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Review

Liver Regeneration and its Impact on Post-hepatectomy Metastatic Tumour Recurrence

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Abstract. *Hepatic resection remains the primary potentially curative therapeutic modality for liver metastases. The regenerative process that occurs postoperatively is a complex phenomenon, orchestrated by molecular cascades involving growth factors, cytokines, proteolytic enzymes and other proteins. Unfortunately, some of these molecules, such as hepatocyte growth factor, tumour growth factor beta and matrix metalloproteinases also promote tumour growth and may contribute to the recurrence of liver metastasis. The reactivation of dormant micrometastases or the intrahepatic accumulation of circulating malignant cells has been suggested as the responsible mechanism, although not clearly understood. Current clinical and experimental research has developed inhibitors of several regenerative molecules, attempting to treat tumour reappearance within the liver. Despite the considerable progress of the last decade, multiple queries remain to be clarified concerning liver regeneration, as well as its impact on post-hepatectomy tumour recurrence. This review describes the responsible molecular pathways and the clinical importance of post-hepatectomy liver regeneration, and investigates how the regenerative process may promote metastatic tumour recurrence.*

Metastatic liver tumours are derived predominantly from primary colorectal cancer (CRC). They affect about 30% of patients with CRC and determine its prognosis. Long-term survival is achieved in selected patients by hepatic resection, with five-year survival rates ranging from 20-40% for individuals undergoing hepatectomy for CRC liver metastases. Unfortunately, despite the progress in tumour staging and surgical techniques, local hepatic and/or systemic extrahepatic recurrences occur in the rest of the patients, usually 12 to 18 months postoperatively (1-3). Approximately half of CRC recurrences are limited to the liver and appear earlier than extrahepatic recurrences; the latter mainly affect the lymph nodes and the lungs. The number of metastatic lesions, the stage of primary tumour, the surgical margins and the performance or non-performance of an anatomic resection, may all influence the time and the prognosis of recurrences (4-6).

The performance of hepatectomy for the treatment of liver metastases triggers the process of hepatic regeneration, where numerous cells and molecules mediate multiple molecular pathways. Ample growth factors, which contribute to neoplastic development, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and hepatocyte growth factor (HGF), are also present during liver regeneration. Concurrently, several clinical and experimental studies have suggested that specific molecules which regulate liver regeneration may also promote the outgrowth of residual dormant micrometastases postoperatively, leading to progression of the disease (7, 8). However, the presence of micrometastases and their association with tumour recurrence, the time of the development of new metastatic lesions and the responsible regenerative factors that support neoplastic progression remain only partly understood. Clinical research attempts to discover new therapeutic modalities which could inhibit the initiation of tumour cell proliferation shortly after hepatectomy is performed.

Post-hepatectomy Liver Regeneration

The liver is located in a 'strategic' position, which allows it to function as a filter and a biochemical defence against foreign and toxic chemicals, antigens, bacteria and cells originating from food consumption or the blood circulation.

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Table I. *Simultaneous signalling events that occur after partial hepatectomy.*

Activated biological factor or pathway after partial hepatectomy	Time after partial hepatectomy
Urokinase	5 min
Notch intracellular domain (NICD) translocation to cellular nucleus	5 min
Beta-catenin translocation to cellular nucleus	5-10 min to 6 hours
Hepatocyte growth factor receptor (HGFR)	30-60 min
Epithelial growth factor receptor (EGFR)	30-60 min
Increase of plasma concentration of: Hepatocyte growth factor (HGF), norepinephrine, interleukin 6 (IL-6), tumour necrosis factor alpha (TNFα), transforming growth factor beta 1 (TGFβ1) and hyaluronic acid	1-2 hours
Nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3)	30-60 min
Hepatocyte gene expression reprogramming	30 min
Metalloproteinase 9 (MMP-9)	30 min

Cytokines, growth factors, paracrine and neuroendocrine factors are activated after partial hepatectomy, mainly within the first 60 minutes (12, 13, 45, 52).

The portal vein is its main blood supplier that directly connects the liver with the small and large intestine, the spleen and the pancreas. In addition, the liver regulates protein levels, lipid and carbohydrate concentration, ammonia blood levels and bile production (9-11). Due to this wide array of functions, the liver constitutes a key organ for the body's well-being and it is safeguarded by a unique regenerative ability. This ability has been observed in all vertebrate organisms and it may be stimulated when hepatic mass loss occurs or when the organ is transplanted from small donors to large recipients of the same species (12, 13).

The liver regains its original volume on regeneration, even if 70% of its original mass is resected, with the prerequisite that the remaining tissue is normal and free of disease (14). Hepatic mass loss may be induced by the administration of toxic chemical compounds, such as carbon tetrachloride, although partial hepatectomy (PHx) of 2/3 of the liver parenchyma is the most popular experimental model for the study of liver regeneration in rodents (15, 16). PHx triggers a sequence of molecular and cellular events within almost 5 minutes of initiation that continues for several days. The cells responsible for liver regeneration and tissue repair are mature hepatocytes and biliary epithelial cells; although other parts of liver parenchyma may contain and activate stem cells (17). *In vivo* experiments on rodents reported that hepatocyte regeneration starts within approximately 24 hours and biliary cells follow a little later. Moreover, it was revealed that progenitor cells, such as oval cells, contribute substantially to liver regeneration, when hepatocytes are inhibited from acting or become exhausted (18). Progenitor cells eventually transform into hepatocytes or biliary epithelial cells (17). Notably, sinusoidal cells, such as stellate, Kupffer and sinusoidal endothelial cells also participate actively in the process, which resembles wound healing and tumour progression (Figure 1). However, sinusoidal cells replicate in a delayed fashion, compared to the hepatocytes (19).

Accumulating evidence suggests that considerable hemodynamic changes occur following hepatectomy, even in the absence of blood extravasation. The arterial supply through the hepatic artery appears to remain unaffected, although the portal supply per unit of liver tissue triples; the portal vein flow in the hepatic sinusoids elevates the blood pressure and causes decreased oxygen levels within the liver (20, 21). Similarly, the concentration of intestinal and pancreatic nutrients, including aminoacids, carbohydrates, lipids, insulin, toxins, growth factors and numerous cytokines are increased three fold in a 2/3 hepatectomy (13).

Interestingly, when a hepatectomy is performed, more than 100 genes, inactivated in the normal liver, are expressed rapidly leading to activation of multiple biological factors (Table I) (22, 23). HGF, stored in liver matrix in large quantities but also traced in other organs, is rapidly diminished 1-2 hours after PHx, while its plasma levels substantially increase by 10- to 20-fold. In general, there is no agreement that a single agent alone can lead to liver regeneration; however, HGF is considered to be the primary contributor as its receptor (cMet) is activated early in the process, exerts significant mitotic action on hepatocytes and triggers multiple biological events during regeneration, such as massive liver enlargement (24-26). EGF is produced by duodenal Brunner's glands and constantly supplies the liver through the portal vein; its receptor is also activated soon after hepatectomy and enhances regeneration. Recent experiments on rodents indicated its important and supportive regenerative action, in conjunction with the one exerted by HGF on hepatocytes (27, 28).

Tumour necrosis factor (TNF) plasma levels increase after PHx and contribute to early regenerative events *via* altered integrin signalling, induction of metalloproteinase 9 (MMP-9) expression by hepatocytes and activation of tumour growth factor alpha (TGFα) (29-31). Rodents with genetic deletion of TNF receptor 1 show slow or deficient regenerative ability after PHx (32). Moreover, the activation of MMP-9 that occurs within 30 minutes after liver resection causes matrix remodelling, affecting signalling through

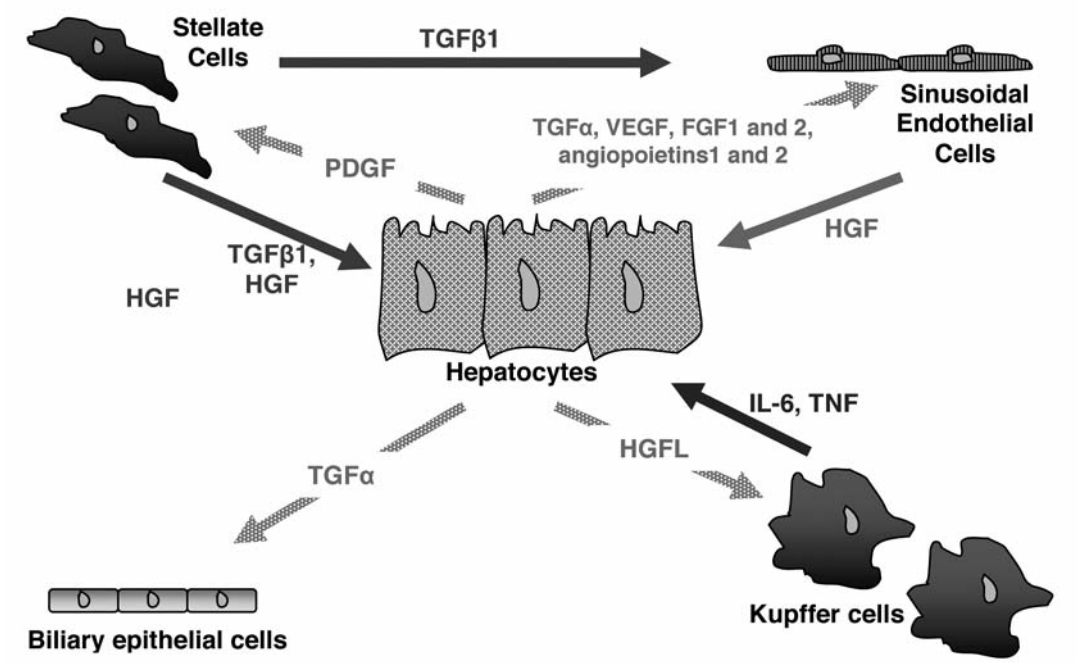

Figure 1. *Hepatic cell interactions during liver regeneration. HGF: Hepatocyte growth factor, HGFL: hepatocyte growth factor-like protein, TGF: tumour growth factor, FGF: fibroblast growth factor, TNF: tumour necrosis factor, IL-6: interleukin 6, VEGF: vascular endothelial growth factor, PDGF: platelet-derived growth factor (13, 52).*

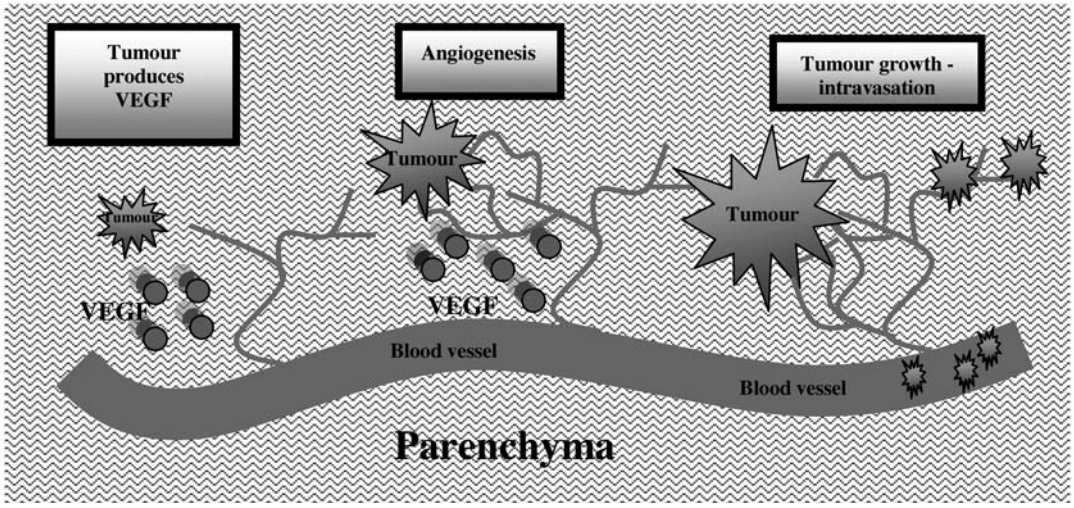

Figure 2. *The role of vascular endothelial growth factor (VEGF) in tumour progression. VEGF provokes neoangiogenesis, tumour growth and metastasis.*

integrins and releasing bound growth factors and peptides which promote the regenerative process (33, 34). Matrix alterations are also regulated through urokinase plasminogen activator (uPA), whose activity increases very early over the entire tissue of the remnant organ. Plasminogen is promptly converted to plasmin and fibrinogen degradation products appear (35, 36). Furthermore, platelets, containing HGF, TGFα and serotonin appear to play a crucial role in liver regeneration (37). Interestingly, serotonin exerts a regulatory activity on hepatocyte proliferation, creating a unique synergy among a biological molecule (serotonin), a corpuscle (platelet) and an organ (liver) (38, 39).

TGFβ1 is produced primarily by stellate cells, although it may be traced in most tissues (40). It exerts mito-inhibitory activity and hinders hepatocyte proliferation, suppresses urokinase expression, as well as HGF expression and activation (40, 41). Extracellular matrix (ECM) remodelling following PHx causes a massive release of TGFβ1 in the circulation, where this molecule is inactivated *via* its connection with alpha 2-macroglobulin (42). TGFβ1 in association with activin are considered very important factors in the termination of liver regeneration (43, 44).

Normal liver weight is re-established postoperatively within one week of PHx in rodents and 8 to 15 days in humans (13). Regenerated hepatic lobules are considerably larger and the hepatocyte layers are twice as thick, compared to the normal parenchyma. The lobes are slowly reorganised and, after several weeks, hepatic histology is completely restored (45, 46). Nevertheless, clinical data shows that liver regeneration is significantly impaired in damaged livers due to viral hepatitis. This could be attributed to a declined response of injured hepatocytes to cytokines (47).

Hepatectomy Promotes Metastatic Tumour Recurrence

Multiple clinical studies on patients with metastatic hepatic lesions report that tumour growth is stimulated by major hepatectomies (6, 48, 49). Moreover, other interventional strategies, aiming at reducing the tumour burden, such as portal vein embolisation or two-stage hepatectomy, trigger liver regeneration and may also induce the recurrence of the disease (50-52). The growth of normal liver and metastases was investigated in a series of 556 hepatectomised patients with malignant lesions, 48 of whom underwent portal vein embolisation preoperatively (53). It was concluded that the metastatic growth was significantly more rapid than that of normal parenchyma, although the growth rate varied widely. The variations depended on the patients, the location of the tumours within the liver, their size and number.

The performance of anatomic resections, following liver segments, has been demonstrated to increase patient survival, due to wider and clear surgical margins, limited vascular distribution and lower recurrence rates (54). However, the preservation of hepatic parenchyma should also be emphasised, as it contributes to prompt and effective liver regeneration (54, 55). Therefore, the decision to undertake a potentially curable aggressive resection in colorectal liver metastases should always take into consideration the benefits of a more conservative approach, which would permit future repeated metastasectomies (5).

Bilobar CRC metastases constitute a therapeutic challenge and the combination of portal vein occlusion and two-stage hepatectomy is usually the preferred approach (56). However, multiple clinical evidence indicates that portal vein occlusion triggers accelerated tumour growth due to increased tumour cell division, causes high levels of cytokines, such as HGF, and alters blood supply (57). Radiofrequency ablation (RFA) may provide a reliable treatment of this high tumour progression in the non-occluded liver portion, through the destruction of small neoplasms, during the interval between portal occlusion and hepatectomy. Interestingly, it has been reported that RFA does not induce increased tumour growth and has no effect on liver regeneration (58, 59).

Neo-adjuvant chemotherapy is considered mandatory in cases of bilobar disease, as both the preferred therapeutic modalities are associated with liver regeneration that enhances the growth of CRC metastases (60, 61). It has to be noted though that while chemotherapy increases resectability, it also affects liver function. Steatohepatitis is a chemotherapy-associated risk that may cause hepatic failure and death. Concurrently, highly effective chemotherapy may increase survival and hence indirectly contribute to the formation of new metastases (62). Mentha *et al*. studied 23 patients who were subjected to the chemotherapy treatment for bilobar disease and revealed the presence of a dangerous halo (an area at the periphery of metastasis of proliferating tumour cells) in half of the patients, which increased after the first operation, despite the initial administration of systemic chemotherapy. Results from this study suggested that this dangerous halo should be taken into consideration during the first operation, and should be resected through aggressive surgery aiming at a wider than 1 mm resection margin (63).

Accelerated residual tumour growth has also been observed in children with malignant embryonal hepatoblastoma, who were treated with partial hepatectomy. Interestingly, HGF was intratumourally produced and reached high serum levels after surgery. It was suggested that this growth factor facilitated hepatoblastoma recurrence (64).

The above clinical data have also been confirmed through various experimental studies on laboratory animals. Rat experiments showed that 70% hepatectomies induced considerable hypertrophy in the remnant liver (65). However, regenerative hepatotrophic agents enhanced the growth of remaining micrometastases, leading to recurrence. Using a tumour model in rats and nude mice, Man *et al*. (66). studied the positive effect of ischemia-reperfusion during hepatectomy on tumour growth and recurrence. Cell adhesion, cell migration and angiogenesis were reported to be the responsible molecular pathways. Experimental data from partial hepatectomies performed on mice suggests that pro-inflammatory cytokines are involved in metastatic recurrence. The increased expression of TNFα, interleukin 1 beta (IL-1β) and IL-6 has been discovered to correlate with increased malignant cell proliferation (67). Murine studies, where partial hepatectomies of 37 or 70% have been performed indicate that

the recurrence of hepatic metastases, as well as systemic tumour progression, occur mainly in the late phase of liver regeneration, rather than the early one. Additionally, major resections appear to influence significantly neoplastic growth and the extent of extrahepatic lesions, predominantly in the lungs, comparing with minor surgery (8). The influence of portal vein ligation in metastatic recurrence has also been examined in a rat model (68). This technique provoked hepatic tissue atrophy up to 25% and caused the increased expression of numerous genes which are implicated in tumour growth.

Molecules Implicated in Liver Regeneration that may Enhance Metastatic Recurrence

The metastatic tumour recurrence after liver resection may be attributed to circulating cancer cells and/or dormant micrometastases. Multiple clinical and experimental studies have demonstrated that diagnostic and therapeutic interventions such as colonoscopy, tumour manipulation or operative resection cause significant release of viable tumour cell in the systemic circulation (69-72). Furthermore, experimental data on rodents revealed that 10^5 to 10^6 malignant cells per gram of tumour tissue (pulmonary, mammary or colon adenocarcinoma) might be shed into the systemic circulation every 24 hours. This cell liberation occurs mainly when the neoplasms commence angiogenic processes and induce the development of metastases (73-75). In contrast, micrometastases observed in liver remnants of hepatectomised patients cause increased rates of tumour recurrence (76). As histological techniques usually show limited sensitivity in detecting micrometastases, genetic methods are currently tested in animal models, attempting to reveal early and accurately the existence of micrometastatic lesions (77).

Despite the fact that they attract great research interest, micrometastases remain only partly explained. They may reside in proximity to the main metastases or they may originate from the bone marrow. The state of dormancy potentially occurs through the balance between proliferation and apoptosis, and may be regulated by a variety of molecules, including angiogenic factors (vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1 alpha (HIF1α)), immunological factors (HLA class I antigens), growth factors (EGF) and matrix proteins (thrombospondin); also by oncogenes, metastasis suppressor genes and phenotypic characteristics (low levels of Ki-67) (78-80). Interestingly, hepatectomy causes major alterations in growth factors and cytokines, changing the environment of dormant micrometastases and probably leading to their activation. Concurrently, the matrix breakdown perioperatively and the regenerative process that follows, may promote tumour cell detachment and migration within the liver remnant or the systemic circulation, enhancing intra- or extrahepatic tumour recurrence.

Certain molecules mediating liver regeneration are considered to play a significant role in tumour recurrence and have been studied by multiple research groups (52). HGF, EGF, VEGF, TGF-β1 and MMPs attract great interest among numerous other agents that also pertain to the regenerative process.

HGF is chiefly produced and released by stellate, sinusoidal endothelial and Kupffer cells (81, 82). It acts through a tyrosine kinase receptor that is encoded by c-Met protooncogene and exerts mitogenic effects on hepatocytes and other cells, as well as morphogenic and angiogenic effects on normal and neoplastic cells. Additionally, HGF stimulates tumour infiltration and migration *via* augmented MMP activity. Proteinase activity under HGF influence may cause breaches in the basement membrane and facilitate metastases (83, 84). Research on human tissue reveals that high expression of HGF receptor was associated with Dukes' C CRC and high metastatic potential, suggesting its efficacy as a metastatic marker (85). Experimental data on mice showed that CRC liver metastases are suppressed by genetically promoting the expression of an HGF antagonist (86). Clinical studies on patients subjected to hepatic resection for CRC metastases report that the plasma levels of HGF, along with VEGF, in the early postoperative period correlated with high tumour recurrence (7). Therapeutic exploitation of HGF inhibition against tumour growth has lead to the development of antibodies and inhibitors, which are currently being tested in animal models (87, 88). The potential appears significant for the treatment of many cancer types, but the multifunctional character of this growth factor makes the clinical trials particularly challenging and demanding.

EGF functions through a tyrosine kinase receptor of the ErbB family. This receptor mediates the activity of numerous other ligands also involved in liver regeneration, such as TGF-α and amphiregulin (89). Clinical and experimental studies correlated the levels of EGF receptor and its ligands with increased colon liver metastasis, malignant cell motility and proliferation, as well as angiogenesis *via* VEGF up-regulation (90-93). The synthesis of EGF receptor antagonists has been successful and the United States Food and Drug Administration has approved two drugs, cetuximab (Erbitux) and panitumumab (Vectibix), for clinical use, while many others are under clinical or experimental investigation (94). Cetuximab is an IgG1 monoclonal antibody that is currently used against metastatic CRC in monotherapy or in combination with other agents and panitumumab is an IgG2 monoclonal antibody approved as a single agent for metastatic CRC.

VEGF is considered the initial regulator of angiogenesis and vascular permeability. It constitutes a protein family of 5 members and appears to be present in a wide variety of tumours mediating the formation of neovessels. It is up-regulated approximately 2 hours after PHx and remains

increased throughout the regenerative process (13). VEGF is expressed in colorectal, liver, breast, gastrointestinal, lung, ovarian, bladder, uterus and intracranial cancer (95). Several studies have indicated that this growth factor promotes tumour vascularity, chemoresistance and the development of metastasis (96) (Figure 2). Numerous antiangiogenic agents have been developed against various tumour types and several others are under clinical investigation. Bevacizumab (Avastin), a monoclonal antibody, is approved for treatment of metastatic CRC and sunitinib, a tyrosine kinase inhibitor, for gastrointestinal stromal tumours. However, it appears that current drugs of this category show a limited efficacy as monotherapy and thus are used in combinational chemotherapy. Another issue is the vascular disturbances caused in normal tissues by anti-VEGF agents (97, 98).

TGF-β1, also up-regulated during liver regeneration, promotes the formation of tumour stroma, angiogenesis and immunosuppression. It further contributes to colon metastasis facilitating adhesion molecule expression, such as the integrins (99, 100). Hayashi *et al*. studied resected CRC metastatic liver tumours and observed high expression of TGF-β1 at the interface between the lesions and the hepatic parenchyma. This expression induced hepatocyte apoptosis and was suggested as a potential mechanism of tumour development (101). Clinical studies by Tsushima *et al*. measuring the plasma levels of this factor in patients with CRC, not only correlated TGF-β1 with the extent of the disease, as was previously indicated *via* tissue measurements (102), but also suggested its efficacy to predict liver metastasis, if measured two weeks following a potential curative resection (103). TGF-β1 inhibition was targeted in anticancer therapy and many chemical compounds are being tested in preclinical and clinical studies (104). It should be noted though that the function of this growth factor is dual and any pharmaceutical inhibition of TGF-β1 should retain its growth-inhibitory and apoptotic activity (105).

The collagenous structure of the ECM and the dynamic balance between fibrogenesis and fibrolysis are very important for tumour growth (106). MMPs mediate these molecular pathways and are implicated in cancer cell migration. They compose a family of 24 zinc endopeptidases, which not only degrade the ECM, but also non-matrix proteins. MMP-9 is up-regulated within the first 30 minutes following PHx, while MMP-2 after 12 hours and play a crucial role in liver regeneration. Multiple studies implicate both molecules in CRC progression and liver metastasis (107-109). The development of MMP inhibitors continues to attract substantial research interest: many molecules have been produced and tested, but only one has been approved for dental clinical applications (110, 111).

Conclusion

Tumour recurrence after hepatic resection for the treatment of liver metastases is a major clinical problem, as it affects approximately 50% of these patients and results in high mortality. The accumulated evidence suggests that liver regeneration stimulates tumour reappearance *via* circulating malignant cells and/or the stimulation of dormant residual micrometastases. Certain growth factors, cytokines and other molecules involved in numerous regenerative molecular pathways, including angiogenesis and ECM remodelling, are considered responsible for stimulating tumour cell outgrowth. There are research-based attempts to prevent their activity through antibodies and inhibitors, some of which are currently clinically used in anticancer treatment.

Despite the fact that multiple studies have elucidated certain aspects of liver regeneration and its impact in post-hepatectomy tumour recurrence, many underlying processes remain poorly understood. It is suggested that molecules regulating the late phase of liver regeneration may be the key factors in disease progression and thus therapeutic applications should target them, without affecting the early phase of the regenerative process. Many new data will appear in the near future as numerous studies and clinical trials are near completion, which may contribute to further understanding and treatment of liver metastatic recurrence.

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