Application of HGF-Based Liver Injury Repair in TACE Treatment for Hepatocellular Carcinoma

Ailin Li *

Department of Biomedical Engineering, Southern University of Science and Technology, Shenzhen, China

* Corresponding Author Email: 12413053@mail.sustech.edu.cn

Abstract. Trans arterial chemoembolization (TACE) is a widely used interventional therapy for hepatocellular carcinoma (HCC) which combines localized chemotherapy and embolization to block tumor blood supply while delivering chemotherapeutic agents directly to tumor cells. It reduces tumor volume, and prolongs patient survival. However, it may cause acute liver injury due to ischemic insult and chemotherapeutic toxicity. To preserve structural integrity failure rapid restoration of hepatocyte function post-TACE and inhibition of fibrosis in non-tumor liver tissue is of great importance. Currently, no standardized treatment exists for TACE-induced liver damage, and symptom-based whose effects are limited. This study explores the therapeutic potential of hepatocyte growth factor (HGF) in promoting liver repair post-TACE. HGF, secreted primarily by Kupffer and stellate cells, binds to the c-Met receptor, activating key pathways such as ERK and AKT, which drive hepatocyte proliferation and suppress fibrogenesis. Exogenous HGF enhances regenerative processes while synergizing with cytokines such as EGF, VEGF, and IL-6. Preclinical evidence supports its role in improving liver regeneration rates. Although HGF poses potential pro-tumor risks, combination strategies with c-Met inhibitors or timed sequential administration may mitigate oncogenic signaling. Thus, adjunctive HGF therapy represents a promising approach to facilitate liver recovery after TACE.

Keywords: TACE, HGF, hepatocellular carcinoma, liver repair.

1. Introduction

Transarterial Chemoembolization (TACE) combines localized chemotherapy and embolization to block tumor blood supply while delivering chemotherapeutic agents directly to tumor cells which reduces tumor volume, and prolongs patient survival [1, 2]. However, the treatment must balance these benefits against potential damage to healthy liver tissue. Therefore, by demonstrating the promotive effect of exogenous supplementation of HGF (hepatocyte growth factor) on liver injury repair, this study validates the feasibility of combining HGF with TACE and offers a novel strategy for liver regeneration.

2. Significance of Exogenous HGF

2.1. Hepatic Regeneration and Repair

Exogenous hepatocyte growth factor (HGF) binds to the c-Met receptor on hepatocytes, activating intracellular signaling pathways such as PI3K/Akt and MAPK/ERK [3, 4]. This could promote hepatocyte proliferation and suppress apoptosis. Simultaneously, hepatic stellate cell (HSC) activation will be inhibited by HGF thus TGF-β1 and PDGF signaling will be downregulated. Which could reduce extracellular matrix (ECM) deposition [5]. Additionally, HGF upregulates matrix metalloproteinases (MMPs) while inhibiting tissue inhibitors of metalloproteinases (TIMPs) to enhance ECM degradation and facilitate structural reconstruction of the liver.

2.2. Broad Applicability

HGF/c-Met signaling is a highly conserved pathway that plays a central role in liver repair, regardless of the underlying cause [6]. Its function doesn't rely on specific disease triggers, targeting

universal repair mechanisms such as cell proliferation and fibrosis reversal. This adaptability makes it suitable for patients with varying clinical backgrounds.

2.3. Mitigating Risks

For patients lack of sufficient endogenous HGF, exogenous HGF supplementation ensures sustained activation of regenerative pathways. This prevents delayed repair, reduces, necroinflammation, and lowers the risk of portal hypertension and hepatic encephalopathy [5]. Supporting timely regeneration largely improves survival and quality of life.

3. Mechanisms of HGF in Promoting Liver Repair

3.1. Synthesis and Release of HGF

Hepatocyte growth factor (HGF), as a critical factor in liver regeneration process, is a pleiotropic cytokine which is synthesized and activated to involve a precisely regulated multi-step process. Pro-HGF secreted by non-parenchymal cells in the liver is the inactive precursor, including hepatic stellate cells (HSCs), Kupffer cells, and sinusoidal endothelial cells [3, 7]. These cells are activated in response to liver injury signals, such as inflammatory cytokines, oxidative stress, or tissue damage. Mediated by HGF activator (HGFA) and urokinase-type plasminogen activator (uPA) upregulated in the injured liver, accumulation of the inactive pro-HGF precursor in the extracellular matrix (ECM) precedes its activation through proteolytic cleavage [3]. UPA converts plasminogen into plasmin, activating HGFA. Activated HGFA breaks the Arg494-Val495 bond of precursor HGF, generating mature and active heterodimeric HGF protein.

Active HGF binds with high affinity to the c-Met receptor, a tyrosine kinase receptor highly expressed on hepatocytes. This binding induces c-Met dimerization and autophosphorylation, initiating downstream signaling cascades. There are three key pathways. PI3K/Akt pathway promotes cell survival and inhibits apoptosis by phosphorylating Bad (a pro-apoptotic protein) and activating NF-κB [4]. MAPK/ERK pathway stimulates cell cycle progression by activating transcription factors such as c-Fos and c-Jun [4, 7]. STAT3 pathway enhances proliferation and metabolic adaptation. These signals collectively drive hepatocyte proliferation, suppress cell death, and initiate tissue repair (as shown in Fig.1) [3, 4].

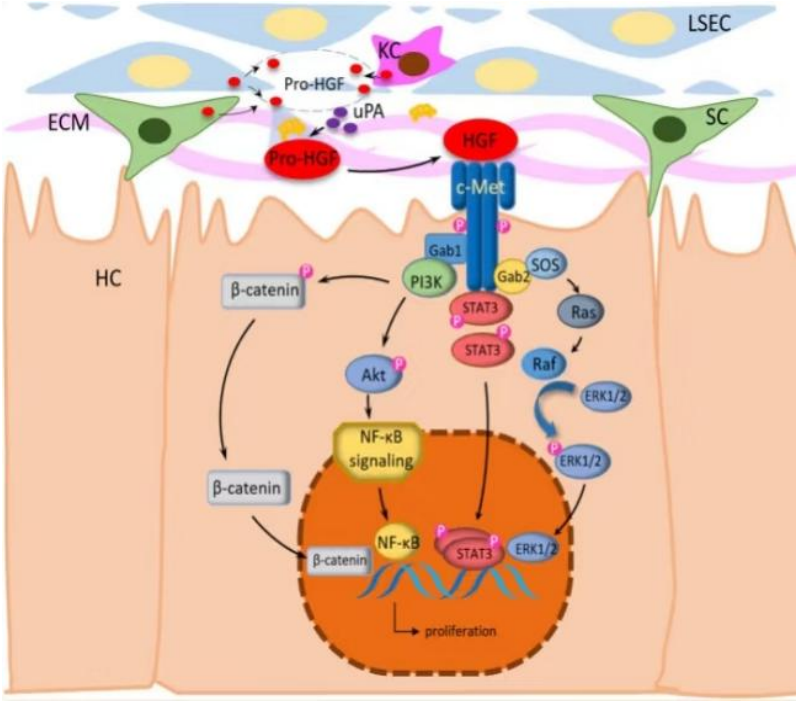

Figure 1. Process of synthesising and releasing of HGF

3.2. Liver Regeneration Process

3.2.1. Initiation phase

Transarterial chemoembolization (TACE) induces controlled ischemic and chemical injury, triggering a robust regenerative response. Within hours, Kupffer cells and endothelial cells release pre-formed pro-HGF, which is rapidly activated by uPA/HGFA. Active HGF binds to c-Met receptors on hepatocytes, initiating downstream signaling. Currently, injury-associated inflammation leads to the release of cytokines such as TNF-α and IL-6 from Kupffer cells [7, 8]. These cytokines activate transcription factors like NF-κB and STAT3, which prime hepatocytes enter the cell cycle. The combined action of HGF and inflammatory cytokines drives quiescent hepatocytes (in G0 phase) into the G1 phase (pre-replicative state). This phase is characterized by three steps. Firstly, upregulation of immediate-early genes. Secondly, increased expression of cyclins (e.g., Cyclin D1) and cyclin-dependent kinases [7, 9]. Thirdly, metabolic reprogramming to support energy and biosynthetic demands.

3.2.2. Proliferation phase

During this phase, hepatocyte proliferation peaks. The HGF/c-Met pathway plays a central role by sustaining the expression of Cyclin D1, which forms a complex with CDK4/6 to phosphorylate retinoblastoma (Rb) protein [9]. Phosphorylated Rb releases E2F transcription factors, enabling the transition from G1 to S phase (DNA synthesis phase). There are several key events as below:

(1) DNA replication: Hepatocytes undergo symmetric division, replenishing lost parenchymal mass.

(2) Angiogenesis: HGF and VEGF promote the formation of new blood vessels to support regenerative tissue [7].

(3) ECM remodeling: MMPs (e.g., MMP-9) degrade fibrotic matrix, facilitating hepatocyte expansion.

(4) Liver volume increases significantly, and functional markers (e.g., albumin synthesis, detoxification capacity) gradually recover.

3.2.3. Termination phase

Liver regeneration is a self-limiting process. As parenchymal mass restores, inhibitory mechanisms become dominant. TGF-β1, produced by activated HSCs and immune cells, emerges as a key regulator of termination [8]. It is able to suppresses HGF expression and c-Met signaling, upregulates cell cycle inhibitors (e.g., p15, p21) and promotes ECM deposition to stabilize tissue architecture. Other factors, such as activin A and IL-1β, also contribute to halting proliferation. This ensures that regeneration ceases once functional liver mass is achieved, preventing uncontrolled growth or fibrosis (shown as Fig.2) [2, 8].

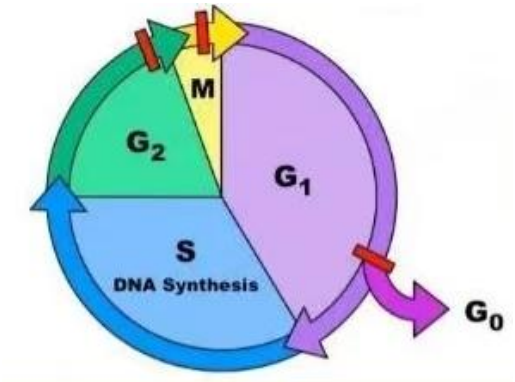

Figure 2. Picture of cell cycle

4. Synergistic Effects of HGF with Other Factors in Liver Repair

Hepatocyte Growth Factor (HGF) does not function in isolation but collaborates synergistically with multiple cytokines and growth factors to enhance liver regeneration. This cooperative network significantly improves the efficiency and comprehensiveness of hepatic repair.

4.1. Epidermal Growth Factor (EGF)

EGF works in concert with HGF to amplify hepatocyte proliferation through co-activation of the ERK/MAPK signaling pathway. This synergistic interaction accelerates the transition of hepatocytes from G0 to G1 phase and shortens the cell cycle duration, thereby enhancing the overall regenerative response.

4.2. Vascular Endothelial Growth Factor (VEGF)

VEGF complements HGF's actions by specifically promoting the repair and regeneration of sinusoidal endothelial cells. This cooperative effect improves hepatic microcirculation to ensure adequate oxygen and nutrient supply in regenerating tissues, and supports the angiogenesis necessary for successful liver reconstruction.

4.3. Interleukin-6 (IL-6)

The priming effect of IL-6, which enhances hepatocyte responsiveness to HGF via STAT3 pathway activation, upregulates anti-apoptotic genes and promotes survival mechanisms to optimize the regenerative response. This synergy between HGF and associated cytokines establishes a potent regenerative microenvironment, accelerating both structural and functional liver recovery. Such multi-factorial cooperation underscores the complexity of liver regeneration and points to the therapeutic promise of simultaneously targeting multiple pathways for improved repair outcomes.

4.4. Comparison of HGF and EGF in Repair Functions

Hepatocyte growth factor (HGF) and epidermal growth factor (EGF) have significant differences in their mechanisms and efficacy when playing roles in liver. In terms of target specificity, the specificity of HGF for the c-Met receptor is high, conferring selective action, while EGF's specificity is lower, limited by the broad tissue distribution of EGFR. In term of hepatocyte proliferation efficiency, HGF is the most efficient stimulator which promotes rapid cell cycle entry and division. In contrast, EGF shows a weaker effect on hepatocyte proliferation [10].

HGF is able to synergize with inflammatory cytokines such as TNF-alpha and IL-6, enhancing the regenerative response during liver injury. However, EGF does not demonstrate significant synergistic effects with these cytokines. In angiogenesis support, HGF contributes to microcirculation repair through VEGF activation, while EGF has no direct effect on blood vessel formation. In anti-apoptotic effects, through PI3K/Akt pathway activation, HGF significantly inhibits hepatocyte cell death while EGF provides only limited protection against apoptosis. These functional comparisons highlight HGF's superior efficacy in liver regeneration through its targeted action, synergistic capabilities, and multi-mechanistic approach to repair.

5. Therapeutic Efficacy and Clinical Translation

5.1. Findings and Implications

Preclinical and clinical evidence indicates that HGF pretreatment improves liver regeneration rates by 30–50% and substantially reduces liver injury following TACE [11, 12]. This protective effect can be explained by the dual mechanisms of HGF: it not only stimulates hepatocyte proliferation but also inhibits key fibrotic pathways. The observed robustness of the regenerative response further underscores the therapeutic promise of HGF and supports the rationale for progressing to larger

clinical trials. Together, these findings highlight the potential of HGF-based interventions to enhance clinical outcomes in TACE patients, especially those with limited regenerative reserve.

5.2. Safety and Clinical Revelance

Clinical trials have demonstrated a favorable safety profile for recombinant human HGF (rh-HGF) in patients with cirrhosis, with no severe adverse events reported [12]. Importantly, its capacity to promote regeneration without worsening fibrosis or portal hypertension highlights its clinical potential. These findings collectively support rh-HGF as a promising therapeutic strategy for promoting liver repair after TACE, particularly in high-risk patients with advanced disease.

6. Potential Risks

The pro-tumor risks associated with HGF/c-Met signaling arise from the shared mechanisms between its physiological roles in tissue repair and processes driving tumorigenesis. Under physiological conditions, HGF promotes hepatocyte proliferation and tissue repair by activating the c-Met receptor. However, in pathological contexts, this pathway may be exploited by tumor cells. Specific mechanisms include several types. Direct pro-proliferative effects shows that the MAPK/ERK and PI3K/Akt pathways activated by HGF are not only critical for normal cell regeneration but also central to the proliferation of many tumor cells [13, 14]. HGF are able to induce epithelial-mesenchymal transition (EMT) which can enhance the invasive and mobility potential of tumor cells [13]. It also upregulates matrix metalloproteinases (MMPs), facilitating degradation of the ECM and promoting metastatic spread [13]. Providing angiogenesis support by stimulating VEGF expression, HGF provides essential nutrients for tumor growth [13]. Based on the possibility of accelerating tumor progression via oncogenic pathway activation, HGF therapy is a significant concern in patients with subclinical tumors or a history of hepatocellular carcinoma [13, 14]. This risk profile necessitates careful patient selection and monitoring, especially in those with prior malignancies. Risk mitigation strategies include combination therapy with c-Met inhibitors that block pro tumor signals (such as cabozantinib), or timed administration during the acute repair phase to reduce long-term exposure. Strictly excluding patients with active malignant tumors must be a key measure

7. Optimization

To maximize the therapeutic potential of HGF while mitigating associated risks, several strategic approaches are proposed.

7.1. Combination Therapy with c-Met Inhibitors

Co-administering HGF with selective c-Met inhibitors (e.g., cabozantinib) may help decouple its regenerative effects from oncogenic signaling [13, 15]. This strategy aims to spatially or temporally block c-Met activity within tumor-prone microenvironments. Consequently, repair pathways in healthy tissue could be selectively activated while potential tumorigenic signals are suppressed.

7.2. Timed and Sequential Administration

Limiting HGF administration to the acute phase following TACE (e.g., within 72 hours) is recommended, as regenerative demand peaks during this period while the risk of tumor stimulation remains relatively low. Employing a short-term, high-dose pulse regimen followed by rapid cessation could optimize liver repair while minimizing risks associated with prolonged exposure.

7.3. Patient Stratification and Monitoring

Strict inclusion criteria should exclude patients with active malignancies, unexplained elevated AFP levels, or recent HCC recurrence. Regular monitoring via imaging, biomarker profiling (e.g.,

AFP, PIVKA-II), and circulating tumor DNA (ctDNA) analysis can help detect early signs of tumor activation.

7.4. Formulation and Delivery Innovations

Developing targeted delivery systems—such as HGF-loaded nanoparticles or liposomes—could enhance localization to injured liver regions, reducing systemic exposure and off-target effects. Alternatively, engineered HGF variants with reduced affinity for c-Met in tumor contexts may offer a safer profile.

7.5. Synergistic Cytokine Cocktails

Combining HGF with other regenerative cytokines (e.g., IL-22, FGF21) may lower the required HGF dose. This approach can reduce risks but still maintain efficacy. Also, these combinations might use complementary mechanisms to improve the overall repair effect.

8. Conclusion

Providing good tumor control and survival benefits, trans arterial chemoembolization is a vital treatment for hepatocellular carcinoma (HCC). However, its applications are limited by acute liver injury caused by ischemic insult and chemotherapeutic toxicity. Hepatocyte growth factor (HGF) is of great importance for reducing TACE-induced liver damage and promoting regeneration. To activate key pathways such as PI3K/Akt and MAPK/ERK, HGF binds to the c-Met receptor, leading to hepatocyte proliferation, less apoptosis, and reduced fibrosis. HGF can further synergize with cytokines such as EGF, VEGF, and IL-6 to promote cell regeneration and help the liver restore its original structure and function. Both in-vitro research and clinical studies show that adding external HGF can increase liver regeneration rates, and have the potential as supportive therapy after TACE. Despite thesea chievement, it is significant that the pro-tumor risks linked to HGF/c-Met signaling should be considered. The pathways of helping regeneration may also encourage tumor cell growth and migration. In conclusion, although HGF therapy is a major advance for liver repair, it is necessary to carefully manage its application scope and methods to balance treatment benefits with potential cancer risks.

References

[1] Llovet, J. M., & Bruix, J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology, 2003, 37 (2), 429 – 442.

[2] Reig, M., Forner, A., Rimola, J., et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. Journal of Hepatology, 2022, 76 (3), 681 – 693.

[3] Michalopoulos, G. K. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. The American Journal of Pathology, 2010, 176 (1), 2 – 13.

[4] Nakamura, T., & Nishizawa, T. Hepatocyte growth factor: from diagnosis to clinical applications. Clinica Chimica Acta, 2013, 327, 1 – 23.

[5] Kisseleva, T., & Brenner, D. Molecular and cellular mechanisms of liver fibrosis and its resolution. Nature Reviews Gastroenterology & Hepatology, 2021, 18 (3), 151 – 166.

[6] Matsumoto, K., & Nakamura, T.HGF and liver regeneration: From discovery to clinical trials. Journal of Gastroenterology and Hepatology, 2018, 33 (4), 791 – 799.

[7] Taub, R. Advances in liver regeneration: Revisiting the role of cytokines and growth factors. Cellular and Molecular Gastroenterology and Hepatology, 2021, 11 (3), 747 – 763.

[8] Tacke, F. Liver regeneration in acute-on-chronic liver failure: mechanisms and therapeutic opportunities. Nature Reviews Gastroenterology & Hepatology, 2022, 19 (12), 785 – 801.

[9] Paranjpe, S., et al. Cell cycle effects resulting from inhibition of hepatocyte growth factor and its receptor c-Met in regenerating rat livers by RNA interference. Hepatology, 2016, 45 (6), 1471 – 1477.

[10] Llovet, J. M., et al. Hepatocellular carcinoma. Nature Reviews Disease Primers, 2021, 7 (1), 6.

[11] Xiang, D., et al. Hepatocyte growth factor promotes liver regeneration after trans arterial chemoembolization in rats. Journal of Cellular and Molecular Medicine, 2020, 24 (2), 1762 – 1772.

[12] Wang, K., et al. Recombinant human hepatocyte growth factor (rh-HGF) for liver cirrhosis: a phase II randomized controlled trial. Hepatology International, 2023, 17 (1), 198 – 210.

[13] Goyal, L., Muzumdar, M. D., & Zhu, A. X. Targeting the HGF/c-MET pathway in hepatocellular carcinoma. Clinical Cancer Research, 2013, 19 (9), 2310 – 2318.

[14] Ogunwobi, O., et al. Hepatocyte growth factor upregulation promotes carcinogenesis and epithelial-mesenchymal transition in hepatocellular carcinoma via Akt and COX-2 activation. American Journal of Cancer Research, 2020, 10 (4), 1157 – 1172.

[15] Rimassa, L., et al. Tivantinib for second-line treatment of MET-high hepatocellular carcinoma: a phase III randomized clinical trial. The Lancet Oncology, 2019, 20 (5), e267 – e278.