laboratory reveals that liver-specific KO of an ECM integrin-linked kinase (ILK) results in enhanced hepatocyte proliferation and hepatomegaly (Gkretsi et al., 2008). ILK over expression results in an increase in liver collagen, whereas ILK knockdown *in vivo* leads to a significant reduction in liver fibrogenesis and wound healing (Shafiei and Rockey, 2006). Changes in ECM actively signal to ILK, which then modulates expression of hepatic genes. A dramatic increase in hepatocyte-specific gene expression is observed in liver tissue of aging ILK KO mice; this increase correlates with enhanced expression of hepatocyte-associated TFs C/EBPs (Gkretsi et al., 2008).

C/EBP α and C/EBP β regulate promoters of liver genes, balancing and antagonizing each other during LR, as described above. Transcriptional activity of C/EBP α leads to gluconeogenesis and growth suppression, but this effect is reversed by an increase in C/EBP β expression during the first 3 days of LR (Greenbaum et al., 1995, Mischoulon et al., 1992). Thus, the ratio of C/EBP α to C/EBP β during the proliferative phase of LR is <1, whereas during termination of LR it is reversed and is >1 in hepatocytes exiting to G₀. Interestingly, C/EBP β is significantly increased in quiescent ILK KO hepatocytes, leading to

a C/EBP α to C/EBP β ratio ≤ 1 and mimicking changes seen after PH in a WT mouse during the proliferative phase of LR (Gkretsi et al., 2008). This result suggests that ILK-mediated regulation of transcription is active during termination of liver regeneration.

Recently, the work summarized in Apte *et al.* demonstrates that liver-specific ILK KO mice have defective termination of LR (Apte et al., 2009). ILK KO liver exhibits sustained cellular proliferation at 3, 5, 7, and 14 days post-PH. At day 14 following PH surgery, ILK KO mice have 158% of their original liver weight, compared to the normal 100% liver mass restoration in WT mice. Microarray analysis reveals changes in expression of the same genes up-regulated during LR in WT mice; however, several of these genes remained elevated at day 14. These data indicate that targeted ablation of ILK in the liver leads to downstream changes in gene expression, inappropriate termination of growth and excess liver weight accumulation.

A further search for molecular mechanisms, deregulated during LR termination in ILK KO mice, led Apte and colleagues to analyze the status of the Hippo/Yki pathway (Mst1/2/YAP in mammals). Mst1/2-mediated phosphorylation of **Yes activator protein (YAP)** has been shown to limit organ size in *Drosophila* and mice by inactivating YAP through phosphorylation and nuclear delocalization (Dong et al., 2007). YAP is a critical transcriptional effector of Mst1/2 signaling and binds promoter regions of target genes to promote cellular proliferation and tissue growth (Pan, 2007, Dong et al., 2007). Increased growth in ILK KO liver may be due to the observed higher YAP protein levels at 5–14 days after PH, and lower phosphorylated YAP at days 3–14 following PH, compared to the control mice (Apte et al., 2009). These results suggest that ILK signaling inactivates Mst1/2-mediated phosphorylation of YAP and leads to a decrease in YAP protein levels during termination of LR.

In the study utilizing Tet-On inducible YAP transgenes inserted into a liver-specific expression cassette, the Pan laboratory showed that liver-specific expression of YAP promotes transcription of genes associated with hepatocyte proliferation, such as *Afp*, *Myc*, *Sox4* and *Ki67*, as well as negative regulators of apoptosis *Birc2/cIAP1*, *Birc5/survivin*, and *Mcl1* (Dong et al., 2007). Long-term induction of YAP expression in liver leads to development of HCC in mice; in humans, YAP protein is elevated and nuclear localized in some liver cancers (Zhao et al., 2007). These findings suggest that a critical function of mammalian Hippo signaling is the control of normal liver tissue growth.

p53 family members control tissue growth by inducing expression of target genes that promote cell cycle arrest and/or apoptosis, and therefore could regulate termination of LR. This potential is supported by the tumor clearance of murine liver carcinomas, triggered when expression of p53 is restored (Xue et al., 2007). Importantly, loss of interaction of p53 with promyelocytic leukemia (PML) protein also leads to development of HCC as a result of a decrease in p53 transcriptional activity toward pro-apoptotic genes (Herzer et al., 2005). Surprisingly little is known about functions of PML in normal liver cells, despite several reports demonstrating loss of PML functions in development of liver cancer (Terris et al., 1995, Son et al., 2005, Herzer et al., 2005). Taken together, these results suggest hepatoprotective functions for p53 and PML in normal quiescent liver. It would be interesting to determine if interactions and transcriptional activities of these tumor suppressors play any roles in normal liver during regeneration.

CONCLUSIONS

The significance of investigating transcriptional regulation of LR

Enhancement of liver regeneration is a desirable goal of regenerative medicine, as human post-PH liver regenerates very slowly compared to rodent species and often involves many complications, leading to liver failure (de Jonge et al., 2009, Haga et al., 2008). Aging alone inhibits LR, which leads to serious complications after surgical removal of cancerous or fibrotic non-functioning liver tissue in elderly patients (Timchenko, 2009). A search for mechanisms that suppress LR in aging mice identified growth hormone (GH) signaling as a negative modulator of C/EBP α /HDAC1/Brm-mediated epigenetic silencing of *Myc* and *FoxM1* during LR in mice (Jin et al., 2009). Importantly, GH was tested in clinical trials and proved to have beneficial effects on liver regeneration in children with chronic liver failure and in transplant patients (Fuqua, 2006). These findings provide an excellent link between a molecular mechanism revealed by studies of LR in animal models and a positive practical outcome in human health care.

Recent microarray analyses of biopsies taken from liver donor grafts, followed by biological function analysis, revealed several significant differences in gene expression patterns between donors with successfully regenerated liver (living donors, LD) and deceased donors (DD) (de Jonge et al., 2009). LD liver has increased expression of genes regulating cell cycle, biosynthesis, and regeneration, while genes linked to hepatic metabolism and energy pathways are down-regulated in LD grafts, compared to DD. These results suggest an intricate and precisely timed balance between proliferative and metabolic cascades of transcriptional activity is necessary for successful regeneration of human liver. Further research into mechanisms regulating transcription during LR is needed to continue the development of new approaches in treatments of liver disease.

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Abbreviations

LR	Liver regeneration
PH	partial hepatectomy
KO	knock-out
KI	knock-in
LPS	lipopolysaccharide
ICAMs	intercellular adhesion molecules
TNFα	tumor necrosis factor
IL6	interleukin 6
Tnfrsf1	Tnf α receptor 1
gp130	glycoprotein 130
VEGF	vascular endothelial growth factor
HGF	heaptocyte growth factor

TFs	transcription factors
Ikkβ	Inhibitor of Kappa B Kinase β
NFAT	nuclear factor of activated T-cells
NICD	intracellular cytoplasmic domain of Notch
RBP-J	recombination signal-binding protein J
Hes-1	hairy and enhancer of split 1
PGE2	prostaglandin E2
HIF1α	hypoxia-induced factor 1 α
Pepck	phosphoenolpyruvate carboxykinase
CREB	ATF/cAMP-responsive element binding protein
CBP	CREB-binding protein
Cdc20	cell division cycle 20
C/EBP	CCAAT enhancer-binding protein
TGFβ1	transforming growth factor β 1
Id	inhibitors of differentiation
Egr1	Zif268/early growth response 1
Nrf2	NF-E2-related factor 2
AREs	antioxidant response elements
Pgc1α	PPAR γ coactivator-1 α
HDAC1	histone H3K4 demethylase LSD1, histone deacetylase 1
CAR	constitutive androstane receptor
FXR	farnesoid X receptor
PAI-1	plasminogen activator inhibitor
ECM	extracellular matrix
ILK	integrin-linked kinase
YAP	Yes activator protein
PML	promyelocytic leukemia
GH	growth hormone
LD	living donors
DD	deceased donors

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Figure 1. Transcriptional cascades during liver regeneration

The progression of liver regeneration is mediated through stages of the cell cycle (G_0 : left; G_1 , S, G_2 , M: right) by transcription factor activities and gene expression (see text for details) in hepatocytes (H – boxes, foreground). Structural elements of the liver (PV – portal vein; BD – bile duct; CV – central vein; HA – hepatic artery; HC – Hering's canal; S – sinusoid; ECM – extracellular matrix; background), and PH-induced regulators (1: LPS, ICAM, complement factors, insulin, acetylcholine, norepinephrine, EGF, xenobiotics; 2: IL6 and TNF α ; 3: VEGF; 4: HGF; 5: TGF β ; 6: bile acids) secreted by and/or signaling to non-parenchymal cells of the liver (CH – cholangiocyte; EC – endothelial cell; KC – Kupffer cell; SC – stellate cell), play specific roles in induction of transcription cascades during liver regeneration.