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The role of hepatocyte growth factor/c-mesenchymal to epithelial transition (HGF/c-Met) signaling pathway In Hepatocellular Carcinoma (REVIEW)

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ABSTRACT
Hepatocellular carcinoma (HCC) is a one of the most common causes of cancer-related deaths, with complex molecular pathogenesis and interactions. Among these, the hepatocyte growth factor (HGF) and its receptor c-Mesenchymal to epithelial transition (c-Met) have garnered attention for their critical roles in liver biology. Under physiological conditions, the HGF/c-Met signaling aids in tissue repair, regeneration, and homeostasis.

Keywords: hepatocyte, critical, interactions, liver

INTRODUCTION

Hepatocellular carcinoma (HCC) is a one of the most common causes of cancer-related deaths, with complex molecular pathogenesis and interactions. Among these, the hepatocyte growth factor (HGF) and its receptor c-Mesenchymal to epithelial transition (c-Met) have garnered attention for their critical roles in liver biology. Under physiological conditions, the HGF/c-Met signaling aids in tissue repair, regeneration, and homeostasis. However, in HCC, the pathway frequently becomes dysregulated, enabling aggressive tumor traits such as proliferation, invasion, and metastasis. Current research reveals that alterations in HGF/c-Met expression or activity are common in HCC and correlate with unfavorable clinical outcomes. As a result, dissecting this signaling axis offers pivotal insights for therapeutic strategies and potential biomarkers of disease progression in HCC. This review examines the underlying mechanisms further.

Historical Perspective

Research on liver cell regeneration in the mid-1980s greatly advanced our understanding of growth factors that govern hepatic repair. During this era, scientists purified hepatocyte growth factor (HGF) from rodent plasma and human platelets, recognizing its potent regenerative effects (Ilangumaran et al., 2016). The molecular characterization of HGF in 1989 revealed its identity as the so-called "scatter factor," previously noted for its ability to enhance cellular motility and promote epithelial morphogenesis (Montesano et al., 1991).
Identification of c-Met as the receptor for HGF marked a pivotal advance in unraveling how HGF/c-Met signaling underpins liver development, embryonic tissue formation, and the repair of damaged organs(Shen et al., 2021). Yet, when dysregulated, HGF/c-Met signaling is intimately tied to the emergence and progression of HCC. Elevated HGF levels, in particular, have been connected to more aggressive clinical outcomes in HCC (Fu et al., 2021).

Structure of HGF and Its Receptor (c-Met)

Although mesenchymal cells are considered the principal source of HGF, other cell types within the liver microenvironment—such as hepatic stellate cells, endothelial cells, and Kupffer cells—can also synthesize it. Once produced, HGF binds to the c-Met receptor, a plasma membrane–anchored tyrosine kinase, to promote tissue renewal under healthy conditions(Zhao et al., 2022). In cancer, however, aberrant activation of this pathway fuels angiogenesis, lymphangiogenesis, and metastatic spread (Wang et al., 2020).

The HGF gene, located on chromosome 7 (7q21), undergoes alternative splicing to yield multiple mRNA variants. Initially, HGF is synthesized as an inactive precursor (pre-pro-HGF), which is cleaved at a specific arginine–valine site to produce pro-HGF(Mizuno et al., 1994).A subsequent proteolytic cleavage step converts pro-HGF into its active heterodimeric form, consisting of an α-chain endowed with four kringle domains and a β-chain with structural similarities to a serine protease. Enzymes such as urokinase-type plasminogen activator and plasma kallikrein mediate this maturation process(Zhao et al., 2022).

The c-Met receptor, which also resides on chromosome 7, forms a mature protein of roughly 190 kDa, composed of an α-subunit (~145 kDa) and a β-subunit (~50 kDa). Upon HGF binding, two c-Met protomers dimerize, leading to the phosphorylation of key tyrosine residues (Y1234, Y1235, Y1349, and Y1356) and the initiation of intracellular signaling cascades (Sakai et al., 2015). Notably, HGF can interact with c-Met through two distinct binding domains: a high-affinity region in the NK1 segment near the receptor's amino terminus and a secondary, lower-affinity site within the β-chain (De Nola et al., 2022).

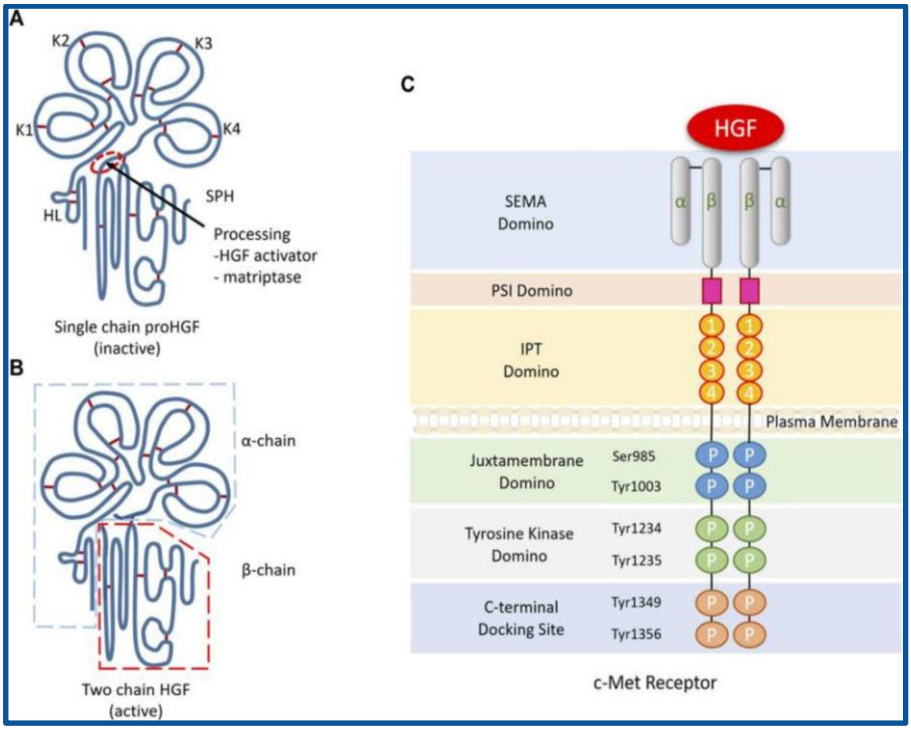

Figure 1: The structure of hepatocyte growth factor (HGF) and c-mesenchymal to epithelial transition (c-Met)

- (A): The α-chain of HGF shows an N-terminal hairpin loop (HL) that is attached to 4kringle domains (K1-K4). The β-chain includes a serine protease homology domain (SPH), which lacks proteolytic activity.
- (B): Active HGF is a heterodimeric molecule, consisting of both an α-chain and a β-chain.
- (C):The c-Met receptor is composed of a small α-chain and a larger β-chain, encompassing extracellular, transmembrane, and intracellular domains. The extracellular portion includes a large semaphorin (SEMA) domain, which facilitates HGF binding. Following the SEMA domain are a plexin-semaphorin-integrin (PSI) domain and four immunoglobulin-plexin-transcription (IPT) domains. Intracellularly, the c-Met β-chain's C-terminal tail contains two phosphorylation sites (Ser985 and Tyr1003), two key tyrosine residues (Tyr1234 and Tyr1235), and a multisubstrate docking site (Tyr1349 and Tyr1356).
- Quoted From: Zhao et al., (2022)

Biological Functions of HGF and c-Met

Hepatocyte growth factor (HGF) exerts diverse actions in epithelial cells, functioning not only as a mitogen that stimulates cell division but also as a motogen that supports cell migration and a morphogen that guides intricate tissue architecture (Nakamura et al., 2011). Because of these multifaceted roles, HGF profoundly influences processes such as tissue regeneration, liver repair, oncogenesis, and wound healing (Imamura and Matsumoto, 2017).

The HGF/c-Met axis is indispensable for the natural repair and regenerative processes of the liver. Evidence from animal models has demonstrated that disrupting c-Met activity compromises liver restoration, increases mortality, and delays healing after hepatic injury (Huh et al., 2004; Zhao et al., 2022). Clinically, HGF levels correlate with hepatic regrowth following living donor liver transplantation, with notable peaks on postoperative days 1, 7, and 14 that track with increases in liver volume (Ray et al., 2018; Hoffmann et al., 2020). Early

elevations in serum HGF and related growth factors appear to jump-start the regenerative response following hepatectomy.

Upon HGF binding, the c-Met receptor undergoes activation, which launches a series of intracellular signaling pathways governing proliferation, migration, and resistance to apoptosis. This signaling cascade also facilitates epithelial–mesenchymal transition (EMT) and is vital for normal placental and neural development, muscle precursor specification, and muscle tissue formation (Giordano and Columbano, 2014). In hepatic tissues, HGF/c-Met activity orchestrates cell differentiation, migration, angiogenesis, and overall liver development (Yu et al., 2021). Animal studies indicate that either HGF or c-Met deletion severely impairs embryonic liver formation (Schmidt et al., 1995). The pathway additionally promotes hepatocyte repopulation and alleviates toxin-induced fibrosis, particularly in partial hepatectomy contexts (Zhang et al., 2020). Although these findings highlight the therapeutic promise of activating c-Met in early-stage liver disease, its clinical application remains challenging, especially in advanced conditions (Yu et al., 2021).

The HGF/c-Met Signaling Pathway in HCC

Research has shown that up to 20–40% of hepatocellular carcinoma (HCC) cases exhibit aberrant c-Met signaling, often triggered by excessive HGF ligand or increased receptor expression. Mechanisms underlying this dysregulation include surplus HGF or c-Met production, gene amplifications, mutations that lead to constitutive receptor activation, loss of microRNAs that normally inhibit c-Met, autocrine loops, or elevated circulating HGF (Panneerselvam et al., 2023).

In the canonical mode, under typical physiological conditions, HGF binding to c-Met promotes receptor dimerization and autophosphorylation on key tyrosine residues. This process activates multiple intracellular networks—most notably the MAPK/ERK, PI3K, p38 MAPK, and Akt/PKB pathways. Adapter proteins such as Grb2, Gab1, PI3K, and STAT3, together with modulators like SHIP1, PLCγ, SHP2, and Shc, then orchestrate signals that drive tumor proliferation and metastatic progression in HCC(Garcia-Vilas and Medina, 2018; Liu et al., 2018; Zhang et al., 2018).

In addition to the canonical route, a variety of alternative mechanisms potentiate c-Met–dependent oncogenesis in HCC. One notable example is Des-γ-carboxy prothrombin (DCP)—a molecule secreted by HCC cells that mimics HGF structurally, engages c-Met, and may serve as a biomarker for diagnosis. Beyond this, c-Met forms interactions with a broad range of other receptors and adhesion molecules—including EGFR, members of the HER family, integrins, β-catenin, CD44, ICAM-1, Plexin B1, VEGF-A, INSR, FAS, MUC1, neuropilins, and FAK—resulting in complex signaling networks that underlie aggressive tumor behavior and therapeutic resistance(Jo et al., 2015; García-Vilas and Medina, 2018).

Factors such as hypoxia, tumor suppressor inactivation, oncogene activation, and reduced microRNA levels all contribute to heightened c-Met expression. Certain c-Met mutations can alter its substrate specificity or boost kinase activity, as seen in hereditary papillary renal carcinoma. Additional modes of upregulation involve gene amplification, autocrine stimulation, microRNA depletion, lncRNA interactions, and ligand-independent c-Met activation by Slug (Zhang et al., 2019). In normal liver growth and regeneration, HGF/c-Met coordinates cell proliferation, migration, apoptosis resistance, and EMT. Mouse models deficient in HGF or c-Met display lethal embryonic phenotypes due to severe hepatic developmental anomalies, while c-Met deletion in hepatocytes disrupts liver regrowth post-partial hepatectomy (Bouattour et al., 2018).

HGF/c-Met Expression in HCC

Tumorigenic pathways in HCC include atypical c-Met activation mechanisms. For instance, DCP produced by HCC cells can mimic HGF and initiate c-Met signaling, offering a potential diagnostic avenue. Crosstalk between c-Met and a wide spectrum of cell surface molecules—including EGFR, HER family receptors, integrins, β-catenin, CD44, ICAM-1, Plexin B1, VEGF-A, INSR, FAS, MUC1, neuropilins, and FAK—generates intricate signaling webs that intensify malignancy and confer resistance to treatments (Jo et al., 2015; García-Vilas and Medina, 2018).

Multiple influences elevate c-Met, among them hypoxia, diminished tumor-suppressor function, hyperactive oncogenes, and low levels of microRNAs that typically restrain c-Met. Certain germline c-Met mutations, as documented in hereditary papillary renal carcinoma, enhance its enzymatic function. Moreover, autocrine loops, gene amplifications, deviations in microRNA, lncRNA-mediated regulation, and Slug-mediated ligand-independent pathways all bolster c-Met activity (Zhang et al., 2019). Within the broader context of liver ontogeny and regeneration, HGF/c-Met modulates cellular expansion, migration, and EMT, while ablation of HGF or c-Met in mouse models leads to embryonic lethality due to profound hepatic defects. Additionally, heightened HGF levels stimulate liver regrowth post-hepatectomy, but c-Met loss in hepatocytes hinders this process (Bouattour et al., 2018).

Role of the HGF/c-Met Axis in HCC Development

Chronic liver ailments, such as hepatitis B or C infections and cirrhosis, necessitate sustained hepatocyte renewal. This increased regenerative demand aligns with elevated HGF and c-Met levels, aiding tissue repair and minimizing fibrosis and inflammation. However, chronic c-Met hyperactivity can also promote HCC onset and progression (Bouattour et al., 2018; Wang et al., 2020).

Aberrant c-Met signaling arises from an array of mechanisms: gene amplification, receptor or ligand overexpression, autocrine loops, mutations, or surplus HGF. While gene amplification occurs at relatively low frequencies (approximately 5% in some studies or 1 out of 159 cases in others), receptor overexpression has been documented in 20–48% of tumor specimens. Elevated c-Met often predicts a worse prognosis, although co-occurring HGF overexpression is not universal in HCC (Wang et al., 2020).

MicroRNAs and suppressor of cytokine signaling 1 (SOCS1) are integral in regulating the HGF/c-Met pathway in HCC. SOCS1 induction diminishes phosphorylation of c-Met, Gab1, and ERK1/2, inhibiting tumor expansion (Gui et al., 2011, 2015, 2017). Conversely, miR-181a exerts tumor-suppressive effects by targeting c-Met, whereas certain oncogenic miRNAs promote HCC through enhanced c-Met signaling (Korhan et al., 2014). Recent findings by Ma et al. (2023) highlight that ASAP2 influences c-Met phosphorylation and downstream AKT and ERK1/2 activities, thus modulating EMT in HCC. Depleting ASAP2 suppresses c-Met activation and impedes HGF-driven tumor proliferation.

Moreover, the HGF/c-Met pathway interacts with additional factors, including mucin-1 (MUC1) and β-catenin, to synergistically advance tumor formation. Loss of regulatory proteins such as Axin1 amplifies tumorigenesis via joint c-Met and β-catenin signaling (Liang et al., 2018; Qiao et al., 2019).

The HGF/c-Met Axis and HCC Severity

The proliferative properties of HCC cells are closely linked to HGF/c-Met signaling. Studies show that silencing c-Met through adenovirus-encoded siRNA diminishes HCC cell growth both in vitro and in vivo (Zhang et al., 2005). Certain lncRNAs, including FLVCR1-AS and HULC, further propel HCC by increasing c-Met expression and sequestering miRNAs like miR-2052 that would ordinarily oppose tumorigenesis (Jia et al., 2013). Cancer-associated fibroblasts (H-CAFs) also contribute through HGF secretion, thus perpetuating c-Met–dependent cellular proliferation in HCC. Neutralizing HGF in H-CAF-conditioned media reduces this proliferative impetus, emphasizing the HGF/c-Met pathway's centrality in tumor expansion (Wang et al., 2020).

Elevated HGF or c-Met commonly correlates with heightened tumor invasiveness and metastatic capacity (Wang et al., 2007). Mechanistic studies implicate the phosphorylation of c-Met and AKT, along with NF-κB activation and matrix metalloproteinase-9 (MMP-9) upregulation, in facilitating extracellular matrix degradation and metastatic spread (Wang et al., 2007). Clinically, excessive c-Met activity is associated with resistance to sorafenib, a standard therapy for late-stage HCC (Ma et al., 2023).

Experiments using Hep3B and HepG2 cells indicate that HGF stimulation—particularly in the p53-deficient Hep3B line—drives c-Met expression and fosters invasiveness via Snail, a key EMT transcription factor (Liu et al., 2016). Overexpression of c-Met similarly intensifies invasive behaviors (Xie et al., 2010). Additional data suggest that stromal neutrophils and mesenchymal cells in the tumor periphery produce abundant HGF, accelerating EMT, proliferation, and metastatic traits (Ding et al., 2010; He et al., 2016).

Angiogenesis is also essential for tumor progression and dissemination. In HCC, imbalanced production of angiogenic mediators—such as VEGF-A, HGF, TGF, and EGF—bolsters blood vessel formation through HGF/c-Met and related signaling. This proangiogenic environment often involves cross-talk with VEGF receptors and suppression of antiangiogenic factors like thrombospondin-1 (Pinto et al., 2023).

Diagnostic and Prognostic Value of HGF and c-Met in HCC

Diagnostic and Prognostic Value of c-Met

High c-Met levels have been linked to advanced disease stages, increased recurrence, and a greater incidence of intrahepatic spread and portal vein complications. Patients whose tumors overexpress c-Met commonly experience reduced survival (Meng and Chen, 2021). In a meta-analysis by Kim et al. (2017), findings from five separate studies revealed conflicting outcomes on overall survival and recurrence-free survival. For instance, Kondo et al. (2013) detected a pronounced association with RFS (HR: 3.10, $p = 0.002$), whereas other investigations (Ke et al., 2009; Lee et al., 2013; Koh et al., 2015) did not observe significant prognostic correlations. These discrepancies highlight ongoing debates about c-Met's prognostic impact. Nevertheless, c-Met status may hold value for predicting responses to targeted therapies directed at the HGF/c-Met pathway (Zhang et al., 2016). In certain cases, higher c-Met expression levels can forecast better responsiveness to cabozantinib and sorafenib, aiding personalized therapeutic decision-making (Xiang et al., 2014; Chu et al., 2013).

Diagnostic and Prognostic Value of HGF

Investigations by Yamagami et al. (2002) and Karabulut et al. (2014) reported that serum HGF levels are frequently elevated in patients with HCC, suggesting its possible utility as a diagnostic marker. However,

questions persist regarding its specificity, given that HGF levels can also rise in cirrhotic individuals without HCC (Unić et al., 2018). While sensitivity has been reported to be as high as 90.62%, specificity lags at 25.81%, implying that HGF alone may not definitively distinguish HCC from underlying liver disease. Hence, HGF is likely most efficacious when combined with other diagnostic tools.

Prognostically, higher baseline HGF concentrations are associated with an increased risk of radiation-induced liver toxicity and poorer survival after radiotherapy or liver transplantation (Hong et al., 2018). Rimassa et al. (2016) similarly linked elevated HGF to shorter survival durations in secondary HCC. Yet another study did not find a significant correlation between HGF levels and patient outcomes (Karabulut et al., 2014). These variable findings underscore the need for integrated assessment methods and nuanced patient stratification when evaluating HGF's clinical significance.

CONCLUSIONS

The HGF/c-Met pathway is vital for an optimal hepatic function as well as hepatic regeneration but can be co-opted by tumor cells in hepatocellular carcinoma, driving disease progression. Dysregulation often manifests as increased receptor or ligand expression, activating diverse signaling cascades that promote proliferation, metastasis, and treatment resistance. Mounting evidence supports a strong connection between heightened HGF/c-Met activity and poor clinical outcomes, underscoring the importance of assessing this pathway for both prognostic and therapeutic purposes. Although early clinical efforts targeting c-Met have yielded mixed findings, emerging strategies that integrate c-Met inhibitors with other treatments are promising. Further research aimed at characterizing patient subgroups and refining combination therapies will enhance our ability to manage HCC more effectively.

REFERENCES

1. Boix, Loreto, Rosa, Jose Luis, Ventura, Francesc, Castells, Antoni, Bruix, Jordi, Rodés, Joan, & Bartrons, Ramon. (1994). C-met mRNA overexpression in human hepatocellular carcinoma. Hepatology, 19(1), 88–91. https://doi.org/10.1002/hep.1840190115
2. Bouattour, Mohamed, Raymond, Eric, Qin, Shukui, Cheng, Ann-Lii, Stammberger, Uz, Locatelli, Giuseppe, & Faivre, Sandrine. (2018). Recent developments of c-Met as a therapeutic target in hepatocellular carcinoma. Hepatology (Baltimore, Md.), 67(3), 1132–1149. https://doi.org/10.1002/hep.29496
3. Chu, Jie Sheng, Ge, Fei Jiao, Zhang, Bo, Wang, Yan, Silvestris, Nicola, Liu, Lie Jun, Zhao, Chuan Hua, Lin, Li, Brunetti, Anna Elisabetta, Fu, Ya Li, Wang, Jun, Paradiso, Angelo, & Xu, Jian Ming. (2013). Expression and prognostic value of VEGFR-2, PDGFR-β, and c-Met in advanced hepatocellular carcinoma. Journal of Experimental & Clinical Cancer Research: CR, 32(1), 16. https://doi.org/10.1186/1756-9966-32-16
4. Daveau, Maryvonne, Scotte, Michel, François, Arnaud, Coulouarn, Cédric, Ros, Gilles, Tallet, Yveline, Hiron, Martine, Hellot, Marie-France, & Salier, Jean-Philippe. (2003). Hepatocyte growth factor, transforming growth factor alpha, and their receptors as combined markers of prognosis in hepatocellular carcinoma. Molecular Carcinogenesis, 36(3), 130–141. https://doi.org/10.1002/mc.10103
5. de Nola, Giovanni, Leclercq, Bérénice, Mougel, Alexandra, Taront, Solenne, Simonneau, Claire, Forneris, Federico, Adriaenssens, Eric, Drobecq, Hervé, Iamele, Luisa, Dubuquoy, Laurent, Melnyk, Oleg, Gherardi, Ermanno, de Jonge, Hugo, & Vicogne, Jérôme. (2022). Dimerization of kringle 1 domain from hepatocyte growth factor/scatter factor provides a potent MET receptor agonist. Life Science Alliance, 5(12), e202201424. https://doi.org/10.26508/lsa.202201424
6. Ding, Wei, You, Hanning, Dang, Hien, LeBlanc, Francis, Galicia, Vivian, Lu, Shelly C., Stiles, Bangyan, & Rountree, C. Bart. (2010). Epithelial-to-Mesenchymal Transition of Murine Liver Tumor Cells Promotes Invasion. Hepatology (Baltimore, Md.), 52(3), 945–953. https://doi.org/10.1002/hep.23748
7. Fu, Jianjiang, Su, Xiaorui, Li, Zhihua, Deng, Ling, Liu, Xiawei, Feng, Xuancheng, & Peng, Juan. (2021). HGF/c-MET pathway in cancer: From molecular characterization to clinical evidence. Oncogene, 40(28), 4625–4651. https://doi.org/10.1038/s41388-021-01863-w
8. García-Vilas, Javier A., & Medina, Miguel Ángel. (2018). Updates on the hepatocyte growth factor/c-Met axis in hepatocellular carcinoma and its therapeutic implications. World Journal of Gastroenterology, 24(33), 3695–3708. https://doi.org/10.3748/wjg.v24.i33.3695
9. Giordano, Silvia, & Columbano, Amedeo. (2014). Met as a therapeutic target in HCC: Facts and hopes. Journal of Hepatology, 60(2), 442–452. https://doi.org/10.1016/j.jhep.2013.09.009
10. Gui, Y., Yeganeh, M., Donates, Y. C., Tobelaim, W. S., Chababi, W., Mayhue, M., Yoshimura, A., Ramanathan, S., Saucier, C., & Ilangumaran, S. (2015). Regulation of MET receptor tyrosine kinase signaling by suppressor of cytokine signaling 1 in hepatocellular carcinoma. Oncogene, 34(46), 5718–5728. https://doi.org/10.1038/onc.2015.20

11. Gui, Yirui, Khan, Md Gulam Musawwir, Bobbala, Diwakar, Dubois, Claire, Ramanathan, Sheela, Saucier, Caroline, & Ilangumaran, Subburaj. (2017). Attenuation of MET-mediated migration and invasion in hepatocellular carcinoma cells by SOCS1. World Journal of Gastroenterology, 23(36), 6639–6649. https://doi.org/10.3748/wjg.v23.i36.6639
12. Gui, Yirui, Yeganeh, Mehdi, Ramanathan, Sheela, Leblanc, Chantal, Pomerleau, Véronique, Ferbeyre, Gerardo, Saucier, Caroline, & Ilangumaran, Subburaj. (2011). SOCS1 controls liver regeneration by regulating HGF signaling in hepatocytes. Journal of Hepatology, 55(6), 1300–1308. https://doi.org/10.1016/j.jhep.2011.03.027
13. He, Min, Peng, Anping, Huang, Xian-Zhang, Shi, Dai-Chao, Wang, Jun-Cheng, Zhao, Qiyi, Lin, Haibiao, Kuang, Dong-Ming, Ke, Pei-Feng, & Lao, Xiang-Ming. (2016). Peritumoral stromal neutrophils are essential for c-Met-elicited metastasis in human hepatocellular carcinoma. Oncoimmunology, 5(10), e1219828. https://doi.org/10.1080/2162402X.2016.1219828
14. Hoffmann, Katrin, Nagel, Alexander Johannes, Tanabe, Kazukata, Fuchs, Juri, Dehlke, Karolin, Ghamarnejad, Omid, Lemekhova, Anastasia, & Mehrabi, Arianeb. (2020). Markers of liver regeneration—the role of growth factors and cytokines: A systematic review. BMC Surgery, 20, 31. https://doi.org/10.1186/s12893-019-0664-8
15. Hong, Theodore S., Grassberger, Clemens, Yeap, Beow Y., Jiang, Wenqing, Wo, Jennifer Y., Goyal, Lipika, Clark, Jeffrey W., Crane, Christopher H., Koay, Eugene J., Dima, Simona, Eyler, Christine E., Popescu, Irinel, DeLaney, Thomas F., Zhu, Andrew X., & Duda, Dan G. (2018). Pretreatment plasma HGF as potential biomarker for susceptibility to radiation-induced liver dysfunction after radiotherapy. Npj Precision Oncology, 2(1), 1–3. https://doi.org/10.1038/s41698-018-0065-y
16. Huh, Chang-Goo, Factor, Valentina M., Sánchez, Aránzazu, Uchida, Koichi, Conner, Elizabeth A., & Thorgeirsson, Snorri S. (2004). Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. Proceedings of the National Academy of Sciences of the United States of America, 101(13), 4477–4482. https://doi.org/10.1073/pnas.0306068101
17. Ilangumaran, Subburaj, Villalobos-Hernandez, Alberto, Bobbala, Diwakar, & Ramanathan, Sheela. (2016). The hepatocyte growth factor (HGF)–MET receptor tyrosine kinase signaling pathway: Diverse roles in modulating immune cell functions. Cytokine, 82, 125–139. https://doi.org/10.1016/j.cyto.2015.12.013
18. Imamura, Ryu, & Matsumoto, Kunio. (2017). Hepatocyte growth factor in physiology and infectious diseases. Cytokine, 98, 97–106. https://doi.org/10.1016/j.cyto.2016.12.025
19. Jia, Chang-Chang, Wang, Tian-Tian, Liu, Wei, Fu, Bin-Sheng, Hua, XueFeng, Wang, Guo-Ying, Li, Tuan-Jie, Li, Xing, Wu, Xiang-Yuan, Tai, Yan, Zhou, Jie, Chen, Gui-Hua, & Zhang, Qi. (2013). Cancer-Associated Fibroblasts from Hepatocellular Carcinoma Promote Malignant Cell Proliferation by HGF Secretion. PLoS ONE, 8(5), e63243. https://doi.org/10.1371/journal.pone.0063243
20. Jo, Jae-Cheol, Choi, Eun Kyoung, Shin, Jae-Sik, Moon, Jai-Hee, Hong, Seung-Woo, Lee, Ha-Reum, Kim, Seung-Mi, Jung, Soo-A., Lee, Dae-Hee, Jung, Seang Hwan, Lee, Sun-Hye, Kim, Jeong Eun, Kim, Kyu-pyo, Hong, Yong Sang, Suh, Young-Ah, Jang, Se Jin, Choi, Eun Kyung, Lee, Jung Shin, Jin, Dong-Hoon, & Kim, Tae Won. (2015). Targeting FGFR Pathway in Human Hepatocellular Carcinoma: Expressing pFGFR and pMET for Antitumor Activity. Molecular Cancer Therapeutics, 14(11), 2613–2622. https://doi.org/10.1158/1535-7163.MCT-14-0780
21. Karabulut, S., Tas, F., Akyüz, F., Ormeci, A. C., Serilmez, M., Soydinç, H. O., Vatansever, S., & Yasasever, V. (2014). Clinical significance of serum hepatocyte growth factor (HGF) levels in hepatocellular carcinoma. Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine, 35(3), 2327–2333. https://doi.org/10.1007/s13277-013-1308-8
22. Ke, Ai-Wu, Shi, Guo-Ming, Zhou, Jian, Wu, Fei-Zhen, Ding, Zhen-Bin, Hu, Mei-Yu, Xu, Yang, Song, Zheng-Ji, Wang, Zhi-Jun, Wu, Jin-Cai, Bai, Dou-Sheng, Li, Jia-Chu, Liu, Kang-Da, & Fan, Jia. (2009). Role of overexpression of CD151 and/or c-Met in predicting prognosis of hepatocellular carcinoma. Hepatology (Baltimore, Md.), 49(2), 491–503. https://doi.org/10.1002/hep.22639
23. Kim, Jung Han, Kim, Hyeong Su, Kim, Bum Jun, Jang, Hyun Joo, & Lee, Jin. (2017). Prognostic value of c-Met overexpression in hepatocellular carcinoma: A meta-analysis and review. Oncotarget, 8(52), 90351–90357. https://doi.org/10.18632/oncotarget.20087
24. Kondo, Shunsuke, Ojima, Hidenori, Tsuda, Hitoshi, Hashimoto, Jun, Morizane, Chigusa, Ikeda, Masafumi, Ueno, Hideki, Tamura, Kenji, Shimada, Kazuaki, Kanai, Yae, & Okusaka, Takuji. (2013). Clinical impact of c-Met expression and its gene amplification in hepatocellular carcinoma. International Journal of Clinical Oncology, 18(2), 207–213. https://doi.org/10.1007/s10147-011-0361-9
25. Korhan, Peyda, Erdal, Esra, & Atabey, Neşe. (2014). MiR-181a-5p is downregulated in hepatocellular carcinoma and suppresses motility, invasion and branching-morphogenesis by directly targeting c-Met. Biochemical and Biophysical Research Communications, 450(4), 1304–1312. https://doi.org/10.1016/j.bbrc.2014.06.142

26. Lee, Su Jin, Lee, Jeeyun, Sohn, Insuk, Mao, Mao, Kai, Wang, Park, Cheol-Keun, & Lim, Ho Yeong. (2013). A survey of c-MET expression and amplification in 287 patients with hepatocellular carcinoma. Anticancer Research, 33(11), 5179–5186.
27. Liang, Yan, Feng, Yun, Zong, Min, Wei, Xufu, Lee, Jin, Feng, Yukuan, Li, Hairi, Yang, Guangshun, Wu, Zhong-Jun, Fu, Xiang-Dong, & Feng, Gen-Sheng. (2018). β-Catenin Deficiency in Hepatocytes Aggravates Hepatocarcinogenesis Driven by Oncogenic β-Catenin and MET. Hepatology (Baltimore, Md.), 67(5), 1807–1822. https://doi.org/10.1002/hep.29661
28. Liu, Jacey J., Li, Yanjie, Chen, Wendy S., Liang, Yan, Wang, Gaowei, Zong, Min, Kaneko, Kota, Xu, Ruiyun, Karin, Michael, & Feng, Gen-Sheng. (2018). Shp2 Deletion in Hepatocytes Suppresses Hepatocarcinogenesis Driven by Oncogenic β-Catenin, PIK3CA and MET. Journal of Hepatology, 69(1), 79–88. https://doi.org/10.1016/j.jhep.2018.02.014
29. Liu, Wen-Ting, Jing, Ying-Ying, Yu, Guo-feng, Chen, Hong, Han, Zhi-peng, Yu, Dan-dan, Fan, Qing-Min, Ye, Fei, Li, Rong, Gao, Lu, Zhao, Qiu-Dong, Wu, Meng-Chao, & Wei, Li-Xin. (2016). Hepatic stellate cell promoted hepatoma cell invasion via the HGF/c-Met signaling pathway regulated by p53. Cell Cycle, 15(7), 886–894. https://doi.org/10.1080/15384101.2016.1152428
30. Ma, Xiao-Lu, Nie, Yan-Yan, Xie, Su-Hong, Zheng, Hui, Tong, Ying, Wang, Yan-Chun, Yan, Tian-Qing, Meng, Xin, Cao, Jia-Zhen, Tang, Wei-Guo, Guo, Lin, & Lu, Ren-Quan. (2023). ASAP2 interrupts c-MET-CIN85 interaction to sustain HGF/c-MET-induced malignant potentials in hepatocellular carcinoma. Experimental Hematology & Oncology, 12(1), 38. https://doi.org/10.1186/s40164-023-00393-3
31. Ma, Yongfang, Liu, Xueke, & Tang, Xiaolong. (2023). ETS-1/c-Met drives resistance to sorafenib in hepatocellular carcinoma. American Journal of Translational Research, 15(2), 896–913.
32. Meng, Wei, & Chen, Tao. (2021). Association between the HGF/c-MET signaling pathway and tumorigenesis, progression and prognosis of hepatocellular carcinoma (Review). Oncology Reports, 46(3), 1–10. https://doi.org/10.3892/or.2021.8142
33. Mizuno, K., Tanoue, Y., Okano, I., Harano, T., Takada, K., & Nakamura, T. (1994). Purification and characterization of hepatocyte growth factor (HGF)-converting enzyme: Activation of pro-HGF. Biochemical and Biophysical Research Communications, 198(3), 1161–1169. https://doi.org/10.1006/bbrc.1994.1164
34. Montesano, R., Matsumoto, K., Nakamura, T., & Orci, L. (1991). Identification of a fibroblast-derived epithelial morphogen as hepatocyte growth factor. Cell, 67(5), 901–908. https://doi.org/10.1016/0092-8674(91)90363-4
35. Moosavi, Fatemeh, Giovannetti, Elisa, Saso, Luciano, & Firuzi, Omidreza. (2019). HGF/MET pathway aberrations as diagnostic, prognostic, and predictive biomarkers in human cancers. Critical Reviews in Clinical Laboratory Sciences, 56(8), 533–566. https://doi.org/10.1080/10408363.2019.1653821
36. Nakamura, Takahiro, Sakai, Katsuya, Nakamura, Toshikazu, & Matsumoto, Kunio. (2011). Hepatocyte growth factor twenty years on: Much more than a growth factor. Journal of Gastroenterology and Hepatology, 26(s1), 188–202. https://doi.org/10.1111/j.1440-1746.2010.06549.x
37. Panneerselvam, Sugan, Wilson, Cornelia, Kumar, Prem, Abirami, Dinu, Pamarthi, Jayakrishna, Reddy, Mettu Srinivas, & Varghese, Joy. (2023). Overview of hepatocellular carcinoma: From molecular aspects to future therapeutic options. Cell Adhesion & Migration, 17(1), 1–21. https://doi.org/10.1080/19336918.2023.2258539
38. Pinto, Elisa, Pelizzaro, Filippo, Farinati, Fabio, & Russo, Francesco Paolo. (2023). Angiogenesis and Hepatocellular Carcinoma: From Molecular Mechanisms to Systemic Therapies. Medicina, 59(6), Article 6. https://doi.org/10.3390/medicina59061115
39. Qiao, Yu, Wang, Jingxiao, Karagoz, Eylul, Liang, Binyong, Song, Xinhua, Shang, Runze, Evert, Katja, Xu, Meng, Che, Li, Evert, Matthias, Calvisi, Diego F., Tao, Junyan, Wang, Bruce, Monga, Satdarshan P., & Chen, Xin. (2019). Axis inhibition protein 1 (Axin1) Deletion–Induced Hepatocarcinogenesis Requires Intact β-Catenin but Not Notch Cascade in Mice. Hepatology (Baltimore, Md.), 70(6), 2003–2017. https://doi.org/10.1002/hep.30556
40. Ray, S., Mehta, N. N., Golhar, A., & Nundy, S. (2018). Post hepatectomy liver failure – A comprehensive review of current concepts and controversies. Annals of Medicine and Surgery, 34, 4–10. https://doi.org/10.1016/j.amsu.2018.08.012
41. Rimassa, Lorenza, Abbadessa, Giovanni, Personeni, Nicola, Porta, Camillo, Borbath, Ivan, Daniele, Bruno, Salvagni, Stefania, Laethem, Jean-Luc Van, Vlierberghe, Hans Van, Trojan, Jörg, Toni, Enrico N. De, Weiss, Alan, Miles, Steven, Gasbarrini, Antonio, Lencioni, Monica, Lamar, Maria E., Wang, Yunxia, Shuster, Dale, Schwartz, Brian E., & Santoro, Armando. (2016). Tumor and circulating biomarkers in patients with second-line hepatocellular carcinoma from the randomized phase II study with tivantinib. Oncotarget, 7(45), 72622–72633. https://doi.org/10.18632/oncotarget.11621
42. Sakai, Katsuya, Aoki, Shunsuke, & Matsumoto, Kunio. (2015). Hepatocyte growth factor and Met in drug discovery. Journal of Biochemistry, 157(5), 271–284. https://doi.org/10.1093/jb/mvv027

43. Schmidt, C., Bladt, F., Goedecke, S., Brinkmann, V., Zschiesche, W., Sharpe, M., Gherardi, E., & Birchmeier, C. (1995). Scatter factor/hepatocyte growth factor is essential for liver development. Nature, 373(6516), 699–702. https://doi.org/10.1038/373699a0
44. Shen, Zhibo, Xue, Wenhua, Zheng, Yuanyuan, Geng, Qishun, Wang, Le, Fan, Zhirui, Wang, Wenbin, Yue, Ying, Zhai, Yunkai, Li, Lifeng, & Zhao, Jie. (2021). Molecular mechanism study of HGF/c-MET pathway activation and immune regulation for a tumor diagnosis model. Cancer Cell International, 21, 374. https://doi.org/10.1186/s12935-021-02051-2
45. Suzuki, K., Hayashi, N., Yamada, Y., Yoshihara, H., Miyamoto, Y., Ito, Y., Ito, T., Katayama, K., Sasaki, Y., & Ito, A. (1994). Expression of the c-met protooncogene in human hepatocellular carcinoma. Hepatology (Baltimore, Md.), 20(5), 1231–1236.
46. Takeo, S., Arai, H., Kusano, N., Harada, T., Furuya, T., Kawauchi, S., Oga, A., Hirano, T., Yoshida, T., Okita, K., & Sasaki, K. (2001). Examination of oncogene amplification by genomic DNA microarray in hepatocellular carcinomas: Comparison with comparative genomic hybridization analysis. Cancer Genetics and Cytogenetics, 130(2), 127–132. https://doi.org/10.1016/s0165-4608(01)00479-4
47. Tavian, D., De Petro, G., Benetti, A., Portolani, N., Giulini, S. M., & Barlati, S. (2000). U-PA and c-MET mRNA expression is co-ordinately enhanced while hepatocyte growth factor mRNA is down-regulated in human hepatocellular carcinoma. International Journal of Cancer, 87(5), 644–649.
48. Unić, Adriana, Derek, Lovorka, Duvnjak, Marko, Patrlj, Leonardo, Rakić, Mislav, Kujundžić, Milan, Renjić, Vesna, Štoković, Nikola, Dinjar, Petra, Jukic, Anita, & Grgurević, Ivica. (2018). Diagnostic specificity and sensitivity of PIVKAII, GP3, CSTB, SCCA1 and HGF for the diagnosis of hepatocellular carcinoma in patients with alcoholic liver cirrhosis. Annals of Clinical Biochemistry, 55(3), 355–362. https://doi.org/10.1177/0004563217726808
49. Wang, Haiyu, Rao, Benchen, Lou, Jiamin, Li, Jianhao, Liu, Zhenguo, Li, Ang, Cui, Guangying, Ren, Zhigang, & Yu, Zujiang. (2020). The Function of the HGF/c-Met Axis in Hepatocellular Carcinoma. Frontiers in Cell and Developmental Biology, 8, 55. https://doi.org/10.3389/fcell.2020.00055
50. Wang, Shih-Wei, Pan, Shiow-Lin, Peng, Chieh-Yu, Huang, Der-Yi, Tsai, An-Chi, Chang, Ya-Ling, Guh, Jih-Hwa, Kuo, Sheng-Chu, Lee, Kuo-Hsiung, & Teng, Che-Ming. (2007). CHM-1 inhibits hepatocyte growth factor-induced invasion of SK-Hep-1 human hepatocellular carcinoma cells by suppressing matrix metalloproteinase-9 expression. Cancer Letters, 257(1), 87–96. https://doi.org/10.1016/j.canlet.2007.07.002
51. Wu, F., Wu, L., Zheng, S., Ding, W., Teng, L., Wang, Z., Ma, Z., & Zhao, W. (2006). The clinical value of hepatocyte growth factor and its receptor—C-met for liver cancer patients with hepatectomy. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, 38(7), 490–497. https://doi.org/10.1016/j.dld.2006.03.007
52. Xiang, Qingfeng, Chen, Weiqiang, Ren, Meng, Wang, Jingnan, Zhang, Hongwu, Deng, David Y. B., Zhang, Lei, Shang, Changzhen, & Chen, Yajin. (2014). Cabozantinib Suppresses Tumor Growth and Metastasis in Hepatocellular Carcinoma by a Dual Blockade of VEGFR2 and MET. Clinical Cancer Research, 20(11), 2959–2970. https://doi.org/10.1158/1078-0432.CCR-13-2620
53. Xie, Bin, Xing, Renxin, Chen, Ping, Gou, Yuanbin, Li, Shan, Xiao, Jing, & Dong, Jiahong. (2010). Down-regulation of c-Met expression inhibits human HCC cells growth and invasion by RNA interference. The Journal of Surgical Research, 162(2), 231–238. https://doi.org/10.1016/j.jss.2009.04.030
54. Yamagamim, Hiroaki, Moriyama, Mitsuhiko, Matsumura, Hiroshi, Aoki, Hiroshi, Shimizu, Toshihiro, Saito, Takahide, Kaneko, Miki, Shioda, Atsuo, Tanaka, Naohide, & Arakawa, Yasuyuki. (2002). Serum concentrations of human hepatocyte growth factor is a useful indicator for predicting the occurrence of hepatocellular carcinomas in C-viral chronic liver diseases. Cancer, 95(4), 824–834. https://doi.org/10.1002/cncr.10732
55. Yu, Jianqing, Chen, George G., & Lai, Paul B. S. (2021). Targeting hepatocyte growth factor/c-mesenchymal–epithelial transition factor axis in hepatocellular carcinoma: Rationale and therapeutic strategies. Medicinal Research Reviews, 41(1), 507–524. https://doi.org/10.1002/med.21738
56. Zhang, Hongwei, Liao, Zhibin, Liu, Furong, Su, Chen, Zhu, He, Li, Yani, Tao, Ran, Liang, Huifang, Zhang, Bixiang, & Zhang, Xuewu. (2019). Long noncoding RNA HULC promotes hepatocellular carcinoma progression. Aging (Albany NY), 11(20), 9111–9127. https://doi.org/10.18632/aging.102378
57. Zhang, Sheng-Zhou, Pan, Fei-Yan, Xu, Jian-Feng, Yuan, Jun, Guo, Shi-Ying, Dai, Gu, Xue, Bin, Shen, Wei-Gan, Wen, Chuan-Jun, Zhao, Dong-Hong, & Li, Chao-Jun. (2005). Knockdown of c-Met by adenovirus-delivered small interfering RNA inhibits hepatocellular carcinoma growth in vitro and in vivo. Molecular Cancer Therapeutics, 4(10), 1577–1584. https://doi.org/10.1158/1535-7163.MCT-05-0106
58. Zhang, Xue-Jun, Olsavszky, Victor, Yin, Yuhan, Wang, Baocai, Engleitner, Thomas, Öllinger, Rupert, Schledzewski, Kai, Koch, Philipp-Sebastian, Rad, Roland, Schmid, Roland M., Friess, Helmut, Goerdt, Sergij, Hüser, Norbert, Géraud, Cyrill, von Figura, Guido, & Hartmann, Daniel. (2020). Angiocrine Hepatocyte Growth Factor Signaling Controls Physiological Organ and Body Size and Dynamic

Hepatocyte Proliferation to Prevent Liver Damage during Regeneration. The American Journal of Pathology, 190(2), 358–371. https://doi.org/10.1016/j.ajpath.2019.10.009

59. Zhang, Yanni, Du, Zhiqiang, & Zhang, Mingqiang. (2016). Biomarker development in MET-targeted therapy. Oncotarget, 7(24), 37370–37389. https://doi.org/10.18632/oncotarget.8276
60. Zhang, Yazhuo, Xia, Mengfang, Jin, Ke, Wang, Shufei, Wei, Hang, Fan, Chunmei, Wu, Yingfen, Li, Xiaoling, Li, Xiayu, Li, Guiyuan, Zeng, Zhaoyang, & Xiong, Wei. (2018). Function of the c-Met receptor tyrosine kinase in carcinogenesis and associated therapeutic opportunities. Molecular Cancer, 17, 45. https://doi.org/10.1186/s12943-018-0796-y
61. Zhao, Yang, Ye, Wenling, Wang, Yan-Dong, & Chen, Wei-Dong. (2022). HGF/c-Met: A Key Promoter in Liver Regeneration. Frontiers in Pharmacology, 13. https://doi.org/10.3389/fphar.2022.808855