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Prometheus' Challenge: Molecular, Cellular and Systemic Aspects of Liver Regeneration

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The fascinating aspect of the liver is the capacity to regenerate after injury or resection. A variety of genes, cytokines, growth factors, and cells are involved in liver regeneration. The exact mechanism of regeneration and the interaction between cells and cytokines are not fully understood. There seems to exist a sequence of stages that result in liver regeneration, while at the same time inhibitors control the size of the regenerated liver. It has been proven that hepatocyte growth factor, transforming growth factor, epidermal growth factor, tumor necrosis factor-alpha, interleukins -1 and -6 are the main growth and promoter factors secreted after hepatic injury, partial hepatectomy and after a sequence of different and complex reactions to activate transcription factors, mainly nuclear factor kappaB and signal transduction and activator of transcription-3, affects specific genes to promote liver regeneration. Unraveling the complex processes of liver regeneration may provide novel strategies in the management of patients with end-stage liver disease. In particular, inducing liver regeneration should reduce morbidity for the donor and increase faster recovery for the liver transplantation recipient.

Key Words: **liver regeneration; transplantation; cytokines; growth factors; hyperplasia; hypertrophy.**

Many types of liver diseases, including hepatitis and cirrhosis, are associated with some degree of liver regeneration. Partially this is compensatory as the liver attempts to restore its mass lost as a consequence of pathologic processes. Nevertheless, the disease itself may be associated by elevations of transcription factors and cytokines that induce proliferation of hepatocytes and non-parenchymal cells. These pathophysiologic responses of the liver may aggravate the pathologic process resulting in augmented fibrogenesis in cirrhosis and the accumulation of mutations in progenitor cells and proliferating hepatocytes, finally leading to the development of hepatocellular carcinoma (HCC) [1].

The incidence of HCC, cirrhosis and other end-stage liver diseases (ESLD) is increasing worldwide [2]. Moreover, cerebral edema, sepsis, and multiple organ failure are the complications of patients with ESLD or acute liver failure. Orthotopic liver transplantation (OLT) is the treatment of choice for helping those patients who are unlikely to recover spontaneously to regain quickly and effectively. Unfortunately, the shortage of cadaver liver grafts is increasing, thereby OLT is not always possible [3, 4]. To solve this problem, living donor liver transplantation (LDLT) is one of the strategies currently used to increase the donor pool [5]. The restoration of the liver tissue in both donor and recipient is based on the innate characteristic and capacity of liver to regenerate. LDLT affects both donor and recipient. Inducing liver regeneration should reduce morbidity for the donor and increase faster recovery for the recipient. Various molecular and cellular pathways are involved in this process, and novel strategies to induce liver regeneration in both the donor and the recipient have been developed.

Regeneration of Liver

The liver has unusual regeneration properties after partial hepatectomy or toxic injury. Partial hepatec-

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tomy, representing the model that most clearly demonstrates the regenerative capacity of the liver, was first described by Higgins and Anderson in 1931 [6]. It has been observed that after a partial hepatectomy in which two-thirds of a rodent liver, including the medial and left lateral lobes, are removed intact, the remnant liver enlarges until the liver mass is restored whereupon the process stops. The term regeneration is not biologically correct because the removed lobes or segments do not grow back. Instead, restoration of liver mass occurs by the compensatory hyperplasia of the cells in the remaining lobes. This suggests that hepatic growth induced by tissue loss is governed by functional rather than anatomical factors. Whatever the nature of these functional controls, they appear to be precise, because growth ceases when the liver regains its original weight. In addition, growth does not become unregulated or autonomous after repeat partial hepatectomies. Therefore, liver "knows" when to start and when to stop growing, although it is still difficult to understand precisely how all these regulatory mechanisms are coordinated in this regulatory process of the liver [7].

Rapid changes in gene expression and activation of receptors and transcription factors occur immediately after partial hepatectomy. Several potential signaling stimuli are released in the liver or in the circulation after the loss of hepatic parenchyma [8]. Liver is composed of different cells including hepatocytes that account about 60% of hepatic cells, endothelial cells, Kupffer cells and "Oval" cells (a population of periportal cuboidal cells with ovoid nuclei believed to represent liver stem cells). Liver regeneration following partial hepatectomy (70% resection) usually does not involve the activation of liver precursor ("stem") cells [7]. Instead, liver mass is replenished by the proliferation of adult hepatocytes (mainly tetraploid cells) [9]. However, liver epithelial cells with the capacity to differentiate into hepatocytes or biliary ductal cells have been recently identified in the bile ductules (canals of Herring) of livers of adult humans and animals. These cells, at least for a period of time during development, express markers of both hepatocytes and biliary cells. Ductular cells appear to form a reserve compartment capable of generating mature hepatocytes and bile duct cells after massive necrosis, toxic injury, and carcinogenesis or in any condition in which hepatocyte proliferation is impaired or slowed by the injury [9]. In all these cases there is proliferation of an "oval cell compartment" constituting of cells with different precursor capabilities at different stages of maturation originating from ductular cells. The oval cells are heterogeneous. Nevertheless, the proliferation of such cells is readily apparent in partially hepatectomized rats given acetylaminoazobenzene [9]. In humans, oval cells participate in the repopulation of the liver after acute massive necrosis [7]. It is believed that even after resection of an entire lobe of liver, the organ will subsequently repair itself over a period of months to completely recover its previous structure. The regeneration is evaluated by a mixture of different variables including liver size, function and histology [10].

AT FUNCTIONAL LEVEL

A functional regenerated liver should perform the duties of a normal liver including major roles in maintaining normal blood sugar levels, manufacturing proteins including albumin and clotting factors, maintaining several biochemical pathways that permit detoxification or breakdown of accumulated toxins and manufacturing bile. If the regenerated liver does all these works properly in an otherwise healthy individual, it is called a functional regenerated liver. It has been proven that some factors affect the regeneration processes and the duration needed for the liver to become functional. These factors include the extent of resection, underlying liver parenchymal disease and to some extent, age and portal pressure [11–13].

In animal model, DNA synthesis starts 12 to 16 h after the standard partial hepatectomy (68–70% resection) and peaks 24 to 48 h. The onset of mitosis follows 6 to 8 h later reaching its maximum 48 h after surgery. Three days after partial liver resection, the original organ mass is almost restored. However, at this stage of liver regeneration, hepatic histology differs substantially from normal. Hepatocytes are grouped into nonvascularized clusters of 12 to 15 cells, and the amount of extracellular matrix (ECM) is clearly reduced as a consequence of hepatocyte proliferation without concomitant ECM synthesis. After this time point, hepatocyte proliferation decreases and stellate cells migrate into the clusters. At the same time, new vascular branches are formed. Finally, normal liver histology and function is re-established 8 to 10 days after surgery [7].

In general, considering size and histopathology in the liver under regeneration, liver functions are restored within 2 to 3 weeks in patients with normal livers. However, hyperbilirubinemia persists longer in patients with chronic hepatitis and cirrhosis [14]. In the first month, normal livers usually regenerate at least twice as rapidly as livers with underlying diseases with the same resection rates. Normal livers reach plateau levels within 1 to 2 months regardless of the massiveness of resection but regeneration takes 3 to 5 months in livers with underlying diseases [15].

AT CELLULAR LEVEL

As already mentioned, liver is composed of hepatocytes, Kupffer cells, epithelial cells, stellate (Ito) cells, and stem cells but its regeneration basically involves

the activation of adult hepatocytes and possibly stem cells [7]. These latter types of cells belong to the family of adult tissue stem cells that have been discovered in various human tissues such as bone marrow, muscle, neural tissue, skin, or fat. Stem cells usually distinguish themselves from other cells through being not necessarily terminally differentiated, owning the capability to continuously proliferate and self-renew and, engendering differentiated progeny of a committed phenotype (potency) [16]. They exhibit either symmetric or asymmetric mitotic activity which is necessary to generate such progeny and for self-maintenance. During development, embryonic and fetal stem cells serve the purpose of generating the more than 200 different cell types of the human body. The occurrence of stem cells in adult tissues, however, probably supports the delivery of differentiated cells during times of tissue repair or regeneration. This is also thought to be the case in the liver and there is a good evidence for the existence of such stem cells even though their exact type, location and potency are still under discussion [17]. Regarding the type of stem cells, liver seems to be an important source for hematopoietic stem cells during fetal development [18] and hematopoietic stem cells persist in the adult liver [19]. Data on the ontologic potential of population of stem cells have established that highly purified hematopoietic cells have the capacity to differentiate into hepatocytes and repopulate the liver after intravenous transplantation [20]. Two competing paradigms are emerging: 1) that pluripotent progenitor cells with multi-lineage differentiation potential are present in several, if not all, tissues; and 2) that tissue-specific pluripotent progenitor cells maintain the capacity for transdifferentiation when placed in the appropriate environment. The identification of a common source for both hepatic and hematopoietic progenitor cells is blurring the distinction between solid organ and blood progenitor cell transplantation and raises the probability of treating hepatic diseases by transplantation with hematopoietic progenitor cells [21]. As many other stem cells, liver stem cells are thought to persist in a microenvironmental niche within surrounding other cells, ECM and secreted factors that provides them with developmental stimuli and maintenance cues for their division, proliferation or differentiation. Such an environment is thought to lie in the canals of Hering (oval cells) [22, 23] and possibly in the periportal ductular zone [24, 25]. In their niche, the oval cells, [26] named after their ovally shaped nucleus, appear to act as bipotential precursors with lineage commitments for biliary cholangiocytes (bile duct epithelium) and hepatocytes. They may contribute to liver regeneration when injury is severe with vast impairment of hepatocyte proliferation as seen for example in cirrhosis or submassive necrosis because of toxins, viruses, or drugs [27, 28]. Hepatocytes are regarded as being unipotent committed stem cells that are normally quiescent and can be induced to generate themselves again [29]. The lack of their response to growth signals also results in activation and rapid proliferation of oval cells. These initially appear near bile ductules, followed by migration into the hepatic parenchyma [27]. Cellular liver tissue regeneration is assumed to be accomplished in a sequence of phases including 1) initiation phase with replicating competence; 2) proliferation phase where expansion of cell population occurs; 3) termination phase where cell growth is suppressed to terminate regeneration at a set point [30]. In addition, a few days after hepatectomy, stellate cells start sending delicate processes between regenerating hepatocytes to make sinusoids and vascular parts of the regenerating organ [31]. Fascinatingly, it has also been suggested that hepatocytes could be derived from transdifferentiating non-hepatic sources. As mentioned before, hematopoiesis and liver development share some common stages and the liver itself contributes to fetal hematopoiesis, [32], thus observations of a hepatic lineage development in stem cells derived from bone-marrow appear quite plausible [29, 33–36]. Alternatively, there is also new evidence that a cell population from the adult liver exhibits a potential for hematopoietic reconstitution [37]. In contrast to *intrahepatic* oval cells that are activated upon heavy and chronic liver damage, these *extrahepatic* cells can migrate from the bone marrow into the liver by the time its own capacity for regeneration is exhausted. It has, however, presently not yet been clarified if and how these stem cell populations interact with one another and the resident liver cells to provide for the appropriate growth environment in cases of necessary regeneration. Most interesting for potential therapeutic applications, hepatic lineages have also been generated from umbilical cord stem cells, [38, 39] adipose stromal cells, [40] or embryonic stem cells [41, 42].

Regeneration of liver is a mixture of hyperplasia and hypertrophy of hepatocytes. Regeneration response is maximal when two-thirds of the liver is resected. More or less than this amount retards growth by suppressing DNA synthesis and mitotic activity. Hypertrophy of hepatocytes begins within hours after hepatectomy, and then with increasing DNA synthesis hyperplasia follows. This sequence begins in the periportal region and spreads toward the pericentral region of the lobule [43–45]. Some studies based on the histological evaluation during liver regeneration have shown that liver regeneration originates from hepatocytes located in zone 2, extends to zone 1 and occasionally to zone 3 and, furthermore, there is a significant increase of sinusoidal endothelial cell pores in zones 1 and 3 within 5 min after hepatectomy that is only maintained in zone 1 after 24 h [46, 47].

TABLE 1

Promoters and inhibitors affecting liver regeneration

Steps of liver regeneration	Factors	Target
Initiation	TNF-α	TNFR $\rightarrow$ $\uparrow$ STAT3 & NF-κB $\rightarrow$ $\uparrow$ activation of genes $\rightarrow$ $\uparrow$ susceptibility of hepatocytes to growth factors
	IL-6	$\uparrow$ STAT3 synthesis and $\uparrow$ susceptibility of hepatocytes to HGF
	LT-β	$\uparrow$ NF-κB only in oval cells $\rightarrow$ $\uparrow$ susceptibility of oval cells to growth factors
	NO	$\uparrow$ S-nitrosylating procaspase $\rightarrow$ $\downarrow$ TNF-α apoptotic activity through caspase-3
	IFN-γ	Affects through TNF-α and LPS
Proliferation	HGF	Met R $\rightarrow$ $\uparrow$ DNA and protein synthesis $\rightarrow$ mitosis
	TGF-α	EGFR $\rightarrow$ $\uparrow$ DNA and protein synthesis $\rightarrow$ mitosis
	EGF	EGFR $\rightarrow$ $\uparrow$ DNA and protein synthesis $\rightarrow$ mitosis
	HSS	Autophosphorylation and restoring of EGFR
	NE	$\uparrow$ exposure of hepatocytes to growth factors
	Insulin	$\uparrow$ exposure of hepatocytes to growth factors
	SOM	$\uparrow$ exposure of hepatocytes to growth factors
	Glucagon	$\uparrow$ exposure of hepatocytes to growth factors
Inhibition	TGF-β	Counteracting TGF-α $\rightarrow$ $\downarrow$ DNA synthesis

TNF-α, tumor necrosis alpha; IL, interleukin; LT-β, lymphotoxin-beta; NO, nitric oxide; IFN-γ, interferon gamma; HGF, hepatocyte growth factor; TGF, transforming growth factor; EGF, epidermal growth factor; HSS, hepatic stimulator substance; NE, norepinephrine; SOM, somatostatin; TNFR, tumor necrosis factor receptor; STAT3, signal transduction and activation of transcription-3; NF-κB, nuclear factor kappaB; LPS, lipopolysaccharide; EGFR, epidermal growth factor receptor.

AT MOLECULAR LEVEL

Promoters of Regeneration

The following proposed model of cytokine and growth factor activation of transcriptional cascade and DNA synthesis occurs during liver regeneration: After partial hepatectomy, either *de novo*-released cytokines or gut-derived cytokines activate hepatic non-parenchymal cells, leading to increased production of tumor necrosis factor (TNF)-α, lymphotoxin (LT)-β, and interleukins (IL) -1 and -6. Other growth factors are also released from other cells in the liver and surrounding organs. These cytokines and growth agents are responsible for activation of nuclear factor kappaB (NF-κB), signal transduction and activation of transcription (STAT)3, possibly caat enhancer binding protein (C/ERB)-β, and other factors in remnant liver cells. As a consequence of the activation of these hepatocyte transcription agents, the primary growth response program (immediate-early genes, AP-1, c-Myc activation, glucose regulation) is initiated, finally resulting in DNA synthesis [1, 7].

More specifically, liver regeneration includes three steps: 1) initiation step, 2) proliferation step, discussed together as promoters of regeneration, and 3) termination step, discussed as the inhibitors of regeneration in the next section.

The initiation step is characterized by priming of quiescent hepatocytes by factors such as TNF-α, IL-6, and nitric oxide (NO). This results in induction of hepatocytes to become sensitive to growth factors and competent for replication. The proliferation step is the step that hepatocytes enter into the cell cycle's G1-phase and are stimulated by complete mitogens including hepatocyte growth factor (HGF), transforming growth factor (TGF)-α, and epidermal growth factor (EGF). These hepatomitogens together with co-mitogenes like norepinephrine and potentiating factors like insulin induce hepatocytes to override the mitogen restriction point at two-thirds of the G1 phase and progress into DNA synthesis. These factors induce cyclins and cyclin-dependent kinases that play critical roles in cell cycle progression [9, 48, 49].

Numerous growth factors including HGF, TGF-α, EGF, hepatic stimulator substance (HSS), glucagon, insulin, and more recently cytokines, TNF, IL-1, and IL-6, or somatostatin (SOM) have been implicated in regulating regeneration process, although the mechanisms involved remain poorly understood (Table 1).

Oval cells express receptors for all these growth factors, providing a molecular pathway by which stellate cells may influence the growth and development of oval cells [27]. The growth factors continue to be expressed at high levels throughout the period of expansion and differentiation of the oval cell population [27].

HGF is a peptide secreted from hepatocytes after partial hepatectomy and binds to tyrosine kinase receptor c-met with high affinity. Because of its high mitogen potency for hepatocytes, a chain of intracellular reactions causing cell proliferation and differentiation is initiated, leading to acceleration of liver function and protection of liver cells from injury [51, 52]. HGF regulates a diversity of processes in the liver in addition to being a direct stimulant of hepatocyte proliferation. HGF is an effective inducer of DNA synthesis in hepatocyte in culture but, moreover, it alters the

morphology and motility of cells. *In vivo* HGF is synthesized in non-parenchymal cells and acts on hepatocytes in a paracrine fashion. It has been suggested that HGF is activated by proteases after hepatectomy [1]. Some studies have demonstrated that HGF cell-surface receptors internalization enhances 15 min after partial hepatectomy to be attached to intracellularly made HGF and maybe that's the *initial factor* that starts regeneration. The processes are still under investigation [53]. HGF has also been shown as being able to induce differentiation of bone marrow cells into a hepatic lineage [27]. TGF-α is another peptide that is secreted by hepatocytes during hepatic injury and increases HGF regeneration effect after partial hepatectomy [54]. TGF-α belongs to a family of structurally related polypeptide growth factors, of which EGF was the first member to be isolated and characterized. TGF-α and EGF signal through a common cell surface receptor tyrosine kinase, called the EGF receptor. Based on experiments on TGF-α expression during liver regeneration after partial hepatectomy, it has been proposed that TGF-α acts in an autocrine fashion as a direct stimulator of DNA synthesis of hepatocytes during liver regeneration [55]. SOM non-specifically acts on injured tissues to stimulate rapid growth and in case of liver injury stimulates regeneration [56].

IL-6 is a cytokine expressed by a variety of cells, influencing liver growth both indirectly by priming hepatocytes to respond to growth factors mainly HGF by inducing expression of HGF and inhibiting hepatocyte apoptosis, and directly as a hepatic mitogen inducing regeneration [57]. Therefore, IL-6 is required for liver regeneration and repair, and transcriptionally up-regulates an array of genes during liver growth. In this regard, IL-6 and TNF-α are among the most important mediators for early signaling pathways in liver regeneration. IL-6 is the main mediator in promoting regeneration after combined ischemia and hepatic resection. IL-6 acts directly on hepatocytes inducing STAT3 to the nucleus and extracellular regulated kinase activity causing early gene activation and mitosis. STAT3 suppresses hepatic apoptosis through inhibition of caspase-3 and -8 activities. In addition, IL-6 is implicated in hepatocytes survival through inhibition of TGF-β–mediated Fas activation [58, 59, 60]. In this regard, the direct anti-apoptotic effects of IL-6 are demonstrated *in vitro* as IL-2 decreases Fas-mediated apoptosis in both IL-6$-/-$ and $+/+$ primary liver cell cultures.

TNF-α is a proinflammatory cytokine influencing liver regeneration and apoptosis following partial hepatectomy. It triggers either cell proliferation or cell death depending on effector pathways. TNF-α has two different receptors TNFR-1 and -2. TNFR-1 is the only one necessary for liver regeneration, and after stimulation activates NF-κB and STAT3. TNF-α also acts as a cell death mediator in a variety of cells types by attaching to TNFR-1 and -2. Inhibition of NF-κB activation increases susceptibility to TNF-α-induced cell death, concurrently with sustained Jun N-terminal kinase activation, an important contributor to cell death responses [61–64]. After partial hepatectomy, TNF-α also signals on TNFR-1 to activate NF-κB that translocates into the nucleus to induce IL-6 expression, and subsequently IL-6 activates STAT3 [65]. After the release of IL-6 and TNF-α and activation of STAT3 and NF-κB, NO is also generated following nitric oxide synthase (NOS)-2, which prevents TNF-α–mediated activation of proapoptotic caspase-3 and protects hepatocytes from cytokine-mediated death by S-nitrosylating procaspases [66].

Lymphotoxin (LT)-β is a cytokine that is expressed by activated lymphocytes and through a receptor-mediated process by activating NF-κB regulates gene expression only in oval cell-mediated but not hepatocyte-mediated liver regeneration, and its absence impairs the oval cell-mediated regenerative response. IL-6 and IL-1β regulate the expression of LT-β through *cis*-acting promoter elements [67, 68]. Interferon-γ is another cytokine combining lipopolysaccharide (LPS) or TNF and regulating liver regeneration by inhibiting hepatocyte replication and enhancing oval cell proliferation [69].

HSS is a cytosolic liver-specific growth factor peptide that involves in hepatocyte protection and proliferation by restoring DNA synthesis and autophosphorylation of EGF receptor (EGFR) tyrosine residue on hepatocytes based on a time-dependent manner [70–74].

A stromal derived factor-1α is produced in the liver and released into the damaged tissue. Thereby CXCR4+ bone marrow stem cells could be recruited to the site of injury via chemotactic gradient. As the progenitor cells enter the liver, they come into contact with another chemokine, stem cell factor, which facilitates the recruitment of stem cells [27]. Then, there is an expansion in the number of stellate cells in the periportal regions of the liver. This results in an increased production of growth factors [27]. There is an increase in soluble fibronectin, an extracellular matrix molecule produced by stellate cells, which provides another avenue for stellate cells to interact in stem cell engraftment [27].

Two receptor-ligand and growth factor signaling systems appear to be mainly involved in liver regeneration: HGF and its receptor (Met) and the EGFR and its relatively large family of ligands and coreceptors [8]. The EGFR is a member of family of four. The other members are ErbB-2 (HER-2, NEU), ErbB-3 (HER-3), and ErbB-4 (HER-4). There are many ligands for EGFR, including EGF, TGF-α, amphiregulin, heparin-binding EGF (HB-EGF), cripto, epiregulin, and β-cellulin [8]. Amphiregulin is expressed early (within

30 min) during liver regeneration after hepatectomy. There is a unique role for amphiregulin that the time course of its expression corresponds with the pattern of tyrosine phosphorylation of the EGFR, which is dramatically enhanced at 60 min after partial hepatectomy [8]. EGFR ligands are not equally interchangeable because removal of amphiregulin seriously affects liver regeneration whereas removal of TGF-α has no effect. EGFR ligands, despite the fact that they share the same receptor, have different effects, not only during liver regeneration but also in most other biological processes. Although all EGFR ligands can induce ErbB signaling, their expression patterns differ and their effectors functions are non-overlapping, ranging from cell motility and proliferation to growth inhibition. Most EGF family members are synthesized as transmembrane precursors, and these may have juxtacrine interactions aside from their soluble counterparts [8]. Unlike the other ErbB proteins, EGFR is coupled to the phospholipase C gamma pathway. Once activated, the ErbB receptor-ligand complex is endocytosed in clathrin-coated pits. By decreasing the rate of ligand dissociation from the cognate receptor EGFR, ErbB-2 heterodimers remain at the cell surface longer and undergo a slower rate of endocytosis when compared with EGFR homodimers. This recycling allows a rapid return of the potent heterodimer to the cell surface for another round of activation [8].

NF-κB is a dimeric transcription factor that is induced after growth factors stimulation and controls the expression of genes encoding cytokines, regulates the cell cycle and is an essential antagonist of apoptosis during liver regeneration. NF-κB consists of different proteins including Rel (c-Rel), p65 (RelA), RelB, p50/p105 (NF-κB1), and p52/p100 (NF-κB2) and all these individual proteins have distinct biological activities. For example, p50 subunit has a definitive protective role in the injured liver by limiting the expression of TNF-α, and inhibition of NF-κB enhances the apoptosis induced by TNF-α. In addition, the p65 subunit has stronger transcription activity than p50, but the role of each subunit is not fully understood [75–78]. The activated form of NF-κB is retained in the cytoplasm and under specific cellular stimulation is phosphorylated and degraded by its inhibitor (IκBα) [79]. Notably, during liver regeneration the signal resulting in NF-κB activation occurs within a few minutes of the partial hepatectomy and is gone within 1 to 2 h when NF-κB levels are again undetectable. In the regenerating hepatic tissue, activation of NF-κB occurs in liver cells, but may also occur in non-parenchymal cells such as endothelial and Kupffer cells that also have receptors for a variety of cytokines.

Even though a lot of details regarding liver regeneration which are still unclear, it is proven that HGF is the single most potent hepatocyte mitogen which, in conjunction with other growth factors (TGF-α, SOM, and IL-6) and also HSS, maintains hepatic regeneration [80]. It is important to note that the HGF levels do not correlate with the degree of liver regeneration [81]. Some studies support that exogenous administration of HGF, TGF-α, and HSS promotes and shortens the time necessary for regeneration after partial hepatectomy in patients with cirrhosis and fulminant hepatic failure; [50, 54, 71] in particular, HGF in transgenic animals may shorten the time to half needed for regeneration [82]. In addition to the above-mentioned factors, norepinephrine and insulin are also necessary for regulation of growth of regenerating liver by exposing the hepatocytes to growth factors [80, 83].

Inhibitors or Stop Signals for Regeneration and Their Mechanism

After regeneration is complete a stop signal should keep the regenerated liver to an appropriate functional size. Inhibitors and stop signals of hepatic regeneration are not clearly well known and only little information is available. On the top of the list is the protein TGF-β that inhibits DNA synthesis in regenerating hepatocytes, is secreted from both hepatocytes and platelets and modulates liver regeneration (Table 1) [84, 85]. TGF-β is believed to act on various cell and tissue types by counteracting the growth-promoting effects of other growth factors, such as TGF-α. Also the cation-independent mannose 6-phosphate receptor protein, which is overexpressed in hepatocytes in the course of liver regeneration and indirectly by targeting TGF-β to hepatocytes, acts as a negative regulator for regeneration [86].

It is clear that after hepatectomy the regenerating processes should suppress the growth inhibitors to help the liver regenerate as effectively as possible. After partial hepatectomy, TGF-β will be increased within 2 to 6 h and one of the main factors that is known to help this procedure is insulin growth factor (IGF) binding protein-1 (IGFBP-1), which is a hepatocyte-derived protein that reduces the level of TGF-β and helps continuing the normal liver regeneration [87, 88].

TGF-β1 and TNF have been shown to suppress the differentiation of progenitor hematopoietic stem cells into megakaryocytes and down the myeloid lineage [27].

AT GENE LEVEL

In normal cell cycle of all cells including the hepatocytes, the G_1 phase is the Gap 1 and S-phase is for the DNA synthesis and G_2 phase is the Gap 2, and M phase is the part in which the chromosomes and cytoplasm separate and G_0 is exiting from the cell cycle. Hepatocytes in general are not terminally differentiated cells

and even cells situated in the G_0 phase can undergo proliferation upon appropriate stimulation [30]. HGF affects hepatocytes at G_1 phase and promote cell cycle to S-phase and DNA synthesis [89]. It is also important to mention that the TGF-β enters the cell cycle and inhibits the hepatocytes regeneration through G_1 arrest [45, 90].

The multi-step process of liver regeneration is constituted of at least two critical phases: the transition of the quiescent hepatocyte into the cell cycle (priming) and the progression beyond the restriction point in the G_1 phase of the cycle. These steps appear to be under separate controls, priming by the TNF and IL-6 cytokines and cell cycle progression by the growth factors (HGF and TGF-α) [9]. In the first phase, quiescent hepatocytes need to become "competent" to enter the cell cycle and replicate. These cells go through an initial stage, "priming" ("competence"), which corresponds to the G_0 to G_1 transition, before they acquire the capacity to respond to a set of factors that make the cells progress through the G_1 phase and replicate. In the next phase, competent hepatocytes can enter G_1, progress through the cell cycle and undergo DNA replication [7].

The priming phase corresponds to the first 4 h after hepatectomy and is best characterized by the expression of immediate early genes [91, 92]. Several years ago it was observed that more than 70 growth-response genes are activated in the remnant liver during the early stages of liver regeneration and that the number has been expanded over the years to more than 100. Most important such genes (c-fos, jun B, c-jun, c-myc) are those encoding transcription factors and proteins that have been identified as "proto-oncogenes" because somatic mutations or overexpression of these genes can lead to malignant transformation. Delayed genes (Bcl-x_L) are also expressed between the first 4 to 8 h after partial hepatectomy [9]. Activation of proto-oncogenes (c-fos, c-myc, c-Ha-ras, c-met, c-Erb B1, TGF-α, and TGF-β) in the immediate early gene response involves both transcriptional and post-transcriptional mechanisms. Important to note that post-translational modification of proteins such as NF-κB (it occurs in the absence of protein synthesis and leads to dramatic increase in DNA binding capacity) is a key element in making hepatocytes become responsible to growth factors at the start of liver regeneration [7]. In particular, the first initial activated transcriptional factors in liver regeneration include NF-κB, STAT3, AP-1, and C/EBPβ, which then in part cause secondary activation of multiple genes including growth factor genes that in turn causes the hepatocytes more suseptible to growth factors and help them enter the cell cycle to move from G_1 to S-phase and DNA synthesis and regeneration [9, 26, 93–96].

Mediators of acute phase reactants mainly IL-6 and TNF secreting from both injured liver cells and nonparenchymal liver cells within minutes to the extracellular fluid are the main promoters of gene-expression toward stimulation and liver regeneration [97, 98]. The transcription factor C/EBPα is one of the known main factors associated with regeneration arrest during compensatory regeneration through affecting the genes responsible for regeneration [99, 100].

MONITORING THE REGENERATED LIVER

Liver regeneration can be assessed by a number of tests including liver weight, synthesis rates, certain protein levels and specific enzyme markers, mitotic counts, DNA counts, immunohistochemical staining of nuclear antigens, and gene expressions.

Flow cytometry is an accurate method for monitoring hepatic regeneration with poly- or monoclonal antibodies against special receptors on hepatic cells like CD4 CD11b, but requires complex equipment and special labs. Measurement of protein and enzyme levels for regeneration monitoring such as putrescine, ornithine decarboxylase, thymidine kinase, α-fetoprotein, and early pregnancy factor are non-invasive tools but are not accurate because of the nutritional status of the host. Mitotic count is another method to monitor liver regeneration but it only measures a short segment of the cell cycle (the M phase) and cannot be observed by light microscopy. For DNA synthesis evaluation, thymidine and BrdU as the fundamental elements should be measured but this procedure requires a pre-injection of radioactive isotopes and nucleotides, thus rendering it dangerous to use in humans.

Immunohistochemical staining for nuclear antigens (Ki-67, proliferating cell nuclear antigen [PCNA], DNA polymerase α, and nuclear organizer region proteins) is another method to monitor. PCNA protein measurement by immunoblot is simple, accurate and reproducible marker for liver regeneration and the percentage of hepatocytes stain for PCNA can be calculated. Gene expression rates such as histone 3 mRNA that shows those hepatic cells that entered the S-phase, needs recombinant DNA technology to monitor regeneration and is time consuming. It is therefore recommended that clinicians **can** use at least two different independent methods to monitor liver regeneration [101–105].

In addition, special measuring techniques include galactose elimination test, single-photon emission computed tomography (CT) with 99m-technetium galactosyl human serum albumin scintigraphy (GSA-LV) [106] or Technetium-99m-diethylene triamine pentaacetic acid-galactosyl human serum albumin (99mTc-GSA). In particular, asialoglycoprotein receptor (ASGP-R) is a hepatocyte cell surface receptor specific for galactose-terminated glycoproteins and 99mTc-GSA is an analogue ligand to ASGP-R and when administered will bind to these receptors with high specificity and its

accumulation in liver cells corresponds with the characteristics of liver function tests. This test is more accurate than CT scan alone because CT scan only shows volume changes but not function, whereas this test shows that the remnant and regenerated liver are functional or not [107–110].

In adults, the liver does not always regain its preoperative size after hepatectomy (liver volume may not change significantly beyond 1 year after surgery) [111]. Patients' body size and intrinsic liver function or liver blood flow, represented by indocyanine green (ICG) at 15 min (retention rate at 15 min after an intravenous injection of ICG), may be related to regenerated liver size (a significant correlation is observed between liver volume at 1 year and body surface area, and, moreover, a significant inverse correlation is noticed between liver volume and plasma retention rate of ICG) [111].

The $ShvO_2$ (hepatic venous hemoglobin oxygen saturation) seems to be a simple index of the regenerative status of the remnant liver, and a useful method for monitoring liver regeneration after hepatectomy. The $ShvO_2$ represents the sum of hemoglobin oxygen saturation in the blood at the venous ends of all sinusoids, and its value reflects the oxygen supply/demand relation in the liver; i.e., factors producing an imbalance between oxygen supply and demand should cause a corresponding deviation in the $ShvO_2$ levels [112]. Furthermore, the $ShvO_2$ could be related to the changes in hepatic energy charge when using experimental animals (rats) inspired with varying concentrations of oxygen, and it might be a valuable indicator of energy status of liver during hepatic surgery. Decreased $ShvO_2$ levels are synchronized with increased DNA synthesis in the remnant liver. Energy charge levels are also significantly decreased at day 1 after hepatectomy, suggesting that the regenerating liver demands an increased amount of oxygen for mitochondrial oxidative phosphorylation to restore hepatic energy charge [112].

ORGANS THAT AFFECT THE HEPATIC REGENERATION

Pancreas affects the hepatic regeneration by secreting hepatopoietin A, a mitogen and growth factor for hepatocytes and polyamines like spermidine that helps to maintain hepatic integrity. In addition, pancreatic exocrine secretions trigger hepatocyte proliferation by unknown mechanisms. All of these have been shown through combined resection of pancreas and liver. Moreover, after combined liver and pancreas resection, the anti-inflammatory IL-10 expression is induced in spleen, which down-regulates the release of the TNF-α, thereby inhibiting liver regeneration. It seems that intact pancreas plays a key role in modulating the secretion of IL-10 as a suppressor of hepatic regeneration [113–116].

The intestine, by regulating the release of pancreatic hormones (e.g., insulin) by some secretions like glucagon-like-peptide-1, affects the processes of liver regeneration. Moreover, in wide intestinal resection with the absence of bile in the lumen, liver regeneration related with cyclin E-associated kinase inactivation will be delayed, thereby indicating the role of both intestine and bile in the processes of regeneration [117, 118].

SUPPORTIVE CARE FOR KEEPING THE REGENERATED LIVER FUNCTIONAL

Particular strategies, substances, medicines, and nutritional support can affect the process of regeneration. Prostaglandins (PGs) have long been known to possess cytoprotective effects. In particular, it has been demonstrated that PGs and prostacyclin affect the regeneration process. PGE_1 after partial hepatectomy increases in remnant cells and stimulates cAMP production and increases ATP level in both remnant and regenerating liver and enhances DNA synthesis. It exerts a protective effect on liver injury and augments the liver regeneration through increasing in HGF production. It is known that cyclooxygenase (COX) enzyme modulates the production of PGs, and that inhibition of this enzyme (e.g., by non-steroidal anti-inflammatory drugs), particularly COX-1 form, negatively affects the process of regeneration in the liver. Thus, exogenous administration of PGs is recommended [119–126].

Sympathetic nervous system inhibition promotes liver accumulation of oval stem cells and assists in the regeneration process [127]. From another viewpoint, nutrition can promote growth of the remnant liver and maintain regeneration. Total parenteral nutrition, when enriched with glutamine, and a balance between long and medium chain triacylglycerols augment liver cell proliferation and liver regeneration. In addition, glucose alone inhibits regeneration; however, when combined with other nutrients it does not seem to affect this process [128, 129]. Lipid emulsions and a mixture of standard aminoacids, especially branched chain aminoacids (valine, leucine, and isoleucine), enhance the regeneration [130, 131]. It has also been demonstrated that high concentration of aminoacids in portal venous circulation is one of the most powerful trigger factors for liver regeneration [132].

Even though oxygen concentration in portal vein may not affect the regeneration process directly [133], the regenerating liver requires increased amount of oxygen for mitochondrial oxidative phosphorylation to restore hepatic energy charge. Thus, preoperative hyperbaric oxygenation induces compensatory hypertrophy and regeneration of the predicted remnant liver and as already mentioned, postoperatively hepatic venous hemoglobin oxygen saturation can be used as an index of liver regeneration in the remnant liver [133, 134]. During ischemia, Kupffer and T cells are acti-

vated initially in the ischemic area and then in nonischemic area. Soon after, they mediate the activation of platelet adhesion and neutrophil inflammatory response that infiltrates the injured liver and increases the expression of more adhesion molecules on endothelial cells and more generation of reactive oxygen radicals. The methods by which ischemia/reperfusion injury can be diagnosed include ASGP-R ligand on hepatocytes, showing ischemic damage histologically, hepatobiliary scintigraphy, an easy method in clinics, and electron microscopy, the diagnostic gold standard [135–145]. Reactive oxygen radical scavengers can be used to protect ischemia/reperfusion injury syndrome.

Notably, potential therapies for both short and long-term saving of grafts and regeneration include: 1) antibodies to degenerative cytokines using free radical scavenging enzymes, e.g., superoxide dismutase or catalase; 2) pre-treatment with endothelin (ET)-1 receptor antagonist; 3) treatment with platelet activating factor receptor antagonist, indirectly modulating the plasma ET-1 level; 4) treatment with IL-6, which, through its anti-inflammatory properties against TNF-α, limits hepatic warm ischemia/reperfusion injury: IL-6 appears to be a key protective molecule in reducing injury and promoting regeneration after combined ischemia and major hepatectomy [144]. IL-6 has both mitogenic and anti-apoptotic [146] effects on hepatocytes and protects the regenerating liver against ischemic injury [7]. Besides, TNF/IL-6–induced NOS has a cytoprotective role in liver regenerating liver [147]; 5) estrogen and its derivates, which, through an unknown pathway, limits hepatocellular ischemia injury; 6) HGF, which helps hepatic microcirculation and regeneration in ischemically damaged liver following transplantation; 7) down-regulation of Kupffer cells with calcium blockers and pentoxifylline [148–157]. Finally, "ischemic preconditioning," probably a receptor-mediated adaptive process inducing endogenous protection against ischemia-perfusion injury in the regenerated liver, is another potential therapeutic strategy currently under investigation [158].

FACTORS THAT IMPAIR REGENERATION

Prolonged period of cold preservation of the liver from cadaveric split or living donor up to 10 h impairs TNF-α and IL-6 production and adversely affects the regeneration process [159]. Concomitant infection, especially with gram negatives with circulating endotoxins, increases the proteolytic activity and impairs liver regeneration [160].

The most common innate and native problems of the body and liver that impair the regeneration process include lack of C3α and C5α complement components, two potent inflammatory mediators, which attenuate the activation of transcriptional factors NF-κB and STAT3 and impair regeneration [161]. Lack of IGFBP-1, which activates transcriptional factor C/EBPβ, may affect liver regeneration to proceed properly [162]. Leptin is an adipocyte-derived antiobesity hormone. Patients with fatty liver and nonalcoholic hepatic steatosis are characterized by liver steatosis and hyperleptinemia. Hyperleptinemia is because of abnormal leptin receptors and peripheral leptin resistance. Leptin levels correlate directly with the severity of hepatic steatosis. Apart from the acquired liver diseases, some genetic diseases may negatively affect the leptin receptors. Consequently, fat is accumulated in the hepatocytes and impairs their proliferation through inhibition of transcriptional factor STAT3, thereby impairing regeneration. Moreover, fatty hepatocytes have decreased tolerance against ischemic injury, reversely affecting their regeneration capability [163–168].

PROTOCOL FOR REGENERATION

Apart from the innate capacity of the liver against rejection, there are mechanisms or factors that may help the graft survive and continue the regeneration process, including cytokines IL-4 and IL-10 that suppress alloimmune response in transplantation and maintain the tolerance to allografts. Thus, monitoring the levels of these cytokines is important for the evaluation of acute allogarft rejection and regeneration. In addition, they can be administered for supporting the graft [169, 170]. Induction of antigens (e.g., donor blood) through the portal vein is another technique for transplantation tolerance [171]. Besides, an immunosuppressive protein, human analogue of liver suppressor factor-1, increases the transplant tolerance, and liver regeneration after injury via undetermined mechanisms [172, 173]. One of the problems that may occur during transplantation is the passenger leukocyte syndrome, i.e., the migration of leukocytes from the allograft into the recipient. This event may result in alloantibody production against host antigens and may induce hemolysis. Therefore, supportive management like plasma exchange therapy should be undertaken to improve survival especially in patients with sufficient residual capacity of liver regeneration [174–177]. It should be considered that host cellular responses to allograft are enhanced in the regenerating small-for-size grafts, and, furthermore, graft's own regenerative potential suppresses rejection of hepatic transplants [178, 179].

Finally, to induce liver regeneration, the patient should undergo administration of appropriate doses of HGF, IL-6, IL-10, PGE_1, and sympathetic blockers through transcutanous infusions via the portal vein, and high-dose glutamine and branched-chain aminoacids. If transcutanous unilateral portal vein embolization with hyperbaric oxygen administration is added to this procedure, the result and the rate of regeneration

is faster and comparable. Moreover, molecular adsorbents recirculating system (MARS) has recently been approved to be used as a bridging therapy of affected liver to modulate the regeneration process through increasing the hepatic growth factors EGF, TGF-β1, and IGF-1 [180]. There is also a new report advocating that IGF-1 is a new therapeutic strategy for improving liver regeneration although this has to be confirmed by future studies [181].

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