# Hepatocyte Growth Factor



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Katsuya Sakai,[1] Takayoshi Kinoshita,[2] and Kunio Matsumoto[1]

[1]Division of Tumor Dynamics and Regulation,

Cancer Research Institute,

Kanazawa University

[2]Department of Biological Science,

Graduate School of Science,

Osaka Prefecture University

**Contact Information**

Kunio Matsumoto, Ph. D.

Division of Tumor Dynamics and Regulation,

Cancer Research Institute

Kanazawa University

Kakuma, Kanazawa 920-1192

Japan

Tel: +81-76-264-6745

Fax: +81-76-234-4513

E-mail: kmatsu@staff.kanazawa-u.ac.jp

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## Abstract

Hepatocyte growth factor (HGF) exerts biological activity through the Met receptor tyrosine kinase. HGF plays essential roles in the embryonic development of the liver and placenta, and in the migration of myogenic precursor cells. In mature tissues, HGF plays roles in tissue protection and regeneration, including in the liver and kidney. HGF participates in invasion, metastasis, and drug resistance. Drug development targeting HGF-Met has been challenging. One focus has been the use of recombinant HGF as a biological drug and another has been the use of HGF-Met inhibitors for cancer treatment. Clinical trials using HGF or HGF-Met inhibitors are ongoing.

## I. Introduction

In 1984, hepatocyte growth factor (HGF) was reported to be a mitogenic protein for hepatocytes in primary culture. The primary structure of HGF became evident with cDNA cloning in 1989, when HGF was identified as a novel growth factor. A scatter factor was identified as a fibroblast-derived factor that enhances motility and the spreading of epithelial cells, and in 1991, it was found to be identical to HGF. Likewise, in 1991 the purification of a fibroblast-derived growth factor that targets a variety of epithelial cells independently revealed that it was identical to HGF.

A tumorigenic *met* oncogene was initially isolated from chemically transformed human osteosarcoma cells in 1984. The primary structure of the *met* proto-oncogene clarified in 1987 predicted that the Met is a receptor-type transmembrane tyrosine kinase. The Met was identified as a functional receptor for HGF in 1991. Following the molecular cloning of HGF and the identification of Met as a HGF receptor, diverse approaches revealed a variety of developmental, physiological, and therapeutic roles for HGF. Elucidation of the HGF-Met pathway in tumor biology has facilitated the clinical development of different types of inhibitors for HGF-Met.

## II. Structure of HGF and the Met receptor

HGF is a heterodimeric molecule composed of an α-chain and a β-chain, which are linked by one disulfide bridge (Fig. 1A). HGF is biosynthesized as a prepro-form of 728 amino acids, including a signal sequence and both α- and β-chains. After cleavage of a signal peptide of the first 31 amino acids, a single-chain HGF is further cleaved between Arg494 and Val495, and this resulted in the formation of a two-chain mature HGF. Single-chain HGF is biologically inactive and processing into a two-chain form is coupled to its activation. Several serine proteases, mainly HGF activator, urokinase-type plasminogen activator, matriptase, and hepsin are responsible for the processing of HGF. There are various forms of HGF such as those produced through the alternative splicing of HGF mRNA. A variant with five amino acids deleted in the first kringle domain is the second major form of HGF. N-terminal smaller variants consisting of the N-terminal hairpin and the first kringle domains (designated NK1) and the N-terminal hairpin plus the first and

second kringle domains (designated NK2) are naturally biosynthesized variants of HGF, though expression of these variants is either very low or restricted in some cell lines.

The Met receptor is composed of structural domains, the extracellular Sema, PSI (the similar structure is found in the plexins, semaphorins and integrins) and IPT (a similar structure is found in the immunoglobulin-like fold shared by plexins and transcriptional factor) domains, the transmembrane domain, the intracellular juxtamembrane, and tyrosine kinase domains (Fig. 1B). HGF exhibits a 50% homology to an amino acid sequence in HGF-like protein. HGF and HGF-like protein contain four kringle domains in the α-chain. HGF-like protein specifically binds and activates Ron receptor tyrosine kinase, a family of the Met receptor.

Binding of HGF to the Met receptor induces the phosphorylation of tyrosine residues in the activation loop of a tyrosine kinase domain, which results in the activation of tyrosine kinase and the subsequent phosphorylation of tyrosine residues in the C-terminal multifunctional docking site. Phosphorylation of the C-terminal tyrosine residues plays a critical role in both the direct and indirect recruitment of various intracellular signal transducers (Fig. 1B). Association of the adapter protein Gab-1 (Grb2-associated binding protein 1) with Met provides docking platforms for the further binding of signaling molecules, which leads to biological responses that are unique to the HGF-Met pathway.

NK1 and NK2 bind the Met receptor as smaller N-terminal variants of HGF. NK1 serves a minimum set of domains that are responsible for high-affinity binding of HGF to the Met receptor, while β-chain binds to the Met with a lower affinity compared with the α-chain. The extracellular complex structure between HGF and Met was proposed using structural analyses such as small-angle X-ray scattering (Fig. 1C). NK1 and NK2 exhibit antagonistic activity on HGF-induced mitogenesis, while they function as agonists in terms of cell motility activity. NK4 is composed of an N-terminal hairpin and four kringle domains, and it binds to Met but does not activate Met, thereby being antagonistic to HGF.

Crystal structures have been revealed in selected domains of HGF and Met: NK1 and β-chain in HGF; and, Sema, PSI, and tyrosine kinase domains in Met. The complex structures for NK1 and heparin, the β-chain of HGF and Sema, and the PSI domains of Met have also been determined. The crystal structures for the NK1 dimer, the complex structures of β-chain and Sema + PSI domains, and tyrosine kinase domains are shown in Fig. 2.

## III. Biological activities

HGF exhibits multiple biological activities in a wide variety of cells (Table. 1). HGF is mitogenic for differentiated epithelial cells (e.g., hepatocytes, renal tubular cells, bronchial and alveolar epithelial cells, gastric epithelial cells, and keratinocytes, etc.), vascular endothelial cells, mesenchymal/stromal cells (e.g., cardiomyocytes, articular chondrocytes, and osteoclast-like cells, etc.), and stem cells such as hepatic stem cells, hematopoietic progenitor cells, and skeletal satellite cells, as well as precursor cells that differentiate into myocytes. HGF as a "motogen" stimulates motility and migration in various cells. Among the multipotent characteristics of HGF, its morphogenic activity is unique. HGF induces branching tubulogenesis in epithelial cells, including renal tubular cells, mammary gland epithelial cells, and hepatic bile duct epithelial cells.

HGF promotes cell survival in several cell types, including hepatocytes, renal epithelial cells, vascular endothelial cells, cardiac myocytes, and neurons. HGF increases the activity and/or gene expression of proteases involved in the breakdown of extracellular matrix components, including urokinase-type plasminogen activator and matrix metalloproteases. Induction of these proteases plays an important role in the branching of tubulogenesis, as well as in migration and invasion of cells. HGF induces the epithelial to mesenchymal transition of dermomyotome cells in embryos.

## IV. Developmental roles

The essential roles of HGF in the development of mammalian fetal tissues have been defined via the targeted disruption of either HGF or the Met receptor gene using knockout mice that are embryonically lethal due to impaired organogenesis of the placenta and liver.

In the placenta, the number of epithelial trophoblasts in the labyrinthine layer is markedly reduced, leading to an impaired exchange of oxygen and nutrients between the maternal and embryonic blood streams. The embryonic liver is reduced in size and shows extensive apoptotic cell death, indicating that hepatoblasts/hepatocytes in the embryonic liver require HGF for proliferation and/or survival.

Activation of the HGF-Met pathway plays a decisive role in the generation of skeletal muscle that is derived from long-range migrating muscle precursor cells. In $Met^{-/-}$ mice, there is an impairment of the long-range migration of Met-positive myogenic precursor cells from the dermomyotome in the somite to limb buds and the diaphragm, which results in an absence of skeletal muscles of the limb and diaphragm. Since HGF is strongly expressed in the limb bud mesenchyme and septum transversum (which develops into the diaphragm), HGF provides spatially defined chemoattractant-like motogenic signals for the migration of myogenic precursor cells. A similar chemoattractant-like function of HGF was noted in the migration of myogenic precursor cells into the tongue.

Epithelial-mesenchymal interactions mediate crucial aspects of normal development, affecting tissue induction, morphogenesis, and organogenesis. Involvement of HGF in epithelial-mesenchymal interactions and in the morphogenesis of organs has been revealed in organ culture experiments. Cultured embryonic organs undergo morphogenic steps that mimic their development *in vivo*. In organ cultures, neutralizing the anti-HGF antibody inhibits both the morphogenesis of developing lung epithelia and the branching tubulogenesis of developing epithelia in kidneys and mammary glands. In tooth germ culture, inhibition of HGF expression impairs the morphogenesis of tooth epithelium. Thus, HGF is known to be a mesenchymal-derived paracrine factor that supports the morphogenesis of developing epithelia during the organogenesis of the lung, kidney, and tooth.

In the nervous system, HGF has chemoattractant-like functions. Developing axons can be guided to their targets by diffusible molecules and factors bound to the cell surface that act either as chemoattractants or repellents. Transplanted limb buds attract motor axons in

amphibians and birds. In a similar manner, explanted mouse limb bud mesenchyme attracts the axons of motor neurons. HGF has been identified as a chemoattractant factor that is derived from the limb bud mesenchyme. The developmental and morphogenic roles of HGF are summarized in Table 2.

## V. Physiological functions

Regeneration of the liver is a dramatic phenomenon in higher animals. When 70% of the liver is resected, the cells in the remaining liver rapidly proliferate, and the original liver mass is restored within a week. HGF was initially implicated as a hepatotrophic factor that enhances liver regeneration, and the hepatotrophic role of HGF has been definitively demonstrated in a variety of experimental hepatic disease models. Likewise, HGF plays physiological roles in the regeneration and/or protection of various tissues, as demonstrated in different types of disease models in different tissues (Table 2).

A conditional knockout of the Met gene in mice has helped to define the roles of the HGF-Met pathway in tissue protection and repair (Table 3). Hepatocytes subjected to selective loss of functional Met are highly susceptible to cell death even after mild liver injury, indicating that the anti-apoptotic activity of HGF plays a role in protection of the liver. Liver- or hepatocyte-specific $Met^{-/-}$ mice have shown delayed liver regeneration associated with persistent inflammatory reaction, and are susceptible to fibrotic change in the liver. After bile duct ligation, hepatocyte-specific $Met^{-/-}$ mice were more susceptible to chronic inflammation and fibrotic change compared with control mice. The effects shown by these liver- or hepatocyte-specific $Met^{-/-}$ mice indicate the physiological roles of the HGF-Met pathway in the protection, regeneration, anti-inflammation, and anti-fibrosis of the liver.

In addition to the liver, characterizations of a variety of conditional Met knockout mice indicate that the HGF-Met pathway plays important roles in the regeneration, protection, and homeostasis in various cells and tissues (Table 3). For instance, a loss of functional Met in renal tubules had no appreciable defect in renal function, but when tubular cell-specific $Met^{-/-}$ mice were subjected to renal injury, they displayed a higher serum creatinine, more severe morphologic lesions, and increased apoptosis compared with control mice.

In podocyte-specific $Met^{-/-}$ mice, no pathology was seen, but the mice developed more severe podocyte apoptosis and albuminurea in comparison with control mice when subjected to toxic renal injury for podocytes. Disruption of the Met gene in epidermal keratinocytes has clearly demonstrated an indispensable role for the HGF-Met pathway in skin wound healing. Because migration of keratincocytes post-wounding is almost completely impaired in $Met^{-/-}$ keratinocytes, re-epithelialization was severely suppressed, indicating a definitive role for the HGF-Met pathway in skin wound healing.

Increased HGF levels in sera or tissue fluid have been noted in patients with distinct types of diseases, including acute hepatitis, fulminant hepatitis, acute renal rejection after transplantation, pneumonia, cardiac infarction, severe acute pancreatitis, and Crohn's, Huntington's, Parkinson's, and Alzheimer's diseases. Increased HGF levels in sera or tissue fluids are likely to reflect physiological responses to tissue and cellular damage.

## VI. Tumorigenesis and tumor progression

Aberrant activation of Met is associated with tumor development or progression to a tumor with malignant characteristics. Overexpression of Met through transcriptional upregulation has been noted in several cancers, including thyroid, ovarian, pancreatic, prostatic, renal, hepatocellular, breast, and colorectal. Overexpression of Met through gene amplification has been found in cancers with highly invasive and malignant characteristics, including gastric and esophageal carcinomas, medulloblastoma, and non-small-cell lung carcinomas (NSCLC). Autocrine and paracrine activation of Met through overexpression of HGF has been noted in breast cancer, glioblastoma, rhabdomyosarcoma, osteosarcoma, and in NSCLC with acquired and intrinsic resistance to EGFR tyrosine kinase inhibitors.

Missense mutations in the Met gene are causative genetic disorders in inherited, and in some sporadic, papillary renal carcinomas. Mutations found in papillary renal carcinomas are located in the tyrosine kinase domain of the Met receptor, and these Met mutations are likely to be gain-of-function mutations. In addition to papillary renal carcinoma, missense mutations in the Met gene have been found in different types of cancers, including lung

cancer, hepatocellular carcinoma, and gastric cancer in the Sema, IPT, juxtamembrane, and tyrosine kinase domains.

Although aberrant activation of the Met is involved in the tumorigenic transformation of cells, the Met activation in tumor cells participates in the progression to malignant tumors that is characterized by invasiveness, metastatic behavior, and/or resistance to anticancer therapies. Cell-cell adhesion, cell-extracellular matrix association, proteolytic breakdown of the extracellular matrix, and cellular locomotion regulate the invasiveness of tumor cells. Because HGF affects these processes, HGF exhibits profound effects on the invasive behavior of a wide variety of tumor cells. Gene transfer experiments that involve autocrine activation of the Met receptor confer invasive and metastatic behavior in cancer cells. Although tumor-stromal interaction closely affects the invasive and metastatic behavior of carcinoma cells, HGF is a key stromal-derived factor that confers invasive characteristics in cancer cells in a variety of tumor microenvironments.

Gefitinib and erlotinib, selective inhibitors for epidermal growth factor receptor (EGFR) tyrosine kinase, show favorable responses in NSCLC, particularly those expressing activating mutations in EGFR. However, almost without exception, the patients develop acquired resistance to EGFR tyrosine kinase inhibitors within several years. Met gene amplification has been detected in ~20% of patients with acquired resistance to gefitinib or erlotinib. HGF induces resistance to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer. High-level expression of HGF has been noted in 60 and 19% of patients with acquired and intrinsic resistance to EGFR tyrosine kinase inhibitors, respectively. In addition to EGFR tyrosine kinase inhibitors, HGF in a tumor microenvironment has conferred resistance to BRAF inhibitors in malignant melanoma and breast cancer. Collectively, the over-expression of HGF in cancer cells and/or stromal cells and Met overexpression in cancer cells closely participate in the resistance to several molecular targeted drugs.

Pathological and clinical studies have indicated that the presence of hypoxic regions within neoplastic lesions correlates with a poor prognosis and an increased risk of the

development of distant metastases. A hypoxic condition has been known to induce the transcriptional activation of the Met receptor gene and the subsequent amplification of HGF-Met signaling, thereby increasing the invasiveness of cancer cells. A connection between hypoxia and the Met receptor seems to explain why hypoxia often correlates with invasive and metastatic behavior.

The concept of a cancer stem cell proposes that tumors are organized in a cellular hierarchy, and they are maintained by a subpopulation of cells displaying stem cell characteristics, i.e., self-renewal and differentiation that contributes to cellular heterogeneity and tumor bulk. The HGF-Met pathway plays an important role in regulating the stemness and invasiveness of cancer stem cells. In a brain tumor model, cancer stem cells aggressively invaded surrounding normal brain tissues. Met gene expression was much higher in tumor-initiating cells, compared to non-tumor-initiating cells. Strong Met tyrosine phosphorylation was seen in the population of the cancer stem cells, and HGF enhanced the invasion of the brain tumor-initiating cells. In colon adenocarcinomas, myofibroblast-derived factors, specifically HGF, activated Wnt/β-catenin signaling and subsequently the clonogenicity of colon cancer stem cells. Therefore, together with Wnt activity, HGF plays a role in maintaining the stemness of colon cancer stem cells through tumor-stromal interaction in the microenvironment. The promotion of stemness by HGF has also been noted in cases that include human prostate cancer and basal-like breast cancer.

## VII. Therapeutic approaches using HGF

Based on the evidence that activation of the Met receptor leads to tissue protection and repair against tissue injury, but also to invasive and metastatic progression of cancer cells in tumor tissues, two distinct therapeutic approaches can be considered: one is application of HGF, i.e., Met-agonist, for treatment of organ injuries; and the other is application of inhibitory molecules against the HGF-Met pathway to inhibit cancer invasion and metastasis.

Experiments to explore the therapeutic potential of HGF in the treatment of diseases have been performed in various disease models in different tissues (Table 2). Administration of human recombinant HGF into mice or rats stimulates the proliferation of hepatocytes after liver insult caused by partial hepatectomy or hepatotoxins. Through its anti-apoptotic action, HGF has been used to abrogate the onset of acute hepatitis and fulminant hepatic failure. Likewise, the administration of HGF has accelerated tissue regeneration and/or attenuated tissue injury in other organs. HGF has suppressed the onset of acute renal failure caused by the administration of nephrotoxic drugs or renal ischemia. HGF administered to rats with cardiac ischemia-reperfusion injury has reduced the extent of apoptosis in cardiac myocytes, thereby reducing the infarcted area.

Chronic inflammatory diseases are characterized by fibrotic changes in tissues, including liver cirrhosis, chronic renal failure, lung fibrosis, and cardiomyopathy. These fibrotic diseases are progressive and currently incurable. Administration of HGF into rats with liver cirrhosis has been used to decrease the accumulation of hepatic extracellular matrix components, thereby abrogating the mortality rate due to hepatic dysfunction. HGF has prevented renal fibrosis and the concomitant renal dysfunction in models of chronic renal failure or renal fibrosis. Although mechanisms responsible for the anti-fibrotic action of HGF are not fully understood, HGF suppresses the expression of transforming growth factor-β, a key growth factor during the onset of tissue fibrosis, while HGF enhances the protease activities responsible for the degradation of extracellular matrix components, including matrix metalloproteinases.

The neurotrophic actions of HGF have been expanded to include therapeutic approaches for the treatment of injury or diseases of the nervous system. An infusion of HGF into the brain has been used to prevent neuronal death in the hippocampus and in the cerebral cortex. Intrathecal administration of HGF has suppressed disease progression and prolonged the life span in rat models for amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disorder characterized by the progressive loss of motor neurons and the degeneration of motor axons. Likewise, the intrathecal administration of HGF has been used to promote functional recovery after spinal cord injury in the common marmoset.

The efficacy and safety of the intramuscular injection of a naked plasmid encoding the human HGF gene was investigated in patients with critical limb ischemia in a multicenter, randomized, double-blind, placebo-controlled trial. HGF achieved a significantly higher improvement rate than the placebo, including the improvement of resting pain and a reduction in ulcer size. In this instance, HGF gene therapy improved the quality of life, without major safety problems. Thus, HGF gene therapy has been found to be safe and effective for critical limb ischemia. A phase-I clinical trial of recombinant HGF protein for the treatment of patients with acute kidney injury has been completed and is ongoing for the treatment of patients with ALS.

## VIII. Drug development for cancer treatment

Several distinct approaches to inhibition of the HGF-Met pathway have been demonstrated, including small synthetic inhibitors for Met tyrosine kinase, ribozymes, small-interfering RNA, neutralizing monoclonal antibodies, soluble forms of Met, antagonistic domains in HGF, and uncleavable single-chain HGF. Among these approaches, the development of small-molecule Met tyrosine kinase inhibitors and monoclonal antibody against HGF or Met progressed earlier than the others, and several inhibitors against HGF-Met either are currently in clinical development or is already being marketed (Table 4).

Crizotinib was originally developed as a Met tyrosine kinase inhibitor, and it strongly inhibits anaplastic lymphoma kinase (ALK). Because the fusion oncogene EML4-ALK has been effective for a distinct clinicopathologic subset of patients with non-small cell lung cancer (NSCLC), crizotinib has been approved for the treatment of these patients who also have demonstrated an ALK mutation.

MetMAb is a humanized monovalent monoclonal antibody against Met receptor that blocks the binding of HGF to the Met, while rilotumumab and SCH900105 are humanized monoclonal antibodies against HGF. Among small molecule tyrosine kinase inhibitors, some have a relatively higher selectivity to Met while others are multi-target tyrosine kinase inhibitors. Effectiveness, target cancer, and advantages/disadvantages of each of these

therapeutic tools (small molecule Met tyrosine kinase inhibitors, anti-HGF, or anit-Met) will be clarified in further clinical trials.

## IX. Perspectives

Earlier studies on the biological and physiological functions of HGF as motogenic and morphogenic factors during development and tissue regeneration/protection have been definitively demonstrated in genetic mouse models lacking functional HGF or Met. Conditional knockout mice lacking functional Met in selective cells/tissues have revealed not only implicated functions from earlier studies but also unpredicted functions from earlier studies. On the other hand, decreased Met function has been found to increase the risk of developing autism spectrum disorders in extensive analysis among autism families. Selective deletion of functional Met in selective regions/neurons in the forebrain in mice showed changes associated with the autism spectrum disorder. Thus, a large-scale gene analysis in humans will further clarify the relationship between aberrant HGF-Met function and disorders, and the corresponding animal models will explore new therapeutic approaches.

Progress during the past decade in the development of the potential therapeutic use of Met activators (HGF or HGF gene) and Met inhibitors (Met tyrosine kinase inhibitors, antibodies against HGF/Met) should be emphasized. The use of recombinant HGF and the HGF gene has entered into the development phase in clinical trials. Several HGF-Met inhibitors are in clinical trials for the treatment of patients with malignant tumors and some of them have been successfully marketed. Clinical study on abnormal HGF-Met function in the pathogenesis of malignant tumors will explore further therapeutic uses of HGF-Met inhibitors for the treatment of patients with malignant tumors.

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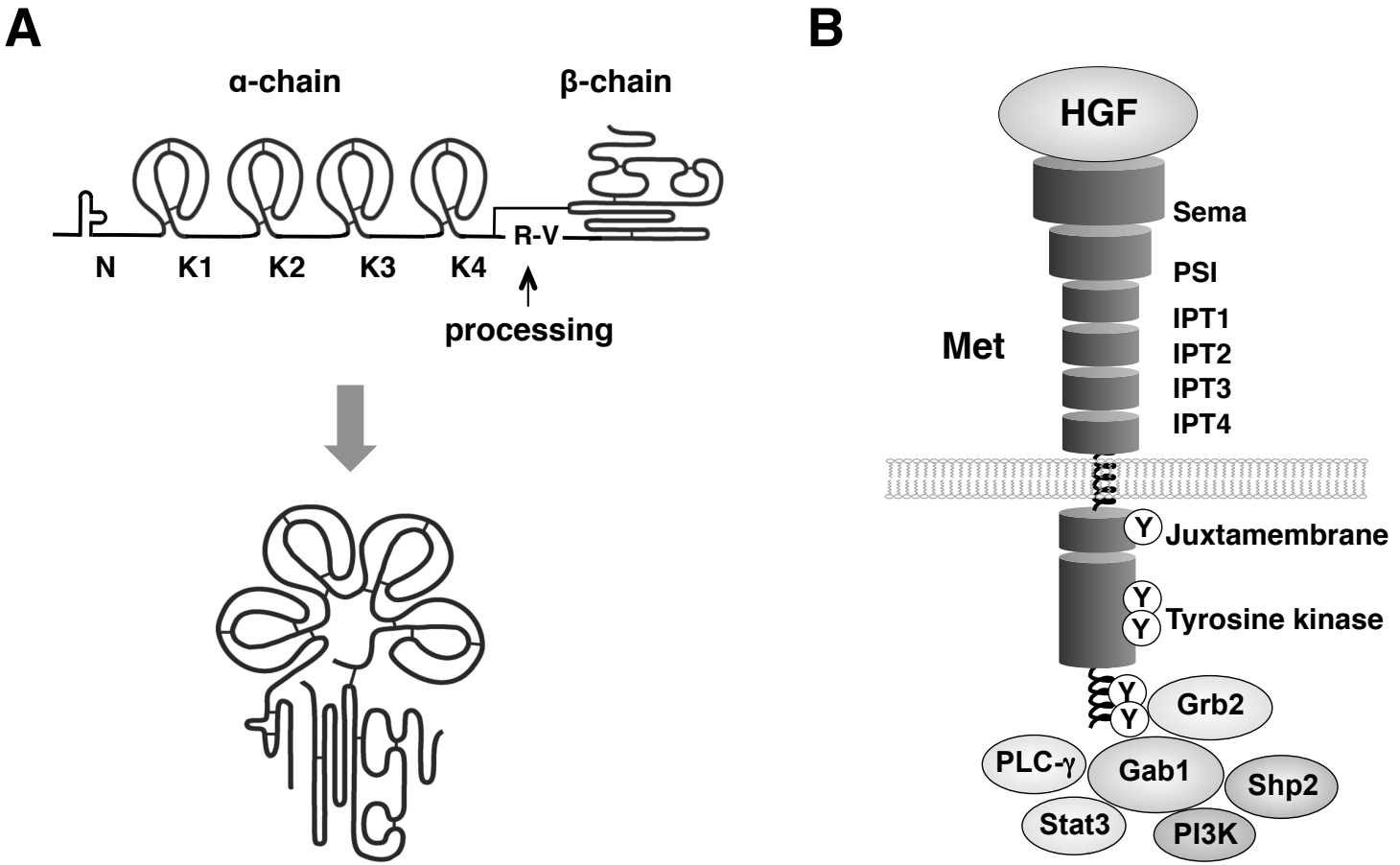
**Table 1**. Target cell types of HGF

| Tissue type | Target cell type |
|---|---|
| Hepato-bilialy and pancreas | hepatocyte<br>hepatoblast<br>bile duct epithelial cell<br>pancreatic β-cell |
| Gastrointestinal | gastric epithelial cell<br>intestinal mucosal epithelial cell |
| Kidney | renal tubular cell<br>podocyte |
| Lung | bronchial epithelial cell<br>alveolar type II epithelial cell |
| Nervous | neuron (hippocampal neuron, cerebral cortex neuron, midbrain dopaminergic neuron, cerebellar granular neuron, motor neuron, thalamic neuron, sensory neuron, sympathetic neuron, parasympathetic neuron, subventiricular zone neural stem-like cell), Schwann cell, astrocyte, oligodendrocyte progenitor cell |
| Cardiovascular and lymphatic | cardiomyocyte (in hypoxic condition)<br>vascular endothelial cell<br>lymphatic vessel cell |
| Hematopoietic and immune | dendritic cell<br>hematopoietic stem/progenitor cell<br>monocyte-osteoclast<br>macrophage (conditionally) |
| Skin and eye | keratinocyte<br>melanocyte<br>hair bulb keratinocyte<br>corneal epithelial cell |
| Muscle, bone, and joint | muscle satellite cell<br>myogenic precursor cell<br>articular chondrocyte |
| Glands | mammary gland epithelial cell<br>submandibular gland epithelial cell<br>salivary gland epithelial cell<br>prostate epithelial cell<br>thyroid cell |
| Placenta | cytotrophoblast |

Fig. 1A, B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β-chain
N
K1
K2
K3
K4
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B
HGF
Sema
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IPT2
IPT3
IPT4
Met
Y
Juxtamembrane
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Y
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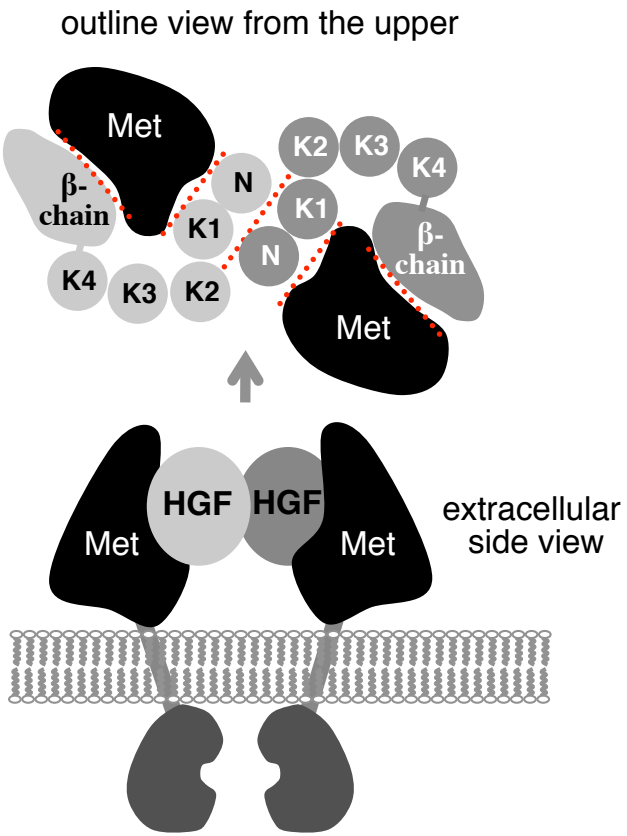
PLC-γ
Gab1
Shp2
Stat3
PI3K

Fig. 1C

C


outline view from the upper
Met
β-chain
K4
K3
K2
K1
N
N
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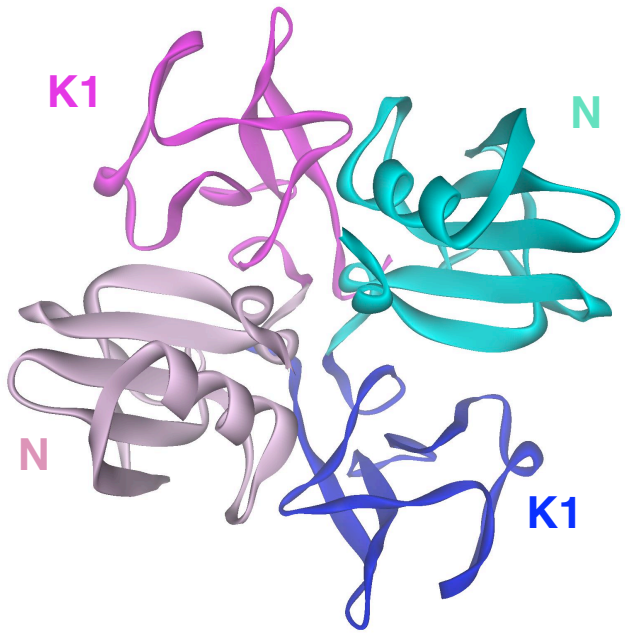
K2
K3
K4
β-chain
Met
HGF
HGF
Met
Met
extracellular side view

Fig. 3A, B

A


K1
N
N
K1

B

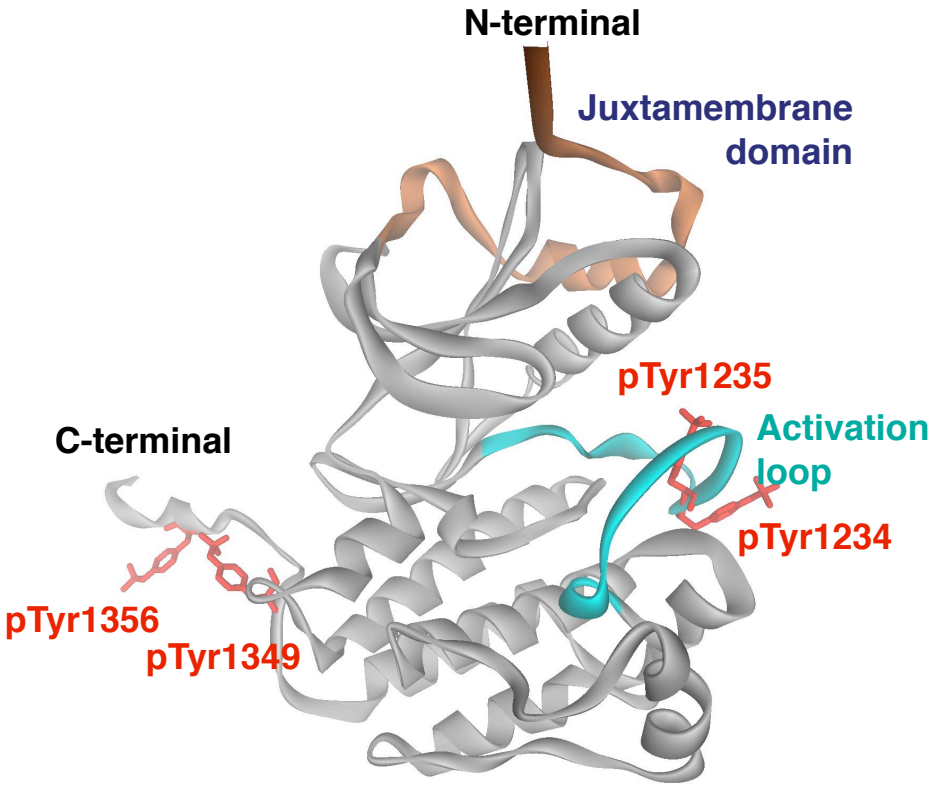

N-terminal
Juxtamembrane domain
pTyr1235
Activation loop
C-terminal
pTyr1234
pTyr1356
pTyr1349

Fig. 3C

C