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Review Article

Hepatocyte Growth Factor in Physiology and Infectious Diseases

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Abstract

Hepatocyte growth factor (HGF) is a pleiotropic cytokine composed of an α-chain and a β-chain, and these chains contain four kringle domains and a serine protease-like structure, respectively. The receptor for HGF was identified as the c-met proto-oncogene product of transmembrane receptor tyrosine kinase. HGF-induced signaling through the receptor Met provokes dynamic biological responses that support morphogenesis, regeneration, and the survival of various cells and tissues, which includes hepatocytes, renal tubular cells, and neurons. Characterization of tissue-specific *Met* knockout mice has further indicated that the HGF–Met system modulates immune cell functions and also plays an inhibitory role in the progression of chronic inflammation and fibrosis. However, the biological actions that are driven by the HGF–Met pathway all play a role in the acquisition of the malignant characteristics in tumor cells, such as invasion, metastasis, and drug resistance in the tumor microenvironment. Even though oncogenic Met signaling remains the major research focus, the HGF–Met axis has also been implicated in infectious diseases. Many pathogens try to utilize host HGF–Met system to establish comfortable environment for infection. Their strategies are not only simply change the expression level of HGF or Met, but also actively hijack HGF–Met system and deregulating Met signaling using their pathogenic factors. Consequently, the monitoring of HGF and Met expression, along with real-time detection of Met activation, can be a beneficial biomarker of these infectious diseases. Preclinical studies designed to address the therapeutic significance of HGF have been performed on injury/disease models, including acute tissue injury, chronic fibrosis, and cardiovascular and neurodegenerative diseases. Likewise, manipulating the HGF–Met system with complete control will lead to a tailor-made treatment for those infectious diseases.

The HGF-Met signaling pathway

Hepatocyte growth factor (HGF) was originally identified and molecularly cloned as a mitogenic protein for hepatocytes in culture [1,2]. HGF is identical to the scatter factor, a fibroblast-derived factor that promotes the dispersal of sheets of epithelial cells [3,4], and a fibroblast-derived epithelial morphogen that induces the branching tubulogenesis of epithelia grown in three-dimensional cultures [5]. Thus, HGF is a unique growth factor that elicits multiple cellular responses including mitogenesis, cell motility and morphogenesis. These early findings implicated biological and pathophysiological roles for HGF in epithelial wound healing, tissue regeneration, tumorigenesis, and cancer invasion.

The receptor for HGF was identified as the c-met proto-oncogene product of transmembrane receptor tyrosine kinase (RTK) in 1991 [6,7]. Historically, Met was first identified as the product of a human oncogene, Tpr-Met [8,9]. Tpr-Met was generated following a chromosomal rearrangement induced by the treatment of a human osteogenic sarcoma cell line with the carcinogen N-methyl-N'-nitronitrosoguanidine. This genomic rearrangement fuses two genetic loci. These include the *translocated promoter region* from chromosome 1q25, which encodes a dimerization leucine zipper motif, and *MET* from chromosome 7q31, which contributes the kinase domain and C terminus of the Met. Tpr-Met is a prototype for RTK-derived oncogenes generated following chromosomal translocation.

Mice lacking HGF die in utero 13.5-15.5 days after post-gestation, and this is characterized by the impaired development of the placenta in many epithelial organs, particularly the liver [10]. Mice lacking the *Met* gene also show embryonic lethality and liver pathology [11]. Moreover, HGF provides spatially defined chemoattractant-like motogenic signals for myogenic precursor cells. The migration of myogenic precursor cells from the dermo-myotome in the somite to the limb buds and diaphragm is impaired in $Met^{-/-}$ mice. With this condition, the skeletal muscles of the limbs and diaphragm are not formed in mutant mice [12].

Moreover, the definitive roles of the HGF–Met pathway in tissue protection and repair have been demonstrated using a conditional ablation of the *Met* gene in mice (Table 1). Characterization of these tissue-specific *Met* knockout mice has indicated that the HGF-Met system plays a promoting role in the regeneration, protection, and homeostasis of tissues, but it also plays an inhibitory role in the progression of chronic inflammation and fibrosis. However, the biological actions that are driven by the HGF–Met pathway all play a role in the acquisition of the malignant characteristics in tumor cells—invasion, metastasis, and drug resistance in the tumor microenvironment (Fig. 1).

Contrary to the relationship between many cytokines and their receptors, the relationship between HGF and Met is considered bi-unique; HGF is the only ligand for Met, and Met is the only receptor for HGF. Exceptionally and interestingly, *Listeria monocytogenes* surface protein Internalin B (InlB) is known to bind to the extracellular domain of Met and to induce the "scattering" of epithelial cells for bacterial entry [34]. A recent report have noted that Leukocyte Cell-Derived Chemotaxin 2 (Lect2), which is an identical molecule to chondromodulin-II (ChM-II), binds to the α-chain of the Met receptor and inhibits Met activation [35].

HGF belongs to a unique group of plasminogen-related growth factors/cytokines [36]. This group originated because of a divergent evolution from an ancestral gene that gave rise to a number of plasma proteins with serine proteinase activity, which includes plasminogen, urokinase- and tissue-type plasminogen activators (u-PA, t-PA), and prothrombin [36–39]. HGF is a glycosylated protein composed of α- and β-chains linked by one disulfide bridge [1,2] (Fig. 2A). The α-chain contains an N-terminal hairpin loop and four kringle domains (a cysteine-rich, double-looped structure involved in protein-protein interactions that is found in coagulation factors), while the β-chain harbors a serine protease homology domain that is inactive due to the loss of catalytic residue [40]. HGF is biosynthesized in a prepro-form, including a signal sequence and both α- and β-chains. HGF lost its proteinase activity to evolution, but retained the requirement for proteolytic processing. After cleavage of a signal peptide of the first 31 amino acids and extracellular secretion, a single-chain HGF is further cleaved between Arg494 and Val495 by serine proteases such as HGF-activator, matriptase, and hepsin [41,42]. Mature HGF is composed of 697/692 amino acids. HGF binds to sulfated glycosaminoglycans such as heparan sulfate and dermatan sulfate thus accumulates in the extracellular matrix [43–45].

HGF and Met show a unique expression pattern. HGF is expressed mainly in mesenchyme-derived cells such as fibroblasts and smooth muscle cells, whereas Met expression predominantly occurs in epithelial cells. This different feature facilitates a paracrine mode of signaling that promotes mitogenesis, motogenesis, morphogenesis, wound healing, and tissue regeneration [46]. On the other hand, an autocrine mode of HGF-Met signaling has also been found in mesenchymal stem cells and cancer cells [47–52].

Like HGF, the HGF receptor Met is synthesized as a 190 kDa glycosylated precursor that contains an extracellular ligand-binding region, a single-pass transmembrane segment, and a catalytic cytoplasmic region. Met is composed of structural domains that include the following domains: extracellular Sema (the domain found in semaphorin receptors), the PSI (the domain found in plexins, semaphorins and integrins), four IPTs (the domain found in

immunoglobulins, plexins, and transcription factors), the transmembrane, the intracellular juxtamembrane, and tyrosine kinase [53] (Fig. 2B). During biosynthetic transport, Met is cleaved within the Sema domain by intracellular endoproteases to generate a 50 kDa α-chain that has a completely extracellular location and a 145 kDa β-chain that contains the rest of the precursor protein. The Sema domain serves as a key element for ligand binding [54], while the involvement of IPT-3 and IPT-4 in the binding to HGF was demonstrated by another approach [55]. Most of the cells respond to HGF at the expression levels around 200 ~ 1500 Met molecules per cell.

The binding of HGF to Met results in the phosphorylation of multiple tyrosine residues within the cytoplasmic region. The phosphorylation of Tyr1234 and Tyr1235 within the tyrosine kinase domain positively regulates the catalytic activity of tyrosine kinase, and the subsequent phosphorylation of C-terminal tyrosine residues Tyr1349 and Tyr1356 recruits intracellular signaling molecules, including growth factor receptor-bound protein 2 (Grb2), GRB2-associated-binding protein 1 (Gab1), phosphoinositide 3-kinase (PI3-K), SH2 containing protein tyrosine phosphatase (Shp2), phospholipase Cγ1 (PLCγ1), and signal transducers and activators of transcription-3 (Stat3). Typical biological activities evoked by Met activation include the promotion of mitogenesis and migration, suppression of cell death, and the induction of epithelial morphogenesis. Among the signaling molecules, Gab1 plays a critical role in HGF–Met pathway-dependent biological responses [56,57]. Gab1 is a scaffolding adaptor that contains the Met-binding site, by which a direct and robust interaction between Gab1 and Met results in prolonged Gab1 phosphorylation in response to HGF. The association of Gab1 and Met is responsible for the unique biological activities of HGF, including epithelial tubulogenesis.

The promotion of cell survival (*i.e.*, suppression of cell death) is a key biological action of the HGF–Met pathway in development, regeneration, and therapeutics. The activation of Met induces the phosphorylation of PI3-K and Akt, and the Akt-induced phosphorylation of Bad inhibits its pro-apoptotic activity (Fig. 3). In parallel, HGF increases the expression of anti-apoptotic Bcl-xL, by which the pro-apoptotic activity of Bax and Bim is inhibited [58,59]. Fas and Fas-ligand play a marked role in the induction of apoptosis. Another anti-apoptotic mechanism involves an extracellular interaction between the extracellular domain of Met and the death receptor Fas [60]. The binding of HGF to Met prevents a functional association between Fas and Fas-ligand, therefore inhibiting the self-aggregation of Fas, a key event required for the induction of Fas-mediated apoptosis. In addition, the intracellular cytoplasmic tail of Met has evolved harboring a tandem pair of caspase-3 cleavage sites,

which bait, trap, and disable the active site of caspase-3, thereby blocking the execution of apoptosis [61].

The cytoplasmic juxtamembrane domain negatively regulates Met-dependent signal transduction. Cbl ubiquitin ligase binds phosphorylated Y1003, and this Cbl binding results in Met ubiquitination and degradation [62]. The suppressor of cytokine signaling 1 (SOCS1) also interacts with Met via its SH2 domain and promotes a turnover of Met. This process is dependent on the poly-ubiquitination of Met, but it is independent of Y1003 residue and Cbl [63]. The phosphorylation of Ser985 in the juxtamembrane domain also regulates Met activation. Ser985 is phosphorylated either by protein kinase-C (PKC) or type II cGMP-dependent protein kinase G (PKG II), and when Ser985 is phosphorylated, HGF-dependent Met tyrosine phosphorylation and subsequent biological responses are suppressed [64–66].

The physiological and pathological roles of the HGF-Met pathways and the ongoing efforts for therapeutic manipulation of the HGF-Met signaling axis have been discussed in many excellent reviews [67–73]. Here, we focus on the role of the HGF-Met pathway in infectious diseases.

HGF-Met system for malaria infection

Plasmodium, the causative agent of malaria, first infects hepatocytes to initiate a mammalian infection. Sporozoites migrate through several hepatocytes by breaching their plasma membranes before infection is established in one of them. The wounding of hepatocytes by sporozoite migration is known to induce the secretion of HGF, which renders hepatocytes susceptible to infection [74]. Leirião et al. further demonstrated that the HGF-Met signaling requirement for infection is mediated by its anti-apoptotic signal effects through both PI3-K/Akt and, to a lesser extent, MAPK pathways [75]. These findings may explain why severe malaria cases are more frequent in hepatitis B virus carriers, who have higher HGF levels, than in controls, and it also explains the mechanism for the therapeutic effect of vitamin A in malaria infection, in part because of the inhibition of HGF production by retinoic acid, a metabolite of vitamin A.

The study of human malaria liver-stage biology *in vitro* is hampered by the low infection efficiency of human hepatocellular carcinoma lines (<0.1%). HC-04 is a novel human hepatocellular carcinoma line that is the only established cell line that supports complete development of human malaria parasites [76]. Tao et al. used online two-dimensional liquid chromatography tandem mass spectrometry to quantify protein expression profiles in HC-04 pre-/post-HGF treatment [77]. The proteomic data and correlative approaches identified several expected markers associated with epithelial-mesenchymal

transition, and, paradoxically, it also identified markers indicative of an epithelial phenotype following HGF treatment. HC-04s are subject to the influence of HGF, but the response is tempered by the up-regulation of proteins that are driving the maintenance of residual epithelial characteristics, which results in a more hepatocyte-like nature. Fine control of the epithelial-mesenchymal transition stages through HGF stimulation is probably required for an appropriate infection by malaria parasites.

***Helicobacter pylori* infection and Met signaling**

Helicobacter pylori (*H. pylori*) chronically infects the stomachs of at least half the world's population, and numerous studies have indicated that the persistent presence of this bacterium in a host increases their risk of several gastric diseases, which includes gastric adenocarcinoma [78,79]. *H. pylori* virulence factors differentially interfere with signaling pathways in gastric epithelial cells [80]. One well established *H. pylori* virulence factor is the presence of a cluster of about 30 genes, known as the cag pathogenicity island (cag PAI). The cag PAI encodes a type IV secretion system (T4SS), which is a multi-molecular complex that mediates the translocation of bacterial factors into the host cell [81,82]. CagA, a major *H. pylori* virulence factor that is produced by most strains of this species, is secreted via the T4SS into gastric epithelial cells, where it plays a pivotal role in the etiology of *H. pylori*-associated gastric diseases [79,83].

Churin et al. demonstrated that *H. pylori* infection activates Met and induces a motogenic response. They further showed that CagA binds Met and deregulates Met downstream signaling, which could be responsible for cancer onset and tumor progression [84] (Fig. 4). Oliveira et al. also showed how *H. pylori* strains with a functional T4SS induces an increase in Met tyrosine phosphorylation and in MMP-2 and MMP-9 activity. This could lead to extracellular matrix degradation and a subsequent invasion of cancer cells, suggesting a role for *H. pylori* in the later stages of gastric carcinogenesis [85]. They further demonstrated that E-cadherin plays a protective role in *H. pylori*-induced cell invasive phenotypes [86]. They found that *H. pylori* decreased the phosphorylation levels of Met in E-cadherin–catenin functional cell lines. Also, depending on the E-cadherin status, infection with *H. pylori* has different effects on the tyrosine phosphorylation of p120-catenin. *H. pylori* alters the E-cadherin–catenin complex, leading to the formation of a multiprotein complex composed of CagA, Met, E-cadherin, and p120-catenin. This complex abrogates Met and p120-catenin tyrosine phosphorylation and consequently suppresses the cell-invasive phenotype induced by *H. pylori*.

Once within gastric epithelial cells, some CagA molecules are tyrosine-phosphorylated by the Src/Abl kinase. Although the importance of CagA phosphorylation has been studied intensively, recently accumulating information suggests that nonphosphorylated CagA also contributes to the development of *H. pylori*-associated gastric illnesses, which includes gastric cancer [87,88]. Suzuki et al. showed that nonphosphorylated CagA is involved in interacting with activated Met, leading to the sustained activation of PI3-K/Akt signaling in response to *H. pylori* infection. This in turn leads to the activation of β-catenin and to NF-κB signaling, which promotes proliferation and inflammation, respectively [89].

Various tumors are known to overexpress Met, which leads to shedding. The amount of shed Met ectodomain fragments has been significantly correlated with the potential for malignancy [90]. Moreover, ectodomain shedding of Met can be induced by EGFR ligands, and HGF in turn is able to transactivate EGFR followed by enhanced activation of ERK or PI3-K pathways [91]. Schirrmeister et al. showed that infection with *H. pylori* provokes a shedding of the surface proteins of Met through a disintegrin and metalloprotease family of proteases, ADAM10 [92], which explains the CagA independent mechanism for Met-dependent phenotypes after *H. pylori* infection.

These published data suggest that HGF-induced activation of Met in gastric epithelial cells has an anticipated impact on *H. pylori*-related gastric diseases, which includes gastric cancer. However, a logical model of HGF and *H. pylori*-induced Met signal transduction has been presented [93]. The molecular interactions included in the model were all assembled manually based on meta-analysis of published experimental results. This model reveals the differences and commonalities in the response of the network upon HGF and *H. pylori*-induced Met signaling. Their data indicated that PLCγ1 represents a key factor in *H. pylori*-induced ERK activation. Inhibition of ERK1/2, which is critically important for the induction of cell scattering in *H. pylori*-infected epithelial cells, could represent a target for the treatment of invasive stomach cancers caused by *H. pylori* infection. Moreover, in light of their observation that the activation of ERK by HGF is not influenced by a PLCγ1 inhibition, the use of specific pharmaceutical inhibitors for PLCγ1 might thus represent a promising therapeutic strategy to prevent the pathogenic effects of *H. pylori* infection. This is an interesting approach to host-pathogen systems biology that aims to decipher the signaling changes brought about by pathogenic bacteria, which could provide an *in silico* prediction of a relevant target against pathogen infection. In addition, McCracken et al. recently developed a *de novo* generation of three-dimensional human gastric organoids *in vitro* via the directed differentiation of human pluripotent stem cells [94]. Using human gastric organoids to model the pathogenesis of human disease, they demonstrated that *H. pylori* infection resulted in a

rapid association of the virulence factor CagA with Met, the activation of signaling, and the induction of epithelial proliferation, and presents a new *in vitro* system to elucidate the mechanisms underlying stomach development and disease. This model is also useful for the screening of efficient therapeutic drugs.

Various species of Helicobacter have been described in animals. It has been suggested that cats and dogs could act as animal reservoirs in the transmission of *H. heilmannii* and other Helicobacter species to humans. In humans, similar to *H. pylori*, *H. heilmannii* accompanies the pathogenesis of chronic gastritis, peptic ulcer disease, gastric cancer and mucosa-associated lymphoid-tissue lymphoma. Met immunoreactivity has been found in the lymphocytes composing the mucosa associated with lymphoid-tissue lymphoma following oral administration of *H. heilmannii* to mice, and HGF immunoreactivity has been recognized mostly in the endothelial cells and macrophages in the mucosa-associated lymphoid-tissue lymphoma [95]. Moreover, the administration of either the antibody against Met or Met inhibitor to infected mice has induced a significant suppression of the mucosa-associated lymphoid-tissue lymphoma lymphomagenesis in mucosa-associated lymphoid-tissue lymphoma after *H. heilmannii* infection.

Listeria infection and Met signaling

Listeria monocytogenes (*L. monocytogenes*) is a foodborne pathogen responsible for human listeriosis, a systemic infection with a 30% mortality rate [96]. Upon ingestion, *L. monocytogenes* not only can survive and multiply in the intestinal lumen, it can also cross the blood–brain barrier and cause meningitis and encephalitis, and it can cross the placental barrier, which can result in abortion and neonatal infection [97]. The ability of *L. monocytogenes* to cross these host barriers relies on its capacity to invade nonphagocytic cells. This ability is mediated by two bacterial surface proteins: internalin (Inl) A and B [98].

InlB is an *L. monocytogenes* surface protein noncovalently bound to its cell wall. Surprisingly, it was reported that InlB interacts with Met [34] (Fig. 4). The binding of InlB to Met mimics HGF signaling and induces membrane ruffling and cell scattering via the activation of the PI3-K, which is a process critical for internalization of *L. monocytogenes* [99]. Further analysis demonstrated that intestinal target cells of *L. monocytogenes* exhibit a constitutive PI3-K activity, rendering InlB dispensable for InlA-dependent intestinal barrier crossing of *L. monocytogenes*. In contrast, the placental barrier does not exhibit constitutive PI3-K activity, which means the InlB-Met pathway is necessary for InlA-dependent *L. monocytogenes* placental invasion [100]. InlB protein has an N-terminal cap region, a leucine-rich repeat domain, an interrepeat Ig-like (IR) region, a B-repeat, and three C terminal GW

modules (which are 80 amino acid repeats that start with the amino acid sequence GW). The structure presented by Niemann et al. indicated that the leucine-rich repeat domain of InlB binds strongly to the first Ig-like domain of Met while maintaining flexibility in the Met N-terminal Sema domain [101]. They also showed that the interaction between the IR domain of InlB and Met is critical for the further activation of Met. As the IR domain alone cannot bind to Met, the interaction between the leucine-rich repeat and Met would serve as a docking site, allowing the IR-Sema interaction that promotes Met activation. Interestingly, the HGF (β-chain)-binding sites for Met do not overlap those of InlB. Despite the fact that InlB is not structurally related to HGF, and that HGF and InlB bind to different regions in Met and induce different Met conformations, InlB has the potential to induce very similar signaling pathways to HGF after Met activation [102].

The potential of InlB to activate Met without competition to HGF allows the application of InlB as an HGF mimic. Mungunsukh et al. engineered a head-to-tail repeat of fragments of the InlB protein from amino acids 36-321 with a linker peptide (2xInlB 36-321) [103]. They demonstrated that this tandem dimmer induces signaling through ERK1/2, PI3-K/Akt, and STAT3 pathways, and has improved migratory activity. This linker peptide also induces proliferation in primary lung cells equivalent to full-length HGF. In a similar manner, Kolditz et al. used structure-based engineering to introduce two intermolecular disulfide bonds into InlB321, resulting in a dimeric protein with a two-fold (C2) symmetry, which is referred to as the InlB321-crystal dimer. In contrast to HGF, the InlB321-crystal dimer is a non-glycosylated protein, and large-scale production can easily be accomplished in *Escherichia coli.* InlB321-crystal dimer elicited the same response as HGF in terms of mitogenic and motogenic effects on human keratinocytes. To facilitate its application as a therapeutic drug for dermal wounds, they developed a hydroxyethyl cellulose gel that could be an appropriate vehicle for InlB321-crystal dimer with regard to its stability [104].

HGF and uropathogenic *Escherichia coli* (*E. coli*) infection

The urinary tract is frequently the source of *E. coli* bacteremia. Bacteria from the urinary tract must cross an epithelial layer to enter the bloodstream. The epithelium plays a central role in host defenses against pathogens. Using an *in vitro* model of epithelial tissue, Wu et al. demonstrated that a loss of epithelial polarity by HGF treatment reduces the ability of renal epithelium to resist invasion by J96, the uropathogenic strain of *E. coli*. This suggests that although HGF seems to be important in the process of epithelial organ regeneration, it may also transiently compromise an organ's resistance to bacterial invasion [105].

HGF signaling and *Pseudomonas aeruginosa*-induced keratitis

Pseudomonas aeruginosa (P. aeruginosa) is a gram-negative bacterium that is one of the most common keratitis-inducing microbial isolates. Jiang et al. reported that HGF signaling impacts the severity of *P. aeruginosa* keratitis. They established important regulatory roles for HGF, the levels of which appear critical to Met signaling, downstream mammalian targeting of rapamycin (mTOR) regulation (promoting or inhibiting), and disease outcome [106]. HGF signaling through Met, if not balanced, results in enhanced *P. aeruginosa*-induced keratitis, whether that balance is manipulated by recombinant HGF application, or by the rapamycin inhibition of mTOR.

HGF-Met pathway and viral infectious diseases

Kaposi sarcoma-associated herpes virus is a principal causative agent of Kaposi sarcoma and primary effusion lymphoma, which arises preponderantly in immunocompromised individuals, particularly patients with acquired immune deficiency syndrome (AIDS). Kaposi sarcoma is the most frequent type of malignant lesion in patients with AIDS, even after the widespread use of combination antiretroviral therapy, and it is characterized by spindle cell proliferation, inflammatory cell infiltration, angiogenesis, edema, and invasiveness [107,108]. Tadeschi et al. evaluated the plasma concentrations of selected cancer-associated inflammatory and immune-modulated cytokines in HIV-positive patients with advanced Kaposi sarcoma and reported that plasma HGF is among the candidates for a novel predictor of clinical responses during combination antiretroviral therapy in HIV-positive Kaposi sarcoma patients [109]. In addition, Dai et al. reported that the HGF-Met pathway is highly activated by Kaposi sarcoma-associated herpes virus *in vitro* and *in vivo* [110]. They also demonstrated that selective Met inhibitor PF-2341066 can induce apoptosis of primary effusion lymphoma via cell-cycle arrest and DNA damage, and it has suppressed tumor progression in a xenograft murine model.

Adult T-cell leukemia (ATL) is an intractable malignancy of CD4 T cells that is etiologically associated with infection by human T-cell leukemia virus-type I. Most individuals in the chronic stage of Adult T-cell leukemia eventually undergo progression to a highly aggressive acute stage. Choi et al. isolated CD4 cells from individuals in the chronic or acute stages of Adult T-cell leukemia and profiled their gene expressions using DNA microarrays [111]. Met gene expression was specific to the acute stage of Adult T-cell leukemia, and the plasma concentration of HGF was increased in individuals in either the acute or chronic stage. They further described how HGF induces the proliferation of a Met-

positive Adult T-cell leukemia cell line, and how this effect can be blocked by antibodies against HGF.

Hepatocellular carcinoma is the most common form of liver cancer worldwide, and chronic infection with hepatitis B virus (HBV) is one of the major causes. HBV infection causes chronic liver inflammation, subsequent cirrhosis, and, ultimately, malignant progression to hepatocellular carcinoma. Studies using Met Tg mice have demonstrated that overexpression of Met alone is sufficient to promote the development of hepatocellular carcinoma [112,113], which suggests the pathological significance of the HGF-Met pathway in hepatocellular carcinoma. Consistently, Ozden et al. have shown that serum HGF levels in patients with chronic hepatitis B reflects the viral load, necro-inflammatory activity in the liver, and the degree of structural progression [114]. Elevated levels of HGF and EGF have been found in HBV-infected individuals, and these growth factors are known to stimulate survival signaling in primary human hepatocytes [115]. Notably, Xie et al. reported that liver tumors from human HGF transgenic (Tg) mice have gene expression patterns that are virtually the same as those from HBV-positive hepatocellular carcinoma patients, which corresponds to patients with a poor prognosis [116]. These findings suggest that HGF or HGF-Met signaling markers are crucial determinants in generating hepatocellular carcinoma and in predicting sensitivity to Met inhibitors.

Hepatitis C virus (HCV) is involved in the initiation and progression of liver fibrosis by regulating genes encoding host proteins. Zhu et al. discovered that cellular microRNA miR-16 levels were increased in patients with HCV infection and were inversely correlated with HGF and Smad7 expression levels in those patients [117]. A human liver cell line infected with an Ad-HCV core adenovirus (coding for the first 191 amino acids of the HCV polyprotein corresponding to the HCV core protein) continued to show upregulated levels of miR-16 associated with decreased expressions of HGF and Smad7. Additionally, interferon-α (IFN-α) could reverse the changes in gene expression induced by HCV infection. These results suggest that the upregulation of miR-16 expression induced by HCV infection is a novel mechanism that contributes to the downregulation of HGF and Smad7 in the development of liver fibrosis.

Collectively, the HGF-Met system plays an important role in many infectious diseases that share similarities with conditions such as cancer, tissue injury, cardiovascular disease, neurodegenerative disease, and auto-immune diseases. The monitoring of HGF and Met expression, along with real-time detection of Met activation, can be a beneficial biomarker of these infectious diseases in terms of diagnosis and/or prediction of disease progression. Although the HGF-Met system is somewhat of a double-edged sword in infectious diseases,

manipulating the HGF-Met system with complete control, either positive or negative, can systemically and/or locally (topically) lead to a tailor-made treatment for those infectious diseases.

To mimic HGF stimulation, the macrocyclic peptide capable of activating Met was discovered [118]. The monomeric macrocyclic peptides are capable of high-affinity binding to the Met, but neither activate Met nor inhibit HGF-induced Met activation. However, dimerization of these peptides conferred them with Met agonistic activity. Dimerized macrocyclic peptides selectively activate Met and exert Met-mediated typical and unique biological activities that are mitogenic, motogenic (enhancement of cell motility), and morphogenic (induction of blanching tubulogenesis). The maximal activities of dimerized macrocyclic peptides are indistinguishable to HGF. The current library of research promotes the clinical application of these small HGF-mimicking peptides, as well as the development of alternative technologies for the production of non-protein regenerative medicines for broad applications in the future.

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Table 1. Physiological roles of HGF deduced from conditional knockout mice

Met$^{-/-}$ Tissue/Cell Types	Characteristics	Ref.
Liver		
Hepatocytes	Highly susceptible to apoptosis after liver injury	[13]
	Impairment in recovery from liver necrosis after liver injury	
	Impairment in Erk1/2 activation and G2/M transition after liver injury	[14]
Hepatocytes	Steatotic change of the liver in aged mice	[15]
	Decrease in mitotic hepatocytes after partial hepatectomy	
	Delayed regeneration after partial hepatectomy	
Hepatocytes	Promoted liver fibrosis after liver injury	[16]
	Extensive necrosis and lower proliferation of hepatocytes after bile-duct ligation	[17]
	Enhanced susceptibility to liver fibrosis	
Oval cells	Decrease in oval cell viability and more prone to apoptosis	[18]
	Reduction in oval cell pool	[19]
	Impairment in migration and differentiation into hepatocytes	
Kidney		
Tubular cells	No appreciable defect in kidney morphology and function	[20]
	Aggravated renal injury and inflammation after acute kidney injury	
Podocytes	Neither albuminuria nor overt pathologic lesions	[21]
	Severe podocyte injury and apoptosis, and albuminuria after toxic injury	
Collecting duct	Increased fibrosis and tubular necrosis after unilateral ureteral obstruction	[22]
	Reduced capacity in regeneration after release of the obstruction	
Ureteric bud	Double knockout of *Met* and *EGF* receptor in ureteric bud Decrease in branching and a reduction in final glomerular number	[23]
Skin		
Keratinocytes	Lack of keratinocyte migration after skin wound	[24]
	Severe impairment epidermal wound closure	
Pancreas		
β-Cell	Mild hyperglycemia, and decreased serum insulin levels at 6 months	[25]
	Loss of acute-phase insulin secretion in response to glucose, and impaired glucose tolerance	
	Diminished glucose tolerance and reduced plasma insulin after a glucose challenge	[26]
	Normal glucose and β-cell homeostasis	[27]
	Susceptible to streptozotocin-induced diabetes	
Nervous System		
Ganglionic eminence	Increased numbers of striatal GABAergic interneurons in the lateral sensorimotor	[28]
	Areas with distinct behavioral deficits	
	Delayed procedural learning	
Cerebral cortex	Larger size in the rostral cortex, caudal hippocampus, dorsal striatum,	[29]

and hippocampus	thalamus, and corpus callosum	
Dorsal pallial	Increases proximal and reduces distal apical dendritic branching of neocortical pyramidal neurons in post-pubertal period	[30]
Forebrain neurons	Reduced volume of cortical tissue	[31]
	Increase in spine head volume, but no change in density of spines	
	Hyperconnectivity in circuit-specific intracortical neurons	
Heart		
Cardiomyocytes	Normal heart development	[32]
	Cardiomyocyte hypertrophy and interstitial fibrosis by 6 months	
	Systolic cardiac dysfunction by 9 months	
Immune System		
Dendritic cells	Impaired emigration toward draining lymph nodes upon inflammation-induced activation	[33]
	Impaired contact hypersensitivity reaction to contact allergens	

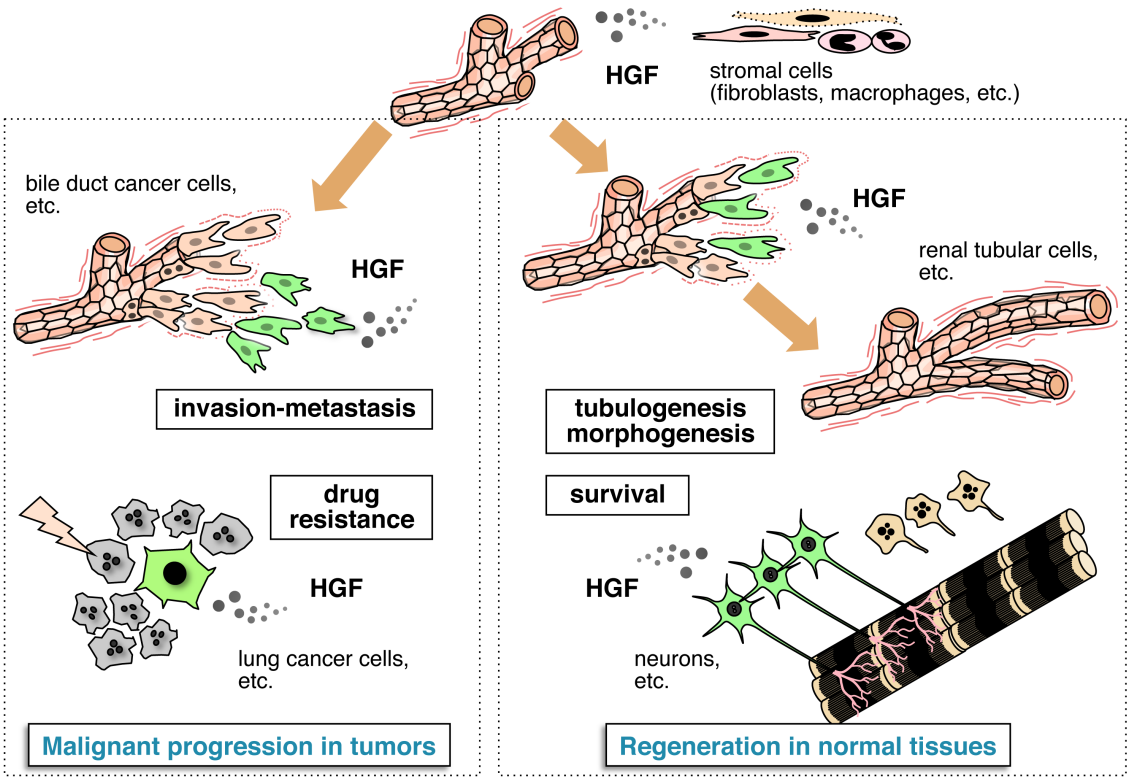

Figure 1

Two-pronged roles of HGF in tissue regeneration and cancer tissues. HGF is mainly expressed in stromal cells. Cells responding to HGF are conceptually shown in green. Dynamic morphogenesis (e.g., blanching tubulogenesis in renal tubular cells) and promotion of cell survival (e.g., for neurons) mediated by the HGF–Met pathway play roles in tissue regeneration after tissue injury (**right portion**). Dynamic cell movement and survival promoted by Met activation participate in invasion-metastasis and resistance to anticancer drugs in cancer tissues (**left portion**).

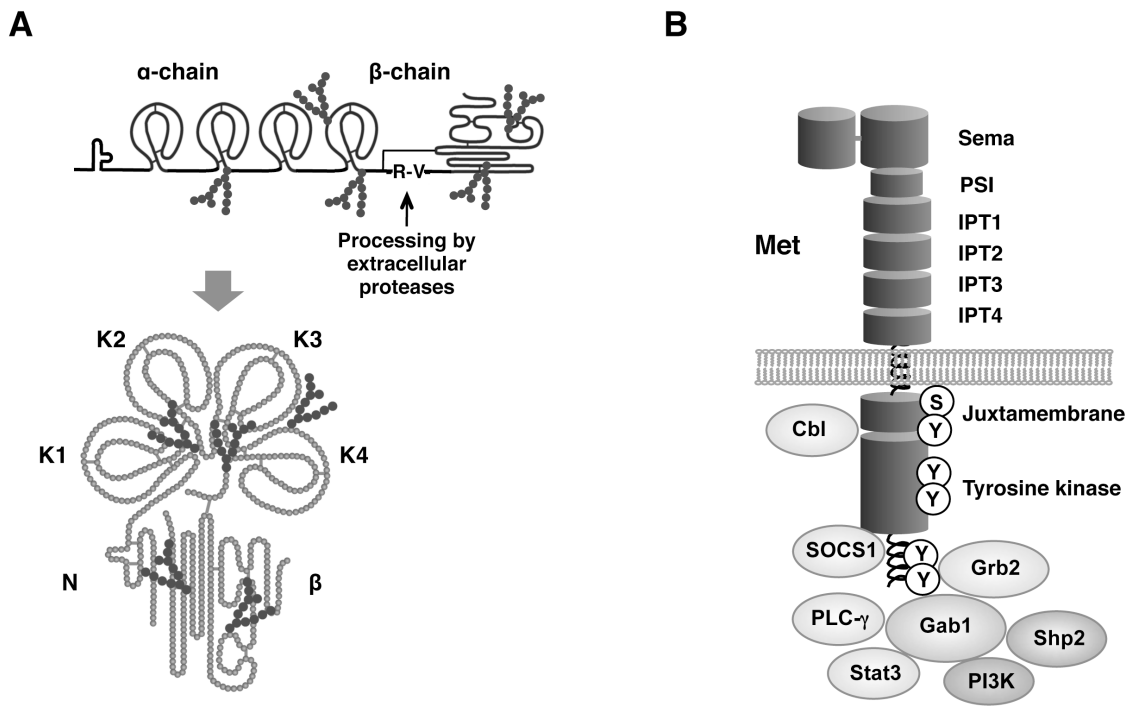

Figure 2

Schematic structures of HGF (**A**) and Met (**B**). A single-chain HGF is cleaved between Arg494 and Val495 by serine proteases and HGF is modified by glycosylation. Domain structure of Met and typical signaling molecules are described.

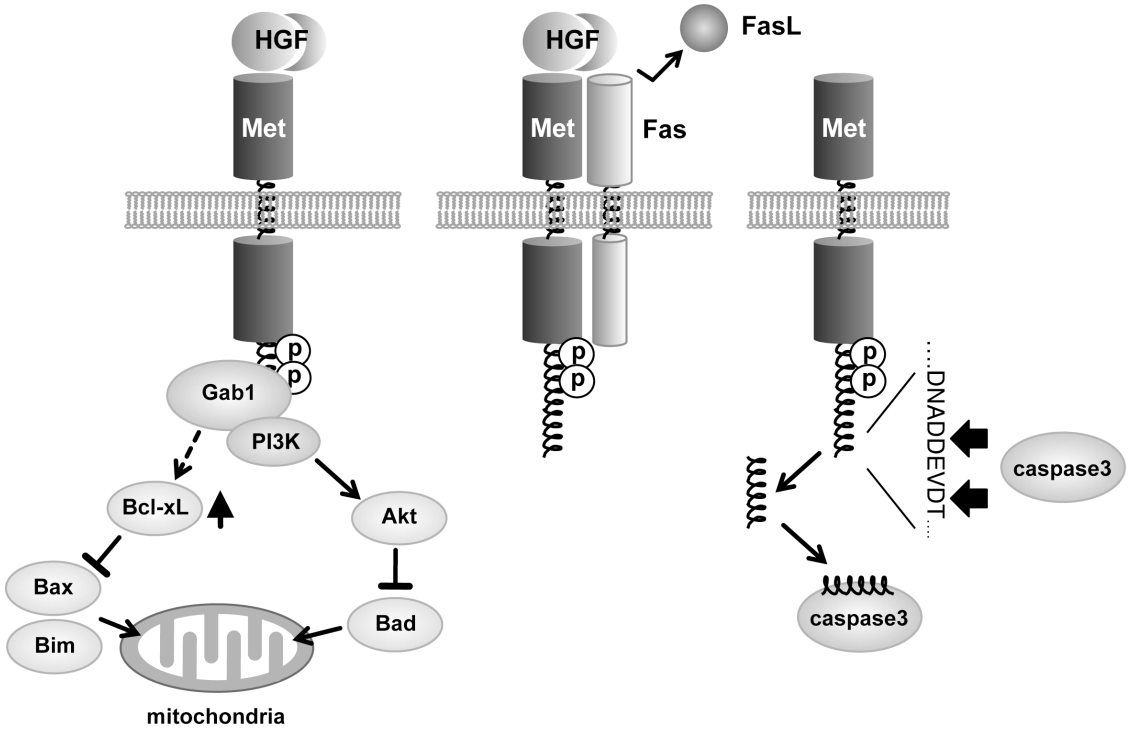

Figure 3

Molecular mechanisms responsible for the promotion of cell survival (suppression of death-inducing signal) are mediated by the HGF–Met pathway.

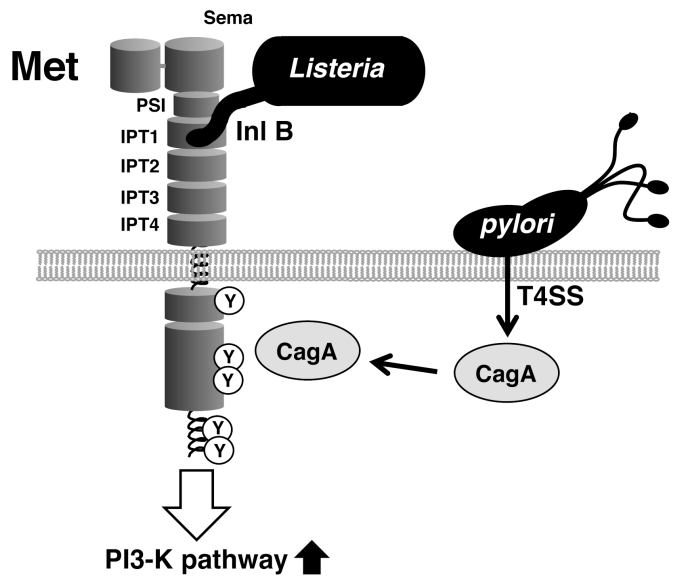

Figure 4

Hijack HGF-Met pathway. Bacterial protein InlB (*Listeria monocytogenes*) or CagA (*Helicobacter pylori*) deregulates Met downstream signaling, which creates a suitable environment for infection.