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Review Article

Liver regeneration: Literature review

Regeneração hepática: Revisão de literatura

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A B S T R A C T

Liver regeneration is a highly organized tissue growth process and is the livers most important reaction to aggression. The complex mechanisms involved in this process encompass a variety of regenerative pathways that are specific to the different types of aggression. The most studied form of liver regeneration is that which occurs after the loss of hepatocytes in an acute injury, such as in the regenerative process of rodents after partial hepatectomy or administration of harmful chemicals (CCl4, paracetamol, allyl alcohol). These experimental models revealed extracellular and intracellular signaling pathways that are used to return the liver to the size and weight equivalent to those prior to the injury. Understanding the liver regeneration process is a challenge that is justified by the numerous interactions of different cellular components, various mitogenic factors (complete and incomplete), complex mitogenic pathways, and acute phase inflammatory proteins. Hepatocytes, cholangiocytes, and liver progenitor cells have been shown to have regenerative behavior. The regenerative activities of hepatocytes and cholangiocytes are typically characterized by phenotypic fidelity (multiplication), however, when normal regeneration is thwarted, hepatocytes and cholangiocytes function as facultative stem cells (dedifferentiate) or transdifferentiate to restore normal liver structure. This review traces the path taken in recent decades in the study of liver regeneration and highlights new concepts in the area.

Keywords: Liver Regeneration. Liver. Hepatocytes. Hepatocyte Growth Factor.

INTRODUCTION

A fascinating aspect of the liver is its remarkable capacity for regeneration[1]. The loss of functioning cells due to injury, whether traumatic, ischemic, chemical, or viral, or partial hepatectomy, induces the hepatic regenerative process[2,3]. This ability of the liver to precisely regulate its growth and mass is particularly remarkable because hepatocytes are stable cells and rarely divide in the normal state[4]. The cells are quiescent in the G0 phase of the cell cycle, with only 0.0012% to 0.01% of the hepatocytes in the mitosis phase[5,6]. This low capacity for cell replication can be stimulated by injury mechanisms, which causes restoration of liver mass and function that is appropriate to the size of the organism[7-8]. The term regeneration, consecratedly used, has only the meaning of recovery of organ volume[1]. What occurs is global hyperplasia of the entire parenchyma until the prior hepatic mass is reestablished with minimal variations (5% to 10%), when there is an abrupt interruption of the process[9-11].

Due to the limitations in the use of human livers, most of the information on the regenerative process comes from in vivo models with small rodents (rats and mice) or in vitro ones, using cultured liver cells[6]. The rat model introduced by Higgins and Anderson in 1931 is the main and most widespread method for studying the hepatic regenerative process[1,12,13]. In this

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model, the middle and left lateral lobes are removed through ligation of the vascular pedicle, resulting in the removal of approximately 70% (2/3) of the total hepatic mass[12-15]. The regenerative process in the rat's liver begins immediately after injury and is completed in 7 to 10 days[1,6,8,9,13,16]. In the human liver, partial restoration seems to occur in two to three weeks, and complete restoration has been observed only after six months[17,18].

1 Initiation of Hepatic Regeneration

An abrupt reduction in liver mass, such as in a hepatectomy, results in an increase in blood flow and portal pressure to the remaining hepatic segments, which is considered an important factor for the initiation of liver regeneration[8]. Several changes occur in hepatocytes soon after hepatectomy in rats, which include increased urokinase activity at one minute and migration of β-catenin and the Notch Intracellular Domain (NICD) to the nucleus at five and 15 minutes, respectively[5,7]. The main receptors, C-MET (hepatocyte growth factor receptor) and EGFR (epidermal growth factor receptor), are activated in approximately 30 minutes[19,20] and more than 100 genes are expressed, which increase in one hour and are sustained up to 14 days after hepatectomy[21]. The plasma membrane of the hepatocyte becomes hyperpolarized within 30 minutes after the initial insult, with rapid sodium intake and elevated intracellular pH[3]. The increase in the urokinase type plasminogen activator (uPA) originates a sequence of proteolysis that converts plasminogen into plasmin. Subsequently, there is activation of metalloproteinases 9 (MMP9), which results in the degradation of specific extracellular matrix proteins, including glycosaminoglycans, and activation of hepatocyte growth factor (HGF)[22-24]. HGF is present in the inactive form in the extracellular matrix (ECM), being activated and massively released in the blood stream in less than one hour[25].

2 Contribution of growth factors and cytokines

The regeneration process is dependent on the presence or absence of many signaling agents that act together or in isolation. Due to the multiple interactions between genes, growth factors, and cytokines, it is unlikely that one signaling agent will completely determine the regenerative process or that, in its absence, regenerative steps will be abolished[11,16].

2.1 Complete Mitogenic Agents

Complete mitogenic agents are capable of inducing DNA synthesis in hepatocyte cultures and mitosis in a resting cell population (G0 phase of the cell cycle). When administered to non-operated animals, they cause an increase in liver volume. The effect of complete mitogenic agents can be potentiated by incomplete or auxiliary mitogenic agents[26].

Hepatocyte growth factor (HGF) is always associated with its C-MET receptor. The early elevation of HGF plasma levels after hepatectomy, preceding the onset of DNA synthesis by many hours, suggests that this factor is the main candidate for the role of inducing the regenerative process[9,13]. HGF is present in the inactive form (pro-HGF) in large quantities in the ECM, especially in the periportal area[27]. Soon after hepatectomy, ECM remodeling occurs, triggering a cascade of events culminating in activation of uPA. Subsequently, through uPA, there is maturation of pro-HGF to HGF and activation of the C-MET receptor in the plasma membrane, allowing its incorporation into the liver cell[3]. HGF binds to its C-MET receptor 30 minutes after hepatectomy[20]. HGF is released into the bloodstream, reaching a concentration 10 times higher than baseline one hour after hepatectomy[25]. Blood HGF levels drop over the next three hours, after which HGF mRNA production starts in the lungs, spleen, and kidneys. In this context, there is a new increase in the concentration of HGF in the bloodstream, with a peak 24 hours after hepatectomy[28]. Norepinephrine stimulates HGF production at this stage[29,30]. In the early regeneration stages of normal livers, HGF is also produced by hepatic stellate cells (HSC), and during late stages, HGF is produced by liver sinusoidal endothelial cells (LSEC) and progenitor cells[31,32].

Epidermal growth factor (EGF) was the first growth factor to be isolated and studied[11]. It stimulates DNA synthesis in most epithelial cells, including hepatocytes. Considered a complete mitogenic agent,

EGF is produced in the salivary glands and in the duodenum Brunner's glands and is constantly present in the portal circulation. The production of EGF in Brunner's glands is optimized by norepinephrine[33]. Serum EGF levels rise within a few hours after a partial hepatectomy, but decrease rapidly, even before DNA synthesis by hepatocytes[3]. When EGF is added in hepatocyte culture, DNA synthesis begins in 24 hours, reaching a peak between 48 and 72 hours[9].

Transforming growth factor alpha (TGFα) is also a ligand to EGFR and has more intense regenerative effects when compared with EGF[34]. It stimulates hepatocytes proliferation in vitro and in vivo[3]. It is not present in the normal liver but is quickly identified after a hepatectomy[35]. There is an increase in TGFα mRNA levels eight hours after hepatectomy, reaching a peak 24 hours after the procedure[36]. TGFα secretion by regenerating hepatocytes possibly constitutes an autocrine loop that stimulates DNA synthesis[9,37].

Heparin-bound epidermal growth factor (HB-EGF) is produced by endothelial cells and Kupffer cells[38-40]. It is a potent complete mitogenic agent in cultures and when administered to rats after hepatectomy it causes a greater regenerative stimulus[38]. HB-EGF gene expression is intensely regulated by cytokines, growth factors, and transcription factors[39]. The HB-EGF produced by LSEC keeps HSCs in a state of quiescence, which is important to prevent liver fibrosis and cirrhosis[41].

Amphiregulin produced by hepatocytes is an early-response growth factor that may contribute to the early stages of liver regeneration. In vitro, it behaves as a primary mitogenic for isolated hepatocytes, acting through EGFR. Its expression increases in the presence of IL-1β (interleukin-1beta) and prostaglandin E2. In addition, its expression is under the control of YAP (yes associated protein) and the hippo kinase, which has shown important regulation in the termination of liver regeneration[8,42].

Epidermal growth factor receptor (EGFR) is a member of the ERB family of receptors, being expressed in all liver cells. EGFR activation is evidenced by tyrosine phosphorylation and peaks 60 minutes after hepatectomy[11]. The EGFR ligands relevant for liver regeneration are the epidermal growth factor, transforming growth factor-alpha, heparin-bound epidermal growth factor, and amphiregulin[5,43].

2.2 Incomplete mitogenic agents

Incomplete or helper mitogenic agents have no direct effect on hepatocyte proliferation, but they can potentiate the effect of complete mitogenic agents and reducing the effect of inhibitory agents. They do not have mitogenic effects when added alone to culture media[9] and do not cause parenchymal increase when administered alone in animal experiments. Many of them act on the precise sequence of events that culminate in the initiation of hepatocyte proliferation.

Tumor necrosis factor alpha (TNFα), produced by hepatic and splenic macrophages, increases rapidly in plasma after hepatectomy. The presence of TNFα is associated with an optimization of cell proliferation signals when cells are already stimulated. Activation of its receptor (TNFR1) triggers the activation of nuclear factor κB (NF-κB), its signaling pathway for liver regeneration[44]. C-MET receptor (for HGF) and EGFR (for EGF and TGFα) have their transduction increase after stimulation caused by TNFα binding[16]. TNFα activates c-Jun N-terminal kinase (JNK) which also modulates gene transcription[45].

Interleukin-6 (IL-6) is produced predominantly by hepatocytes and hepatic macrophages under the stimulation of TNFα[46]. The concentration of IL-6 in plasma increases after partial hepatectomy, peaking at 24 hours, contributing to the activation of the Signal Transducer and Activator of Transcription 3 (STAT3)[47].

Bile acids are increased in the bloodstream after hepatectomy, and their absence slows down the regenerative process. Their elevation occurs predominantly 48 hours after the initial stimulus, so it is unlikely that bile acids contribute to the initial phases of the regenerative process[48].

Insulin is produced in the beta cells of the pancreatic islets and, subsequently, reaches the liver via the portal circulation. Even though it is considered an incomplete or auxiliary mitogenic agent, insulin is essential for the effects of HGF and EGF in hepatocyte culture. However, insulin in hepatocyte culture without the presence of HGF or EGF does not induce hepatocyte

proliferation[49,50]. It is postulated that insulin binds to the C-MET receptor and EGFR together with specific ligands, contributing to the regenerative process[8].

Norepinephrine is not a complete mitogenic agent in hepatocyte culture, but it significantly enhances the effects of EGF and HGF in this method. It is produced at the terminal synapses of sympathetic neurons, the adrenal medulla, and the HSC. It increases after hepatectomy in rats at the same time as the increase in HGF[29]. It has been deemed a collaborator and enhancer of regenerative effects following the activation of C-MET and EGFR[49]. Norepinephrine suppresses the inhibition of hepatocyte proliferation by blocking the Transforming Growth Factor Beta-1 pathway, stimulates the production of HGF by fibroblasts and EGF production by Brunner glands[30,33], and is involved in the activation of STAT3 and NF-κB[51].

2.3 Complex mitogenic pathways

Recently, some signal that participate in the regenerative process networks have been identified, with sequences of steps, being called complex mitogenic pathways.

The WNT/β-catenin signaling system plays an important role in the regulation of progenitor cells in many organs and tissues. Under various conditions of liver injury, the expression of several genes of the WNT family and participation in the regulation of liver progenitor cells have been observed[52,53]. The WNT pathway, which acts synergistically with C-MET and EGFR, is a complex system composed of many steps that culminates in the production of β-catenin, a protein that is identified in the nucleus of hepatocytes within five minutes after hepatectomy[19,54]. There is reference of 19 binding proteins for the WNT pathway that are produced in most liver cells, their cooperation or antagonism in the regenerative process occurring when they bind to atypical receptors coupled to the G protein, receptors that are called "Frizzled". Cyclin D1, a signaling protein and intracellular switch that leads to the proliferation of hepatocytes, is also regulated by this pathway[55].

The Hedgehog signaling is another example of a complex mitogenic pathway. Both the receptor and the signaling protein are expressed in hepatocytes. As observed in rodent research, activation of the Hedgehog pathway is involved in optimizing the hepatic regenerative process[56]. The Hedgehog pathway ligand is bound to a cell surface glycoprotein, Glypican 3 (GPC3), which is attached to CD81 (cell surface protein)[57]. After hepatectomy, GPC3 is separated from CD81 by releasing the ligand from the Hedgehog pathway. The ligand activates the Hedgehog pathway, culminating, in two days, with the appearance of the transcription factor GLI1 (cytoplasmic protein), the final messenger of this pathway, in the nucleus of the hepatocyte and activation of several target genes[58].

Another complex pathway that contributes to cell cycle control and responds to mitogenic agents is the transforming growth factor beta-1 (TGFβ1) signaling pathway, which is a potent mitoinhibitory substance, as it plays an important role in regulating hepatocyte proliferation during liver regeneration[59,60]. Hepatocytes have significantly increased intracellular TGFβ1 concentrations 12 hours after a two-thirds partial hepatectomy in rats. This concentration increase is initially confined to the hepatocytes that reside in the periportal region of the hepatic acinus and later evolves in a wave manner towards the Rappaport zones, reaching the centrilobular region within 36 hours. The increase in intracellular TGFβ1 is, however, transient, and within 48 hours after the initial stimulus, most hepatocytes no longer have significant concentrations of this factor[61]. During the regenerative process, hepatocytes are not effectively inhibited by TGFβ1 because the receptor for this factor is inhibited[29]. In normal rat livers, the inhibition of the TGFβ1 receptor is sufficient to induce DNA synthesis in hepatocytes, suggesting that TGFβ1and the constant effects of EGF and HGF, to which hepatocytes are continuously exposed, have antagonistic roles, creating an effect that keeps the hepatocyte quiescent in the G0 phase of the cell cycle[60].

The HIPPO pathway consists of a cascade of kinases that regulate the YAP protein. The YAP protein interacts with the signaling of the TGFβ1 pathway, facilitating changes in the expression of genes that are associated with the process of cell proliferation in general. After a series of steps during the regenerative

process in rodents, there is inhibition of the HIPPO pathway and increased expression of the YAP protein and its content in the hepatocytes nucleus[62]. The HIPPO pathway can be considered a vast receptor network of multiple, often contradictory signals that contribute to liver regeneration and size enlargement[8].

3 Cellular level of liver regeneration

Liver regeneration after hepatectomy is achieved through the proliferation of all existing cell types in the remaining liver. The hepatocyte is the first cell to respond to regenerative stimuli. Cholangiocytes initiate the process in sequence, and later endothelial and stellate cells[11]. The transition from phase G0 to G1 occurs simultaneously in all liver cells, and a delay in mitosis is observed in non-parenchymal cells due to the existence of a more prolonged G1 phase. In rodents, the replication of non-parenchymal cells occurs 24 hours after the replication of hepatocytes[9,10].

The hepatic regenerative process is divided into 3 stages: 1) initiation phase: quiescent hepatocytes convert from G0 to G1 of the cell cycle when stimulated by inflammatory cytokines (IL-6, TNFα); 2) proliferation phase: with the help of mitogenic agents, hepatocytes progress to S, G2, and M phases (mitosis); and 3) inhibition phase: the proliferation process ends under the effect of negative factors such as TGFβ and activin[4,45,63].

Liver regeneration can occur through cell multiplication, where each liver cell proliferates to regain its own cell type (phenotypically identical) or through the production of new, phenotypically different cells. The latter can occur by: 1) cellular dedifferentiation, which occurs when an already differentiated cell performs a cellular regression to a facultative progenitor cell (oval cell) and subsequent differentiation into other specific cell types, such as the hepatocyte regressing to a progenitor cell and later originating a cholangiocyte; or by 2) cellular transdifferentiation, which is a transformation of a differentiated cell to another specific cell type, without regression to a progenitor cell, such as when a cholangiocyte directly originates a hepatocyte[4,11].

Rodent hepatocytes reach the G1 phase in approximately four hours, progressing to the G1-S phase, with DNA synthesis, 10 to 12 hours after the initial stimulus. The first peak of DNA production occurs at 24 hours, with smaller peaks at 36 and 48 hours after liver resection. The G2-M phase, follows six to eight hours after DNA synthesis (22 to 24 hours after liver resection) reaching a peak 32 to 34 hours after surgery[9,64]. When the mass-to-volume ratio reaches the original organ size, hepatocytes return to their state of quiescence in the G0 phase[1].

In adult rats less than 20 months old, 95% of hepatocytes synthesize DNA during the first three days after hepatectomy[8]. The proliferation of hepatocytes occurs as a wave that sweeps the hepatic acinus from the periportal region towards the centrilobular region. Hepatocytes located in Rappaport zones 1 and 2 replicate DNA earlier than those near the centrilobular vein (zone 3 of the hepatic acinus)[9].

Cholangiocytes play an important role in parenchymal regeneration. In addition to metabolic functions, they exhibit substantial plasticity and, in some contexts, can lead to liver repopulation. Proliferating at almost the same time as hepatocytes, cholangiocytes respond to the same signals to which hepatocytes are exposed (HGF, EGFR ligands, IL-6, serotonin, YAP, and Hedgehog) and express C-MET and EGFR[8].

Hepatic stellate cells (HSC) play a role in liver regeneration by contributing to the synthesis of collagen and other components of the extracellular matrix[65], and produce signaling proteins that are essential for regeneration, including HGF and TGFβ1[13]. They play an important role in the "cell progenitor niche", serving as a support for progenitor cells[66]. In addition, HSC not only promote liver regeneration by producing growth factors for LPC but also exhibit progenitor cell properties. HSC can optionally originate progenitor cells and subsequently form hepatocytes and cholangiocytes[67-69].

Kupffer, endothelial, and stellate cells are essential for normal hepatocyte proliferation, as they produce cytokines and growth factors necessary for the process[45]. Cytokines activate transcription factors such as nuclear factor κB (NF-κB), Signal Transducer and Activator of Transcription 3 (STAT3), and cyclin D1[64].

Liver progenitor cells (LPC) can be named in different ways: oval cells, liver progenitor cells, fetal hepatoblasts, liver stem cells, and atypical ductal cells[70].

They were first described in studies in rats as oval cells due to the nucleus being oval and in increased proportion to the cytoplasm. Anatomically, they are located in the terminal branches of the biliary tree, in Hering's canals (intrahepatic bile ducts), and are positioned between bile cells and hepatocytes. Although LPC are not observed in normal livers in adults, these cells appear in response to severe acute injury[71,72]. Studies with rodents illustrate that hepatocytes and cholangiocytes can be dedifferentiated into liver progenitor cells[73]. The process of differentiation of LPC into hepatocytes and/or cholangiocytes involves a set of interactions that control the various pathways for specific cell differentiation. Macrophages, myofibroblasts, and the NOTCH and WNT activation pathways participate in this process[74-76].

The main liver cells in the dedifferentiation process are the cholangiocytes, or biliary epithelial cells[77-79]. In this process of cell regeneration, cholangiocytes first perform a cell dedifferentiation into LPC, followed by a proliferation of LPC and later a differentiation, giving rise to new hepatocytes and cholangiocytes[72].

Transdifferentiation from hepatocyte to cholangiocyte occurs when there is an impediment to cholangiocyte regeneration. This regenerative process, where the hepatocyte is responsible for the role of facultative stem cell, is observed predominantly in the periportal region and is associated with the presence of HGF, EGF, and TGFβ expression. Hepatocytes, in this case considered as hybrid cells, convert to cholangiocytes, forming of an embryonic ductal plaque, without transformation to an initial progenitor cell[80].

The formation of new hepatic sinusoids during the regenerative process is complex and will last for several days, with a peak in DNA synthesis occurring between four and seven days after hepatectomy in rats[8]. The proliferation of hepatocytes forms small clusters that soon initiate the production of various angiogenic factors (VEGF and angiopoietin 1 and 2), which stimulates the migration of endothelial cells from the liver to form capillaries that subsequently acquire fenestrations, becoming hepatic sinusoidal cells[81]. Vascular endothelial growth factor (VEGF), which is produced by hepatocytes, stimulates endothelial cell proliferation by activating the VEGFR2 receptor and stimulates the VEGFR1 receptor, which induces the production of HGF by endothelial cells[82]. Therefore, there are many paracrine effects that originate from endothelial cells influencing hepatocytes and other liver cells[83]. The whole process results in the presence of endothelial cells early in the sites of hepatocyte proliferation, leading to formation of vascular supply, later acquiring the sinusoidal structure and restoring the original histological hepatic architecture[81].

The cellular response to the various regenerative factors requires the presence of specific receptors on the plasma membrane. The complex formed is internalized in the cell and there is activation of tyrosine kinases and phosphorylation of intracellular proteins. In sequence, there is activation of transcription factors, such as STAT3 and NF-κB, which trigger a series of secondary events and activation of the genes involved in the proliferative process (c-fos, c-myc and c-jun). This sequence of events culminates in DNA replication[3,9,84].

Proto-oncogenes are a group of normal genes that are closely and physiologically associated with cell proliferation. The expression of the proto-oncogenes c-fos, c-myc, p53, c-jun, and c-ras is related to the cell cycle, not only in regenerating livers, but also in a number of other cells[3,9]. The expression of proto-oncogenes after partial hepatectomy is specific, sequential, and highly regulated. Even with the uncertainty about the function of proto-oncogenes, the levels of such proteins can be used to recognize the stages of the pre-replicative period of liver regeneration (initiation and progression). During initiation, there is an increase in c-fos and c-myc expression between 30 minutes and one hour, respectively. Between eight and 16 hours, already in the progression phase, there is an increase in the levels of mRNA for p53 and c-ras[3,9].

Nuclear factor κB (NF-κB) is a protein complex that functions as a transcription factor. This activated complex migrates to the nucleus of the hepatocyte and acts on target sites by promoting a specific sequence of genes. NF-κB activation occurs 30 minutes after hepatectomy in rats and plays an important role in gene expression, cell cycle regulation, and hepatocyte protection against cell apoptosis[44,85,86].

Signal Transducer and Activator of Transcription 3 (STAT3) is a transcription factor activated by the

binding of cytokines (IL-6 and IL-11), norepinephrine, and growth factors in different cell types. STAT3 migrates to the nucleus and induces the transcription of several genes involved in regeneration, such as c-jun and c-fos[16]. STAT3 activation occurs between one and eight hours after hepatectomy in rodents[87,88].

The activation of cyclin D1 and its migration to the nucleus is a no-return event for the hepatocyte to enter the S phase of the cell cycle. There is also expression of cyclin D2 and D3 at lower intensity[89].

4 Termination of liver regeneration

The completion of liver regeneration is possibly triggered by the recovery of the extracellular matrix (ECM). Hepatocytes gradually assume a quiescent phenotype when the ECM is restored[65,90].

At the end of regeneration, new components of the extracellular matrix are synthesized, including glycosaminoglycans and different types of collagen[13]. A series of events, such as the binding of HGF to glycosaminoglycans and the binding of TGFβ to decorin, cause the hepatocyte to return to the G0 phase of the cell cycle. The new ECM, synthesized by the stellate cells that have been stimulated by TGFβ, restores the binding sites of both HGF and TGFβ itself[13,18].

The regulatory key to ECM restoration is communication between hepatocytes and stellate cells. This communication is regulated by an integrin-linked kinase (ILK), a protein that is observed in both cells. ILK is a growth suppressor and a regulator of hepatocyte differentiation[91,92].

At the end of the regeneration process, the liver returns to its original size and volume. The ECM is considered one of the agents that regulates normal liver weight and is involved in the restoration to pre-hepatectomy values[8]. There is evidence that the number of hepatocytes produced in regeneration may exceed the original amount, and to control this derangement, a slight wave of apoptosis may occur[93]. Studies in rats have shown that hepatocyte proliferation ends six to eight days after hepatectomy and that 85% of the ideal ratio of liver to body weight is reached in two weeks[94].

Transforming growth factor beta (TGFβ), produced by hepatocytes and non-parenchymal cells, is a multifunctional cytokine that has both inhibitory and stimulatory effects depending on the cell type and conditions involved[95]. In rats, its administration before and after a partial hepatectomy inhibits the peak of DNA synthesis[9]. Its release from the beginning of regeneration is regulated to bring about the appropriate specific effect for the moment of cell proliferation. At the end of regeneration, binding to decorin, a glycosylphosphatidylinositol (GPI) bound protein of hepatocytes plasma membrane, it has a direct inhibitory effect on C-MET and EGFR[96,97]. In this context, TGFβ is not the agent that interrupts regeneration, but can be considered the "conductor" that orchestrates multiple events in a complex feedback loop, causing the activation of cell apoptosis and the blocking of gene transcription[13,18].

Activin is a member of the TGFβ superfamily. It has a receptor with a structure similar to the TGFβ receptor and a similar signaling pathway. It is produced by hepatocytes and has an inhibiting effect on the proliferation of nearby hepatocytes, demonstrating an autocrine effect. However, it stimulates the proliferation of hepatocyte progenitor cells in experimental rodent models[11].

5 Liver regeneration after chemical injury

Although most of the information on liver regeneration comes from studies after liver parenchymal resection in experimental models, most situations that evoke regenerative responses in human liver disease are associated with injury due to chemicals or viruses. In addition to regenerative signaling pathways, several inflammatory signaling pathways also operate in the removal of injured liver tissue prior to regeneration onset. In chemical aggressions, the signaling pathways of liver regeneration are similar to those that operate after parenchyma removal in a hepatectomy, but it is highly likely that the recruited macrophages also play important roles[8].

Most studies related to chemically-induced liver injury have focused on the effects on hepatocytes using paracetamol and carbon tetrachloride (CCl_4)[98,99]. Cells in the centrilobular regions are the most affected in chemical lesions, probably due to their higher expression

of the family of enzymes known as cytochrome P450, which, in situations of high toxicity, result in the generation of free radicals, toxic to hepatocytes, causing death by necrosis[98,99]. Soon after hepatocytes necrosis, there is infiltration of the affected areas by leukocytes and polymorphonuclear macrophages, resulting in the removal of dead cells. Liver regeneration is manifested by the synthesis of hepatocytes from the unaffected areas of the lobe and migration of proliferating hepatocytes to the injured areas, restoring the lobe's structural integrity and repairing injury[100].

Experimental models for periportal necrosis are limited to the use of allyl alcohol[101,102]. The repair of such lesion takes longer than the centrilobular one, probably due to the elimination of the ECM in the periportal region, which has high concentrations of HGF and EGF, thus eliminating the vital reservoirs of these growth factors, which are essential for the initiation of hepatic proliferation[103].

6 Liver regeneration after vascular occlusion

After portal vascular occlusion, hemodynamic, cellular and molecular changes occur, which result in atrophy of the occluded segment and hypertrophy of the vascularized segment. Hypertrophy is due to cell multiplication in a compensatory way for the readjustment of liver function. Atrophy of liver tissue and loss of volume is mainly caused by hepatocyte apoptosis and necrosis[104].

The key factors that initiate liver regeneration after portal vein occlusion are not yet fully understood. Recent studies have led to the development of different hypotheses to try to explain the initial stimuli of the regenerative process. The predominant concept is the "blood flow theory"[105]. This theory postulates that a significant increase in portal flow per unit of hepatic mass in non-occluded lobes can trigger the initiation of the regenerative process[84,106]. The increase in portal flow causes physical stress (shear stress) on the sinusoidal surface of the liver, which stimulates sinusoidal endothelial cells, hepatocytes, and Kupffer cells to start the regeneration process[107]. There is also greater accessibility of hepatotrophic factors (growth factors, hormones, and nutrients) from the intestine, pancreas, and spleen, which are present in greater quantities due to the concentration of portal flow[8], increasing in quantity in the non-occluded hepatic lobes, stimulating regenerative activity[108].

Changes in portal flow result in inverse changes in hepatic artery flow[109]. Portal venous hyperperfusion is accompanied by hepatic arterial hypoperfusion, which results in inadequate tissue oxygenation in the non-ligated segment. Relative hypoxia can activate adaptive mechanisms that initiate and sustain the regenerative process[110].

After selective portal ligation in rat livers, a regenerative response is observed in non-ligated lobes similar to the response in lobes maintained after hepatic parenchymal ablation[111]. However, these lobes show a smaller increase in the rate of DNA synthesis and a lower final weight when compared with lobes remaining after hepatectomy[112,113].

Studies in rats after selective portal ligation have shown that NF-κB, IL-6, and STAT3 are present in both ligate and non-ligated lobes, peaking at 30 minutes, one hour, and two hours. In both lobes, there is also a peak in 30 minutes of mRNA expression of the c-fos, c-myc, and c-jun genes[114,115]. The rapid signaling of these changes suggests that the increase in portal flow per unit mass may be an instantaneous, sufficient trigger for this cascade of signals stimulating regenerative activity[8]. The ligated lobe has a lower expression of p53, c-Ha-ras, cyclin E, cyclin D1, cyclin A, and Cdk2 complex when compared with the non-ligated ones. This may be a critical point for the G1 phase and may be the threshold between atrophy or hypertrophy of the corresponding hepatic segment[115,116].

The search for understanding liver regeneration has yielded great progress in recent decades. The process of liver regeneration is studied more than in any other organ and understanding the underlying mechanisms, not only the positive but also potentially negative consequences, can create therapeutic opportunities. In the liver, the various regenerative strategies adopted depend not only on which cellular component is most affected, but also on which pathology is the initial underlying trigger for the injury. The desire to understand liver regeneration to make a difference for our patients has never been more intense.

R E S U M O

A regeneração hepática é um processo de crescimento tecidual altamente organizado e é a reação mais importante do fígado à agressão. Os mecanismos complexos envolvidos neste processo abrangem uma variedade de vias regenerativas que são específicas para os diferentes tipos de agressão. A forma mais estudada de regeneração hepática é aquela que ocorre após a perda de hepatócitos em uma lesão aguda, como no processo regenerativo de roedores após hepatectomia parcial ou administração de produtos químicos lesivos (CCl4, paracetamol, álcool alílico). Estes modelos experimentais revelaram vias de sinalização extracelular e intracelular que são usadas para retornar o fígado ao tamanho e peso equivalentes aos anteriores à lesão. A compreensão do processo de regeneração do fígado é um desafio que se encontra justificado nas inúmeras interações de diferentes componentes celulares, vários fatores mitogênicos (completos e incompletos), vias mitogênicas complexas e proteínas inflamatórias de fase aguda. Hepatócitos, colangiócitos e células progenitoras do fígado provaram ter comportamento regenerativo. As atividades regenerativas de hepatócitos e colangiócitos são tipicamente caracterizadas pela fidelidade fenotípica (multiplicação), no entanto, quando a regeneração normal é frustrada, os hepatócitos e os colangiócitos funcionam como células-tronco facultativas (desdiferenciam) ou se transdiferenciam para restaurar a estrutura normal do fígado. Esta revisão traça o caminho percorrido nas últimas décadas no estudo da regeneração hepática e destaca novos conceitos na área.

Palavras-chave: *Regeneração Hepática. Fígado. Fator de Crescimento de Hepatócito. Hepatócitos.*

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