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REVIEW

Growth factors and cytokines involved in liver regeneration

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ABSTRACT. The regenerative ability of the liver is essential for maintaining physiological functions and the injury repair process. The biological mechanisms that regulate liver regeneration remain poorly defined. These mechanisms are notable issues in clinical practice that affect the treatment of hepatic loss caused by hepatectomy, hepatic poisoning, or chronic viral infection. Increasing evidence shows that numerous growth factors, cytokines, and metabolic pathways influence the liver regenerative process. Of particular importance are cytokines and growth factors, which affect different stages of liver regeneration. In this review, we summarize the results obtained from studies that focused on the role of growth factors and cytokines in liver regeneration to reflect on the clinical implications and areas for further study.

Key words: liver regeneration, growth factors, cytokines

As described in the ancient Greek mythology of Prometheus, the liver has an extraordinary regenerative ability [1]. This capacity was confirmed in rodents with 70% partial hepatectomy (PHx), which is a classic animal model of liver regeneration, and the entire regenerative process lasted approximately 7-10 days after surgery [2]. Liver regeneration involves a series of intracellular events triggered by injury-induced extracellular signals, which alter the expression or activity of factors involved in transcriptional and post-transcriptional modifications, and these transcriptional and post-transcriptional responses produce reprogrammed hepatocytes, which transition from a quiescent state to an actively proliferating state [3]. The liver regeneration process is divided into three phases. During the initiation phase, hepatocytes shift from the resting state to the replicating state. In the productive phase, the expansion of the hepatocyte population occurs, and during the termination phase, the proliferation of hepatocytes is gradually inhibited [4, 5]. The regenerative ability of the liver plays an important role in maintaining various normal physiological functions and in repairing liver damage. The success of the treatments for various liver diseases, such as liver resection, liver transplantation, chronic hepatitis virus infection or toxic liver injury, has also been determined. Therefore, understanding the mechanisms of liver regeneration is crucial to guide clinical therapeutic efforts. The activation, proliferation and differentiation of liver cells during the regeneration process are controlled by numerous growth factors and cytokines that are expressed in the liver or by cells recruited from the circulatory system to the liver [6]. In recent decades, the functions of growth factors and cytokines in the liver regenerative process have been elucidated based on *in vivo* animal models and *in vitro* cell culture assays. In this review, we summarize the roles of growth factors and cytokines during the liver regeneration process after PHx, which may shed light on the regulatory mechanism of liver regeneration.

GROWTH FACTORS

Hepatocyte growth factor (HGF)

HGF is a major hepatocyte mitogen that binds to the tyrosine kinase receptor, c-Met, which is expressed in parenchymal and non-parenchymal liver cells [7]. HGF is synthesized by liver non-parenchymal cells and other extrahepatic organs, including the lungs, kidneys, and spleen [8]. Following PHx, the serum level of HGF increases rapidly to reach a concentration up to 10 to 20 times within 1-3 hours [2, 9]. In the initiation phase following PHx, HGF is expressed by non-parenchymal liver cells and other extrahepatic organs and binds to the HGF/c-MET receptor, activating the STAT3, PI3K/AKT, mTOR, and RAS/RAF pathways and promoting hepatocyte transformation to the proliferative state [10]. In the productive phase, the release of HGF can be stimulated by interleukin-6 (IL-6) and tumour necrosis factor (TNF-α), which are mainly produced by Kupffer cells that regulate the immediate response after injury and secrete cytokines, participating in acute-phase protein production [11].
The overexpression of HGF in transgenic mice can promote liver regeneration and hepatocyte proliferation after PHx [12]. Exogenous administration of an HGF activator or recombinant human HGF (rhHGF)

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significantly increased liver regeneration rates and proliferating cell nuclear antigen labelling indices [13]. In the extracellular matrix (ECM), the HGF precursor is cleaved by a metalloproteinase, and subsequent proteolytic maturation of HGF occurs. In addition, an increase in c-MET phosphorylation was observed in the first hours after PHx [14]. A c-MET defect can delay the liver regeneration process, leading to post-operative liver function failure, which is associated with a high mortality rate [15]. Metalloproteinase activity can be inhibited by tissue inhibitor of metalloproteinases 1 (TIMP-1), and TIMP-1 overexpression in the liver suppresses liver regeneration and hepatocyte proliferation after PHx [16].

Clinically, HGF levels increase after one to three days post operation, during Stage 1, which is related to the degree of growth of the future liver remnant and the associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) [17, 18]. Furthermore, serum levels of HGF were significantly elevated two weeks after living donor hepatectomy and were associated with recipient liver volumes [19, 20]. After major liver resection, bile HGF levels were shown to correlate with the incidence of post-hepatectomy liver failure (PHLF), and bile HGF may be a predictive marker of liver function after PHx [21, 22].

Vascular endothelial growth factor (VEGF)

The VEGF family includes VEGF-A-F in mammals, and these factors play pivotal roles in controlling vasculogenesis, angiogenesis and lymphangiogenesis by activating VEGF receptors (VEGFR 1-3) [23, 24]. VEGF enhances the activity of matrix metalloproteinases and induces the proliferation of endothelial cells (ECs), smooth muscle cells, and fibroblasts in the liver to form new blood vessels [25, 26]. VEGF also plays a central regulatory role in recruiting bone marrow progenitors of liver sinusoidal ECs (LSECs) after PHx [27]. Among the VEGF family members, VEGF-A is particularly upregulated in hepatocytes during the liver regeneration process [28]. VEGF-A administration promotes liver regeneration and the proliferation of LSECs. However, VEGF-A does not enhance the proliferation of hepatocytes without the presence of LSECs *in vitro* [29]. In addition, overexpressing the VEGFR splice variant, VEGF-A165, in the liver before PHx accelerated liver function recovery *in vivo* [30]. Blocking VEGF-A function using neutralizing antibodies inhibited the proliferation of LSECs and hepatocytes after PHx, which subsequently impaired liver regeneration [28, 31].

The VEGFR-1 signalling pathway affects the expression of hepatotropic and proangiogenic growth factors and recruits VEGFR-1-expressing macrophages to reconstitute sinusoids, to facilitate liver recovery [32]. Furthermore, the activity of VEGFR-2 was significantly increased after PHx in transgenic VEGFR-2-luc mice [33]. Serum VEGF-As and platelet-derived VEGF-As levels were shown to be increased following liver resection according to clinical data. Platelet-derived VEGF-A levels were higher after major liver resection relative to minor resection [34].

The epidermal growth factor (EGF) family

The seven EGF family members perform their functions by activating the high-affinity receptors, EGFR/ErbB1, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4, in mammals [35]. EGF is produced by the Brunner's glands of the duodenum, and the level of EGF increases 30 minutes after PHx, which is stimulated by HGF activation [36]. Phosphorylated EGFR levels are elevated one hour following PHx [14]. Transforming growth factor (TGF)-α released from hepatocytes, heparin-binding EGF (HB-EGF) released from KCs and ECs, and amphiregulin enhance the phosphorylation of EGFR after PHx [37-39]. Interestingly, TGF-α knockout mice demonstrate normal liver regeneration after PHx [40]. In HB-EGF-knockout mice, hepatocyte proliferation was transiently delayed, which was possibly due to compensatory upregulation of TGF-α [41]. Overexpression of HB-EGF in the liver strongly promotes the proliferation of hepatocytes and accelerates the regeneration process [42]. Clinically, serum HB-EGF levels increase after liver resection and peak after five days in patients with major liver resection. The maximal serum HB-EGF level was shown to correlate significantly with the future liver remnant volume [43]. Moreover, rats were protected against EGFR knockdown by injecting shRNAs, which decreased the proliferation of hepatocytes after PHx, activated c-Met, ErbB2 and ErbB3, and prolonged liver regeneration. This result demonstrates that the EGFR signalling pathway is important but not essential for liver regeneration [44]. In addition, approximately one third of EGFR-knockout mice died after PHx, and delayed hepatocyte proliferation was observed, however, apoptotic cell numbers were not increased, indicating that EGFR activation does not provide a direct survival signal for hepatocytes [45].

Fibroblast growth factors (FGFs)

There are 22 family members with highly different structural characteristics in humans and mice, and these factors exert their effects by activating four transmembrane tyrosine kinase receptors: FGF receptors (FGFR) 1-4 [46, 47]. Several FGF family members are important for liver regeneration, and the mitogenic effect of these members on hepatocytes has been demonstrated *in vitro* and *in vivo*. Together with other growth factors, they are responsible for vascular angiogenesis and sinusoidal network restoration during liver regeneration [48]. Among these FGF family members, FGF-1 and FGF-2 are mainly produced by hepatocytes and activated hepatic stellate cells (HSCs) [49]. FGF2-deficient mice exhibit delayed hepatocyte proliferation due to a delayed G1/S transition after PHx [48]. In addition, FGFR deficits in a zebrafish model impaired liver regeneration [50]. Furthermore, FGFR signalling upregulated PHx-induced growth factor transcription, which increased the expression of detoxifying enzymes of the cytochrome P450 family. FGFR1/FGFR2-knockout mice showed an increased mortality rate following PHx and severe necrosis in the remaining liver tissue. In FGFR1/FGFR2-deficient mice, the

detoxification of endogenous compounds, drugs and toxic chemicals was impaired, resulting in more frequent liver damage and failure. These results revealed the important cytoprotective role of FGFR1 and FGFR2 during liver regeneration [51]. The administration of FGF-7 protein to primary hepatocytes isolated from the regenerating liver tissues activates ERK1/2 and promotes hepatocyte proliferation [52]. FGF-19 and FGF-21 enhance hepatoprotective activities and are considered to be potential options for the treatment of acute liver injuries [53]. FGF-15, which is a bile acid-induced ileum-derived enterokine, was considered to be critical for bile acid homeostasis and an essential mediator for the promotion of bile acids during liver regeneration [54, 55]. Cholestatic liver and the interruption of bile acid by enterohepatic circulation was shown to impair liver regeneration [56]. Furthermore, the FGF-15/FGFR-4/STAT-3/Fox-M1 axis plays an important role in hepatocyte proliferation, and deficits in FGF-R1, -R2, and -R4 frequently induce liver failure after PHx [57]. However, studies focusing on the effects of FGFs following liver resection in humans are extremely rare and there is a lack of recommendations for their use as biomarkers.

Insulin-like growth factors (IGFs)

IGF-1 and 2 stimulate mitogenesis and survival in numerous cell types [58, 59]. IGF-1 and 2 act through the IGF-I and IGF-II signalling pathways by interacting with type-1 IGF tyrosine kinase receptors (IGF-1Rs), however, the type-2 receptor (IGF-2R) can impair the bioavailability of IGF-2. The activity of IGF is regulated by insulin-like growth factor binding proteins (IGFBPs) [49, 60, 61]. Circulating IGF-1 is mainly produced by the liver in response to growth hormone levels, however, IGF-2 expression levels are downregulated in normal liver. Because the IGF-1R expression level is relatively low in hepatocytes, the effects of IGF-1 cannot be observed in normal liver [62].

Liver regeneration was inhibited in Nrf2-deficient mice due to oxidative stress-regulated insulin/IGF-1 resistance, resulting in impaired activation of p38 mitogen-activated kinase, Akt kinase, and downstream targets following hepatectomy [63]. The growth hormone-IGF-1IGF-1R axis is necessary for liver regeneration after PHx, as determined by liver-specific IGF-IR-knockout mice [64]. Overexpression of IGF-1 in HSCs accelerated liver regeneration after acute liver injury, which was mediated by the upregulation of HGF and downregulation of TGF-β1 [49, 65]. IGF-2 released by pericentral hepatocytes can promote hepatocyte proliferation and repair tissue damage during chronic liver injury, however, this is different from the signalling pathway that occurs after PHx [66]. Enhancing the interaction of IGF-2 with both insulin receptors and IGF-1R promotes the proliferation of hepatocytes. IGF-1 receptor expression is increased in patients with hepatocellular carcinoma and chronic hepatitis [67, 68]. The transcription level of the IGF-I axis is enhanced in cirrhotic liver disease, which may represent the regenerative capacity of the damaged liver [69]. However, it has been reported that serum IGF-1 levels are significantly decreased in patients with chronic liver disease. IGF-1R was shown to be overexpressed in patients receiving liver donations after cold ischemia, indicating that IGF-1R is involved in liver regeneration [67]. IGFBP-1 can be rapidly induced after PH. An IGFBP-1 deficit was shown to inhibit liver regeneration, which was characterized by severe necrosis and reduced DNA synthesis in hepatocytes [70]. Furthermore, hepatocyte proliferation was significantly decreased in liver-specific IGF-1R-knockout mice after PHx, and this result was observed only in male mice, suggesting that hormones influence this phenotype [64]. Based on the sparse information available, data on IGF, IGF-1R, or IGFBPs in post-resection regeneration are rare, and additional studies are needed on human liver regeneration.

CYTOKINES

Interleukin-6

IL-6 is involved in various physiological and pathophysiological processes. Dysregulated and increased IL-6 activity can be found in inflammation, regeneration, and tumour development [71]. On hepatocytes or leukocytes, IL-6 initially binds to the IL-6 receptor (IL-6R), and then the IL-6/IL-6R complex engages with glycoprotein 130 kDa (gp130), a signal-transducing β-subunit, resulting in a hexameric signalling complex, which has been described as "classic signalling" [72, 73]. IL-6 is a sensitive marker of surgical stress, liver regeneration, and the release of acute-phase proteins in the liver [74]. In response to liver injury, IL-6 plays a key role in the acute-phase response and exerts both cytoprotective and mitogenic effects. Following liver resection, the serum IL-6 level increases immediately and reaches a peak within six hours [75]. IL-6 is mainly produced by Kupffer cells and promotes the proliferation of hepatocytes by activating approximately 40 genes that are immediately triggered in the remaining liver after PHx [76, 77].

Signalling regulated by IL-6 includes the JAK-STAT pathway and the Ras-MAPK pathway [77]. IL-6 knockout impairs liver generation, and overexpression of IL-6 promotes hepatocyte proliferation by activating the STAT3 signalling pathway, which increases the expression of genes that maintain metabolic homeostasis after liver resection [78-80]. The administration of recombinant human IL-6 was shown to prevent post-operative mortality after PHx in knockout mice [81]. The loss of the IL-6 response was a main reason for impaired regeneration after hepatectomy in viral hepatitis patients [82]. During ALPPS procedures, IL-6 levels increase, peak after Stage 1, and decrease rapidly after Stage 2, and IL-6 levels are associated with HGF levels [18]. Exogenously administered recombinant IL-6 increases serum HGF levels after hepatectomy [83]. Serum IL-6 levels were also associated with graft volumes after living donor liver transplantation. A smaller graft after living donor liver transplantation indicates a greater increase in IL-6 levels post-operatively and a better regeneration rate [84, 85]. IL-6 pre-treatment was shown to improve oxidative injury and mitochondrial dysfunction after

severe liver injury (87% hepatectomy) and decrease post-operative mortality [86].
In IL-6-deficient mice, the administration of stem cell factor (SCF), which is an important growth factor induced by IL-6 that has hepatocyte mitogenic effects, rescued the defects in hepatocyte proliferation following PHx. In SCF-deficient mice, hepatocyte proliferation was impaired during liver regeneration [87]. Oncostatin M, another IL-6 downstream regulator, plays an important role in liver regeneration. Impaired regeneration of liver mass after PHx was found in oncostatin M receptor-deficient mice [88]. Mice with STAT3-deficient hepatocytes showed increased mortality after PHx, however, hepatocyte proliferation was only marginally inhibited in the surviving mice [89]. Consistent with an important role of STAT3, mice lacking suppressor of cytokine signalling 3 (SOCS3), which inhibits the IL-6 pathway, had enhanced activation of STAT3 after PHx, increased hepatocyte proliferation and accelerated liver regeneration [90].

Tumour necrosis factor-α

TNF-α, which is a member of the TNF superfamily, is an important mediator that stimulates the synthesis of acute-phase proteins in the initial stage of liver regeneration [91]. TNF-α is mainly released by Kupffer cells in the liver and sensitizes hepatocytes to growth factors during liver regeneration [10, 91, 92]. The expression of TNF-α is upregulated within 30-120 minutes after PHx. It directly binds to TNF receptor 1 (TNF-R1), activating the NFκB signalling pathway in Kupffer cells [93, 94]. Furthermore, TNF-α enhances the phosphorylation level of the transcription factor, c-Jun, in the nucleus and induces the transcription of target genes, such as cell division cycle protein 2 homolog (CDC2/CDK-1), to promote hepatocyte proliferation [95]. TNF-α induction requires the adaptor protein, MyD88, which participates in the Toll-like receptor signalling pathway. In MyD88-deficient mice, the activity of TNF-α transcription and hepatocyte proliferation are both impaired, leading to the suppression of liver regeneration [96, 97]. Complement component, C5a, is another TNF-α regulator during liver regeneration. C5a inhibition in mice was shown to downregulate TNF-α expression and delay regeneration after PHx [98]. In addition, intercellular adhesion molecule 1 (ICAM-1) affects TNF-α levels in the liver injury model. The activation of ICAM-1 by leukocytes is important for the release of TNF-α and IL-6 by Kupffer cells [99]. Clinically, TNF-α was significantly increased in patients who received donor lobe hepatectomy in the context of a living donor liver transplantation background. Furthermore, higher preoperative TNF-α levels were associated with relative liver volume after hepatectomy [20].
The administration of TNF-α neutralizing antibodies prior to hepatectomy was shown to decrease serum IL-6 levels and impair hepatocyte proliferation after PHx [100]. Consistent with the results of TNF-α neutralizing antibodies, TNF receptor 1 (TNFR1)-deficient mice showed a failure to activate NF-κB and STAT3, and DNA synthesis was significantly impaired, resulting in delayed liver regeneration and an increased mortality rate after PHx. However, knockout of TNFR2 did not influence hepatocyte proliferation or liver regeneration [101, 102]. Although TNF-α and TNFR1 are important for liver regeneration, excessive release of TNF-α may be deleterious. Hepatocyte-specific EGFR-knockout mice showed increased TNF-α levels, which were related to high lethality after PHx [45]. TNF-α levels were also significantly increased by enhancing the activity of TNF-α-converting enzyme in TIMP-3-knockout mice, leading to severe hepatocyte necrosis and apoptosis after PHx. Treatment with neutralizing antibodies against TNF-α were shown to rescue this injury in hepatocytes [103].

Transforming growth factor β

TGF-β is a growth inhibitor of numerous types of cells, including hepatocytes. It is mainly released by Kupffer cells, platelets, ECs, and hepatocytes [104]. Three types of TGF-β (TGF-β1–3) are present in mammals [105]. They activate receptor complexes consisting of type I and type II transmembrane receptors [106, 107]. The expression level of TGF-β1 is upregulated after PHx, however, the regenerating liver reacts to TGF-β and shows transient resistance, which is important for hepatocyte proliferation and liver regeneration [105, 106, 108, 109]. Transient treatment with TGF-β1 was shown to inhibit hepatocyte proliferation but did not influence liver regeneration [110]. The proliferation of hepatocytes and liver regeneration were accelerated within one week after PHx of type II TGF-β receptor-knockout mice, however, normal regeneration was ultimately achieved [111]. Administration of the activin antagonist, follistatin, to hepatocytes from type II TGF-β receptor-knockout mice enhanced hepatocyte proliferation after PHx, indicating that activin and TGF-β can terminate hepatocyte proliferation in the regenerating liver [112].
The source, receptors and functions of growth factors and cytokines involved in liver regeneration are summarized in *table 1*.

CONCLUDING REMARKS

As presented in *figure 1*, in recent decades, the number of studies on liver regeneration has markedly increased, and the regulatory roles of growth factors and cytokines during this process have been explored. Future research should examine the roles of other growth factors and cytokines in liver regeneration and the molecular mechanisms of the signalling cascades downstream of growth factors and cytokine receptors. Ultimately, these studies could lead to the development of regenerative strategies and more reliable and non-invasive biomarkers to improve the management of liver regeneration.

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Conflict of interest: none.

Table 1.
Growth factors and cytokines involved in liver regeneration.

Biochemical factor	Source and receptor	Function
HGF	Mainly produced by HSCs. The receptor is c-Met [7].	Target pathways include STAT3, PI3K/AKT, mTOR and RAS/RAF pathways. A major hepatocyte mitogen [10, 113].
VEGF	Mainly produced by hepatocytes. Receptors are VEGFR 1, VEGFR 2 and VEGFR 3 [24].	Involved in vascular angiogenesis and recruiting bone marrow progenitors of LSECs [24, 27]
EGF	Mainly produced by Brunner's glands of the duodenum. Receptors are EGFR/ErbB1, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4 [35].	Promoting DNA synthesis and G1/S phase progression [44].
FGFs	Mainly produced by hepatocytes and activated HSCs. Receptors are FGFR 1, FGFR 2, FGFR 3 and FGFR 4 [47].	Target pathways include ERK1/2, STAT-3 and Fox-M1. Involved in vascular angiogenesis and the mitogenic effect of hepatocytes [47, 53].
IGFs	Liver is the major site of synthesis of IGF1 and IGF2. Receptors are IGF-1R and IGF-2R [59].	Target pathways include hepatocytes p38 mitogen-activated kinase and PI3K/AKT. Promote hepatocyte proliferation and differentiation [61].
IL-6	Mainly produced by Kupffer cells. The receptor is IL-6R [72].	Target pathways include the JAK-STAT and Ras-MAPK pathway. Pivotal role in liver regeneration [77].
TNF-α	Mainly produced by Kupffer cells. Receptors are TNFR 1 and TNFR 2 [91].	NFκB signalling pathway is the main target pathway. Promotes hepatocyte survival and proliferation [93, 94].
TGF-β	Mainly produced by Kupffer cells, platelets, endothelial cells and hepatocytes. Receptors are type I and type II TGF-β receptor [104, 105].	Spatiotemporal coordination of different stages of liver regeneration [104, 109].

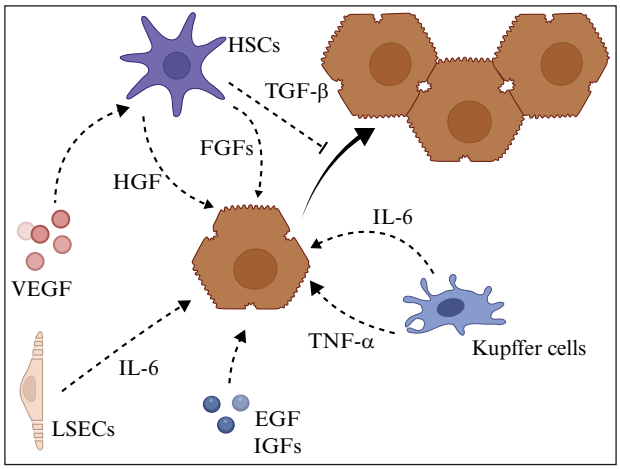

Figure 1
Overview of growth factors and cytokines involved in liver regeneration.

REFERENCES

1. Michalopoulos GK, DeFrances MC. Liver regeneration. *Science* 1997 ; 276 : 60-6.
2. Michalopoulos GK. Liver regeneration. *J Cell Physiol* 2007 ; 213 : 286-300.
3. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. *Am J Pathol* 2010 ; 176 : 2-13.
4. Kang LI, Mars WM, Michalopoulos GK. Signals and cells involved in regulating liver regeneration. *Cell* 2012 ; 1 : 1261-92.
5. Tao Y, Wang M, Chen E, Tang H. Liver regeneration: analysis of the main relevant signaling molecules. *Mediators Inflamm* 2017 ; 2017 : 4256352.
6. Hoffmann K, Nagel AJ, Tanabe K, *et al.* Markers of liver regeneration-the role of growth factors and cytokines: a systematic review. *BMC Surg* 2020 ; 20 : 31.
7. Kim KH, Kim H. Progress of antibody-based inhibitors of the HGF-cMET axis in cancer therapy. *Exp Mol Med* 2017 ; 49 : e307.
8. Kono S, Nagaike M, Matsumoto K, Nakamura T. Marked induction of hepatocyte growth factor mRNA in intact kidney and spleen in response to injury of distant organs. *Biochem Biophys Res Commun* 1992 ; 186 : 991-8.
9. Liu ML, Mars WM, Zarnegar R, Michalopoulos GK. Collagenase pretreatment and the mitogenic effects of hepatocyte growth factor and transforming growth factor-alpha in adult rat liver. *Hepatology* 1994 ; 19 : 1521-7.
10. Zhao Y, Ye W, Wang YD, Chen WD. HGF/c-Met: a key promoter in liver regeneration. *Front Pharmacol* 2022 ; 13 : 808855.
11. Cordero-Espinoza L, Huch M. The balancing act of the liver: tissue regeneration versus fibrosis. *J Clin Invest* 2018 ; 128 : 85-96.
12. Bell A, Chen Q, DeFrances MC, Michalopoulos GK, Zarnegar R. The five amino acid-deleted isoform of hepatocyte growth factor promotes carcinogenesis in transgenic mice. *Oncogene* 1999 ; 18 : 887-95.
13. Kaibori M, Inoue T, Oda M, *et al.* Exogenously administered HGF activator augments liver regeneration through the production of biologically active HGF. *Biochem Biophys Res Commun* 2002 ; 290 : 475-81.
14. Stolz DB, Mars WM, Petersen BE, Kim TH, Michalopoulos GK. Growth factor signal transduction immediately after two-thirds partial hepatectomy in the rat. *Cancer Res* 1999 ; 59 : 3954-60.
15. Borowiak M, Garratt AN, Wustefeld T, Strehle M, Trautwein C, Birchmeier C. Met provides essential signals for liver regeneration. *Proc Natl Acad Sci U S A* 2004 ; 101 : 10608-13.
16. Mohammed FF, Pennington CJ, Kassiri Z, *et al.* Metalloproteinase inhibitor TIMP-1 affects hepatocyte cell cycle via HGF activation in murine liver regeneration. *Hepatology* 2005 ; 41 : 857-67.

17. Schnitzbauer AA, Lang SA, Goessmann H, *et al.* Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012 ; 255 : 405-14.

18. Sparrelid E, Johansson H, Gilg S, Nowak G, Ellis E, Isaksson B. Serial assessment of growth factors associated with liver regeneration in patients operated with associating liver partition and portal vein ligation for staged hepatectomy. *Eur Surg Res* 2018 ; 59 : 72-82.

19. Efimova EA, Glanemann M, Nussler AK, *et al.* Changes in serum levels of growth factors in healthy individuals after living related liver donation. *Transplant Proc* 2005 ; 37 : 1074-5.

20. Sasturkar SV, David P, Sharma S, Sarin SK, Trehanpati N, Pamecha V. Serial changes of cytokines and growth factors in peripheral circulation after right lobe donor hepatectomy. *Liver Transpl* 2016 ; 22 : 344-51.

21. Takeuchi E, Nimura Y, Nagino M, *et al.* Human hepatocyte growth factor in bile: an indicator of posthepatectomy liver function in patients with biliary tract carcinoma. *Hepatology* 1997 ; 26 : 1092-9.

22. Appasamy R, Tanabe M, Murase N, *et al.* Hepatocyte growth factor, blood clearance, organ uptake, and biliary excretion in normal and partially hepatectomized rats. *Lab Invest* 1993 ; 68 : 270-6.

23. Lohela M, Bry M, Tammela T, Alitalo K. VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. *Curr Opin Cell Biol* 2009 ; 21 : 154-65.

24. Melincovici CS, Bosca AB, Susman S, *et al.* Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol* 2018 ; 59 : 455-67.

25. Karamysheva AF. Mechanisms of angiogenesis. *Biochemistry (Mosc)* 2008 ; 73 : 751-62.

26. Meyer J, Lejmi E, Fontana P, Morel P, Gonelle-Gispert C, Buhler L. A focus on the role of platelets in liver regeneration: do platelet-endothelial cell interactions initiate the regenerative process? *J Hepatol* 2015 ; 63 : 1263-71.

27. DeLeve LD, Wang X, Wang L. VEGF-sdf1 recruitment of CXCR7+ bone marrow progenitors of liver sinusoidal endothelial cells promotes rat liver regeneration. *Am J Physiol Gastrointest Liver Physiol* 2016 ; 310 : G739-46.

28. Bockhorn M, Goralski M, Prokofiev D, *et al.* VEGF is important for early liver regeneration after partial hepatectomy. *J Surg Res* 2007 ; 138 : 291-9.

29. LeCouter J, Moritz DR, Li B, *et al.* Angiogenesis-independent endothelial protection of liver: role of VEGFR-1. *Science* 2003 ; 299 : 890-3.

30. Redaelli CA, Semela D, Carrick FE, *et al.* Effect of vascular endothelial growth factor on functional recovery after hepatectomy in lean and obese mice. *J Hepatol* 2004 ; 40 : 305-12.

31. Van Buren G, 2nd, Yang AD, Dallas NA, *et al.* Effect of molecular therapeutics on liver regeneration in a murine model. *J Clin Oncol* 2008 ; 26 : 1836-42.

32. Kato T, Ito Y, Hosono K, *et al.* Vascular endothelial growth factor receptor-1 signaling promotes liver repair through restoration of liver microvasculature after acetaminophen hepatotoxicity. *Toxicol Sci* 2011 ; 120 : 218-29.

33. Alizai PH, Bertram L, Kroy D, *et al.* Expression of VEGFR-2 during liver regeneration after partial hepatectomy in a bioluminescence mouse model. *Eur Surg Res* 2017 ; 58 : 330-40.

34. Aryal B, Shimizu T, Kadono J, *et al.* A switch in the dynamics of intra-platelet VEGF-A from cancer to the later phase of liver regeneration after partial hepatectomy in humans. *PloS One* 2016 ; 11 : e0150446.

35. Burgess AW. EGFR family: structure physiology signalling and therapeutic targets. *Growth Factors* 2008 ; 26 : 263-74.

36. Skov Olsen P, Boesby S, Kirkegaard P, *et al.* Influence of epidermal growth factor on liver regeneration after partial hepatectomy in rats. *Hepatology* 1988 ; 8 : 992-6.

37. Pardo-Saganta A, Latasa MU, Castillo J, *et al.* The epidermal growth factor receptor ligand amphiregulin is a negative regulator of hepatic acute-phase gene expression. *J Hepatol* 2009 ; 51 : 1010-20.

38. Berasain C, Garcia-Trevijano ER, Castillo J, *et al.* Amphiregulin: an early trigger of liver regeneration in mice. *Gastroenterology* 2005 ; 128 : 424-32.

39. Michalopoulos GK. Principles of liver regeneration and growth homeostasis. *Compr Physiol* 2013 ; 3 : 485-513.

40. Russell WE, Kaufmann WK, Sitaric S, Luetteke NC, Lee DC. Liver regeneration and hepatocarcinogenesis in transforming growth factor-alpha-targeted mice. *Mol Carcinog* 1996 ; 15 : 183-9.

41. Mitchell C, Nivison M, Jackson LF, *et al.* Heparin-binding epidermal growth factor-like growth factor links hepatocyte priming with cell cycle progression during liver regeneration. *J Biol Chem* 2005 ; 280 : 2562-8.

42. Kiso S, Kawata S, Tamura S, *et al.* Liver regeneration in heparin-binding EGF-like growth factor transgenic mice after partial hepatectomy. *Gastroenterology* 2003 ; 124 : 701-7.

43. Yamada A, Kawata S, Tamura S, *et al.* Plasma heparin-binding EGF-like growth factor levels in patients after partial hepatectomy as determined with an enzyme-linked immunosorbent assay. *Biochem Biophys Res Commun* 1998 ; 246 : 783-7.

44. Paranjpe S, Bowen WC, Tseng GC, Luo JH, Orr A, Michalopoulos GK. RNA interference against hepatic epidermal growth factor receptor has suppressive effects on liver regeneration in rats. *Am J Pathol* 2010 ; 176 : 2669-81.

45. Natarajan A, Wagner B, Sibilia M. The EGF receptor is required for efficient liver regeneration. *Proc Natl Acad Sci U S A* 2007 ; 104 : 17081-6.

46. Ornitz DM, Itoh N. Fibroblast growth factors. *Genome Biol.* 2001 ; 2 : REVIEWS3005.

47. Gilgenkrantz H, Tordjmann T. Bile acids and FGF receptors: orchestrators of optimal liver regeneration. *Gut* 2015 ; 64 : 1351-2.

48. Steiling H, Wustefeld T, Bugnon P, *et al.* Fibroblast growth factor receptor signalling is crucial for liver homeostasis and regeneration. *Oncogene* 2003 ; 22 : 4380-8.

49. Bohm F, Kohler UA, Speicher T, Werner S. Regulation of liver regeneration by growth factors and cytokines. *EMBO Mol Med* 2010 ; 2 : 294-305.

50. Kan NG, Junghans D, Izpisua Belmonte JC. Compensatory growth mechanisms regulated by BMP and FGF signaling mediate liver regeneration in zebrafish after partial hepatectomy. *FASEB J* 2009 ; 23 : 3516-25.

51. Bohm F, Speicher T, Hellerbrand C, *et al.* FGF receptors 1 and 2 control chemically induced injury and compound detoxification in regenerating livers of mice. *Gastroenterology* 2010 ; 139 : 1385-96.

52. Tsai SM, Wang WP. Expression and function of fibroblast growth factor (FGF) 7 during liver regeneration. *Cell Physiol Biochem* 2011 ; 27 : 641-52.

53. Shan Z, Alvarez-Sola G, Uriarte I, *et al.* Fibroblast growth factors 19 and 21 in acute liver damage. *Ann Transl Med* 2018 ; 6 : 257.

54. Alvarez-Sola G, Uriarte I, Latasa MU, *et al.* Fibroblast growth factor 15/19 (FGF15/19) protects from diet-induced hepatic steatosis: development of an FGF19-based chimeric molecule to promote fatty liver regeneration. *Gut* 2017 ; 66 : 1818-28.

55. Uriarte I, Fernandez-Barrena MG, Monte MJ, *et al.* Identification of fibroblast growth factor 15 as a novel mediator of liver regeneration and its application in the prevention of post-resection liver failure in mice. *Gut* 2013 ; 62 : 899-910.

56. Yokoyama Y, Nagino M, Nimura Y. Mechanism of impaired hepatic regeneration in cholestatic liver. *J Hepatobiliary Pancreat Surg* 2007 ; 14 : 159-66.

57. Padrissa-Altes S, Bachofner M, Bogorad RL, *et al.* Control of hepatocyte proliferation and survival by Fgf receptors is essential for liver regeneration in mice. *Gut* 2015 ; 64 : 1444-53.

58. Asakawa K, Hizuka N, Takano K, *et al.* Human growth hormone stimulates liver regeneration in rats. *J Endocrinol Invest* 1989 ; 12 : 343-7.

59. Kurihara K, Moteki H, Natsume H, Ogihara M, Kimura M. The enhancing effects of S-allylcysteine on liver regeneration are associated with increased expression of mrnas encoding IGF-1 and its receptor in two-thirds partially hepatectomized rats. *Biol Pharm Bull* 2020 ; 43 : 1776-84.

60. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008 ; 8 : 915-28.

61. Valizadeh A, Majidinia M, Samadi-Kafil H, Yousefi M, Yousefi B. The roles of signaling pathways in liver repair and regeneration. *J Cell Physiol* 2019 ; 234 : 14966-74.

62. Caro JF, Poulos J, Ittoop O, Pories WJ, Flickinger EG, Sinha MK. Insulin-like growth factor I binding in hepatocytes from human liver, human hepatoma, and normal, regenerating, and fetal rat liver. *J Clin Invest* 1988 ; 81 : 976-81.

63. Beyer TA, Xu W, Teupser D, *et al.* Impaired liver regeneration in Nrf2 knockout mice: role of ROS-mediated insulin/IGF-1 resistance. *EMBO J* 2008 ; 27 : 212-23.

64. Desbois-Mouthon C, Wendum D, Cadoret A, *et al.* Hepatocyte proliferation during liver regeneration is impaired in mice with liver-specific IGF-1R knockout. *FASEB J* 2006 ; 20 : 773-5.

65. Puche JE, Castilla-Cortazar I. Human conditions of insulin-like growth factor-I (IGF-I) deficiency. *J Transl Med* 2012 ; 10 : 224.

66. Liu J, Hu X, Chen J, *et al.* Pericentral hepatocytes produce insulin-like growth factor-2 to promote liver regeneration during selected injuries in mice. *Hepatology* 2017 ; 66 : 2002-15.

67. Stefano JT, Correa-Giannella ML, Ribeiro CM, *et al.* Increased hepatic expression of insulin-like growth factor-I receptor in chronic hepatitis C. *World J Gastroenterol* 2006 ; 12 : 3821-8.

68. Gong Y, Cui L, Minuk GY. The expression of insulin-like growth factor binding proteins in human hepatocellular carcinoma. *Mol Cell Biochem* 2000 ; 207 : 101-4.

69. Ross RJ, Chew SL, D'Souza Li L, *et al.* Expression of IGF-I and IGF-binding protein genes in cirrhotic liver. *J Endocrinol* 1996 ; 149 : 209-16.

70. Leu JI, Crissey MA, Craig LE, Taub R. Impaired hepatocyte DNA synthetic response posthepatectomy in insulin-like growth factor binding protein 1-deficient mice with defects in C/EBP beta and mitogen-activated protein kinase/extracellular signal-regulated kinase regulation. *Mol Cell Biol* 2003 ; 23 : 1251-9.

71. Schmidt-Arras D, Rose-John S. IL-6 pathway in the liver: from physiopathology to therapy. *J Hepatol* 2016 ; 64 : 1403-15.

72. Boulanger MJ, Chow DC, Brevnova EE, Garcia KC. Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science* 2003 ; 300 : 2101-4.

73. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim Biophys Acta* 2011 ; 1813 : 878-88.

74. Shimada M, Matsumata T, Taketomi A, *et al.* The role of interleukin-6, interleukin-16, tumor necrosis factor-alpha and endotoxin in hepatic resection. *Hepatogastroenterology* 1995 ; 42 : 691-7.

75. Hayashi H, Nagaki M, Imose M, *et al.* Normal liver regeneration and liver cell apoptosis after partial hepatectomy in tumor necrosis factor-alpha-deficient mice. *Liver Int* 2005 ; 25 : 162-70.

76. Mao SA, Glorioso JM, Nyberg SL. Liver regeneration. *Transl Res* 2014 ; 163 : 352-62.

77. Kishimoto T. IL-6: from its discovery to clinical applications. *Int Immunol* 2010 ; 22 : 347-52.

78. Cressman DE, Greenbaum LE, DeAngelis RA, *et al.* Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. *Science* 1996 ; 274 : 1379-83.

79. Gao B, Wang H, Lafdil F, Feng D. STAT proteins - key regulators of anti-viral responses, inflammation, and tumorigenesis in the liver. *J Hepatol* 2012 ; 57 : 430-41.

80. Galun E, Axelrod JH. The role of cytokines in liver failure and regeneration: potential new molecular therapies. *Biochim Biophys Acta* 2002 ; 1592 : 345-58.

81. Blindenbacher A, Wang X, Langer I, Savino R, Terracciano L, Heim MH. Interleukin 6 is important for survival after partial hepatectomy in mice. *Hepatology* 2003 ; 38 : 674-82.

82. Gotohda N, Iwagaki H, Ozaki M, *et al.* Deficient response of IL-6 impaired liver regeneration after hepatectomy in patients with viral hepatitis. *Hepatogastroenterology* 2008 ; 55 : 1439-44.

83. de Jong KP, van Gameren MM, Bijzet J, *et al.* Recombinant human interleukin-6 induces hepatocyte growth factor production in cancer patients. *Scand J Gastroenterol* 2001 ; 36 : 636-40.

84. Chae MS, Moon KU, Chung HS, *et al.* Serum interleukin-6 and tumor necrosis factor-alpha are associated with early graft regeneration after living donor liver transplantation. *PloS One* 2018 ; 13 : e0195262.

85. Oyama T, Sadamori H, Matsukawa H, *et al.* Small liver graft regenerates through immediate increase of HGF and IL-6--possible involvement of sinusoidal tensile/shear stress in small liver graft. *Hepatogastroenterology* 2007 ; 54 : 2078-83.

86. Jin X, Zhang Z, Beer-Stolz D, Zimmers TA, Koniaris LG. Interleukin-6 inhibits oxidative injury and necrosis after extreme liver resection. *Hepatology* 2007 ; 46 : 802-12.

87. Ren X, Hogaboam C, Carpenter A, Colletti L. Stem cell factor restores hepatocyte proliferation in IL-6 knockout mice following 70% hepatectomy. *J Clin Invest* 2003 ; 112 : 1407-18.

88. Nakamura K, Nonaka H, Saito H, Tanaka M, Miyajima A. Hepatocyte proliferation and tissue remodeling is impaired after liver injury in oncostatin M receptor knockout mice. *Hepatology* 2004 ; 39 : 635-44.

89. Moh A, Iwamoto Y, Chai GX, *et al.* Role of STAT3 in liver regeneration: survival, DNA synthesis, inflammatory reaction and liver mass recovery. *Lab Invest* 2007 ; 87 : 1018-28.

90. Riehle KJ, Campbell JS, McMahan RS, *et al.* Regulation of liver regeneration and hepatocarcinogenesis by suppressor of cytokine signaling 3. *J Exp Med* 2008 ; 205 : 91-103.

91. Tiegs G, Horst AK. TNF in the liver: targeting a central player in inflammation. *Semin Immunopathol* 2022 ; 44 : 445-59.

92. Webber EM, Bruix J, Pierce RH, Fausto N. Tumor necrosis factor primes hepatocytes for DNA replication in the rat. *Hepatology* 1998 ; 28 : 1226-34.

93. Liu T, Zhang L, Joo D, Sun SC. NF-kappaB signaling in inflammation. *Signal Transduct Target Ther* 2017 ; 2 : 17023.

94. Yang L, Magness ST, Bataller R, Rippe RA, Brenner DA. NF-kappaB activation in Kupffer cells after partial hepatectomy. *Am J Physiol Gastrointest Liver Physiol* 2005 ; 289 : G530-8.

95. Schwabe RF, Brenner DA. Mechanisms of Liver Injury. I. TNF-alpha-induced liver injury: role of IKK, JNK, and ROS pathways. *Am J Physiol Gastrointest Liver Physiol* 2006 ; 290 : G583-9.

96. Seki E, Tsutsui H, Iimuro Y, *et al.* Contribution of Toll-like receptor/myeloid differentiation factor 88 signaling to murine liver regeneration. *Hepatology* 2005 ; 41 : 443-50.

97. Campbell JS, Riehle KJ, Brooling JT, Bauer RL, Mitchell C, Fausto N. Proinflammatory cytokine production in liver regeneration is Myd88-dependent, but independent of Cd14, Tlr2, and Tlr4. *J Immunol* 2006 ; 176 : 2522-8.

98. Strey CW, Markiewski M, Mastellos D, *et al.* The proinflammatory mediators C3a and C5a are essential for liver regeneration. *J Exp Med* 2003 ; 198 : 913-23.

99. Selzner N, Selzner M, Odermatt B, Tian Y, Van Rooijen N, Clavien PA. ICAM-1 triggers liver regeneration through leukocyte recruitment and Kupffer cell-dependent release of TNF-alpha/IL-6 in mice. *Gastroenterology* 2003 ; 124 : 692-700.

100. Akerman P, Cote P, Yang SQ, *et al.* Antibodies to tumor necrosis factor-alpha inhibit liver regeneration after partial hepatectomy. *Am J Physiol* 1992 ; 263 : G579-85.

101. Yamada Y, Kirillova I, Peschon JJ, Fausto N. Initiation of liver growth by tumor necrosis factor: deficient liver regeneration in mice lacking type I tumor necrosis factor receptor. *Proc Natl Acad Sci U S A* 1997 ; 94 : 1441-6.

102. Yamada Y, Webber EM, Kirillova I, Peschon JJ, Fausto N. Analysis of liver regeneration in mice lacking type 1 or type 2 tumor necrosis factor receptor: requirement for type 1 but not type 2 receptor. *Hepatology* 1998 ; 28 : 959-70.

103. Mohammed FF, Smookler DS, Taylor SE, *et al.* Abnormal TNF activity in Timp3-/- mice leads to chronic hepatic inflammation and failure of liver regeneration. *Nat Genet* 2004 ; 36 : 969-77.

104. Gough NR, Xiang X, Mishra L. TGF-beta signaling in liver, pancreas, and gastrointestinal diseases and cancer. *Gastroenterology* 2021 ; 161 : 434-52 e15.

105. Fabregat I, Moreno-Caceres J, Sanchez A, *et al.* TGF-beta signalling and liver disease. *FEBS J* 2016 ; 283 : 2219-32.

106. Houck KA, Michalopoulos GK. Altered responses of regenerating hepatocytes to norepinephrine and transforming growth factor type beta. *J Cell Physiol* 1989 ; 141 : 503-9.

107. Moustakas A, Heldin CH. The regulation of TGFbeta signal transduction. *Development* 2009 ; 136 : 3699-714.

108. Macias-Silva M, Li W, Leu JI, Crissey MA, Taub R. Up-regulated transcriptional repressors SnoN and Ski bind Smad proteins to antagonize transforming growth factor-beta signals during liver regeneration. *J Biol Chem* 2002 ; 277 : 28483-90.

109. Masuda A, Nakamura T, Abe M, *et al.* Promotion of liver regeneration and anti-fibrotic effects of the TGF-beta receptor kinase inhibitor galunisertib in CCl4-treated mice. *Int J Mol Med* 2020 ; 46 : 427-38.

110. Russell WE, Coffey RJ, Jr., Ouellette AJ, Moses HL. Type beta transforming growth factor reversibly inhibits the early proliferative response to partial hepatectomy in the rat. *Proc Natl Acad Sci U S A* 1988 ; 85 : 5126-30.

111. Romero-Gallo J, Sozmen EG, Chytil A, *et al.* Inactivation of TGF-beta signaling in hepatocytes results in an increased proliferative response after partial hepatectomy. *Oncogene* 2005 ; 24 : 3028-41.

112. Oe S, Lemmer ER, Conner EA, *et al.* Intact signaling by transforming growth factor beta is not required for termination of liver regeneration in mice. *Hepatology* 2004 ; 40 : 1098-105.

113. Huh CG, Factor VM, Sanchez A, Uchida K, Conner EA, Thorgeirsson SS. Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. *Proc Natl Acad Sci U S A* 2004 ; 101 : 4477-82.