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Emerging Multipotent Aspects of Hepatocyte Growth Factor

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Specific tissue interactions between epithelia and mesenchyme (or stroma), *e.g.*, epithelial-mesenchymal (or -stromal) interactions mediate crucial aspects of normal development and tissue regeneration. These events affect tissue induction, organogenesis, cell movement, and morphogenesis of multicellular structures. Extensive and diverse studies have established that hepatocyte growth factor (HGF), a ligand for the c-*met* protooncogene product of receptor tyrosine kinase, is a mesenchymal- or stromal-derived multipotent polypeptide which mediates epithelial-mesenchymal interactions. During embryogenesis, HGF supports organogenesis and morphogenesis of various tissues and organs, including the liver, kidney, lung, gut, mammary gland, tooth, skeletal system, *etc.* In adult tissues, HGF elicits a potent organotrophic function which supports regeneration of organs including the liver, kidney, and lung. In the brain, HGF is a new member of the family of neurotrophic factors. In neoplastic tissue, HGF is involved in tumor invasion and metastasis, through tumor-stromal interactions. While HGF was originally identified as a potent mitogen for mature hepatocytes, the biological functions of this factor reach far beyond the original identifications. Such being the case, use of HGF for purposes of therapeutics is being given increasing attention.

Key words: c-*met*, epithelial-mesenchymal interactions, HGF, morphogenesis, organogenesis, organ regeneration.

Growth factors which share multipotent characteristics regulating proliferation, motility, and differentiation of cells are members of critical molecules responsible for complex biological processes, including embryogenesis, angiogenesis, tissue regeneration, and malignant transformation. Hepatocyte growth factor (HGF) was initially identified in a partially purified form to be a potent mitogen for mature hepatocytes in primary culture (*1-4*). HGF was thereafter completely purified (*5-7*) and was molecularly cloned in 1989 (*8, 9*).

In 1990 to 1991, independent approaches led to isolation of bioactive molecules using different assay method were unexpectedly joined upon molecular cloning of factors. The cloning of cDNAs for scatter factor (*10*), tumor cytotoxic factor (*11*), and fibroblast-derived epithelial growth factor (*12*) revealed these molecules to be identical with HGF. Scatter factor was originally identified as a fibroblast-derived factor which "scatters" tightly growing epithelial cell colonies (*13*). Tumor cytotoxic factor proved to be fibroblast-derived factor which inhibits growth of certain species of carcinoma cells (*14*). In 1991, a fibroblast-derived epithelial morphogen which induces branching tubulogenesis in epithelial cells also proved to be HGF (*15*), and a natural ligand for the receptor-tyrosine kinase, c-*met* protooncogene product was identified as HGF in the same year (*16, 17*).

While HGF is a potent hepatotrophic factor responsible for vigorous regeneration of the liver, it has become a well characterized multipotent growth factor which targets a wide variety of cells (reviewed in Refs. *18-22*). HGF has "trophic" roles for regeneration and maintenance of various tissues and organs (*18, 23*). Recent extensive studies on expression and functional analysis of HGF during embryogenesis revealed a distinct aspect of this factor as a mediator in morphogenic epithelial-mesenchymal interactions essential for organogenesis (*24-34*). Based on its potent motogenic (enhancement of cell motility) and angiogenic activities, it seems clear that HGF is involved in growth, invasion, and metastasis of tumor cells. In this review, we will focus on unique multipotent aspects of HGF as a mediator in specific cell-cell interactions.

Biochemical characteristics of HGF and c-Met

HGF is a heterodimer with a 69 kDa α-chain and a 34 kDa β-chain, linked by a single disulfide bridge (*5-7*) (Fig. 1). The α-chain contains the N-terminal hairpin structure and four homologous "kringle domains" and the β-chain has serine protease-like motif. Thus, HGF has a structural homology with plasminogen (*8, 12, 35-37*). But HGF has no serine protease activity, while plasminogen and its active form, plasmin share no biological activities of HGF (*8*). HGF is translated from a single mRNA, as a single chain preproHGF. Extracellular processing by specific serine protease, HGF-activator or HGF-converting enzyme (*38, 39*), results in conversion from a biologically inactive form to active two chain mature HGF.

There are two known distinct forms of naturally occurring variant HGF, biosynthesized through alternative splicing of pre-mRNA; one form is deleted with 5 amino acids in the first kringle domain (*12, 37*) while the other

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Abbreviations: HGF, hepatocyte growth factor; HLP/MSP, HGF-like protein/macrophage stimulating protein.

form consists of only the N-terminal hairpin domain and two kringle domains (*40, 41*). The former has mitogenic and motogenic activities whereas the latter form has no mitogenic activity but does have motogenic activity (*42, 43*). This smaller variant is likely to be a minimum unit for binding to the c-Met/HGF receptor, with a relatively high-affinity. In accordance with this, deletion of the N-terminal hairpin domain, the first kringle domain, or the second kringle domain in the HGF molecule results in a total loss of biological activities (*43, 44*).

The tumorigenic met oncogene was initially isolated from chemically transformed human osteosarcoma cells. Although the primary structure of the c-*met* protooncogene product predicted it to be a receptor-type tyrosine kinase, it remained orphan (or lonesome) receptor until two research groups independently identified its natural ligand to be HGF (*16, 17*). The c-Met/HGF receptor is heterodimeric molecule composed of a 50 kDa α-chain and a membrane spanning 145 kDa β-chain which contains the intracellular tyrosine kinase domain (*45*). The Met/HGF receptor, when autophosphorylated in response to HGF, binds a number of substrata containing the Src homology region 2 (SH2) domains such as phosphatidylinositol 3-kinase, Grb-2(Ash)/Sos complex, Ras GTPase activating protein, pp60^{Src}, and phospholipase C-γ (*46, 47*). These intracellular signaling molecules associate with a docking site of the tandemly arranged C-terminal tyrosine residues 1349 and 1354. Mutation of these tyrosine residues results in loss-of-function mutation (*46, 48, 49*), while mutation of the juxtamembrane tyrosine residue suppresses the loss-of-function mutation of the Met/HGF receptor (*49*).

While growth factors are often classified into certain families, based on structural similarity, cDNA encoding an unique protein with a similar domain structure to HGF was isolated and the putative protein was termed HGF-like protein (HLP) (*50*). HLP was later shown to be an molecule identical with macrophage stimulating protein (MSP) (*51, 52*), originally purified from human serum. On the other hand, the c-Met/HGF receptor has two distinct family members; Ron and Sea (*53, 54*). Ron tyrosine kinase was identified as a specific receptor for HLP/MSP (*55-57*), but a ligand for Sea tyrosine kinase remains to be identified (Fig. 2).

Biological activities

The growth-regulating activity of HGF for various cell types has been well-characterized, as described in Table I. HGF has mitogenic activity for epithelial cells (*12, 18, 58-68*), endothelial cells (*69-71*), some stromal cells (*72-76*), and various species of carcinoma cells (*58, 78-82*). HGF

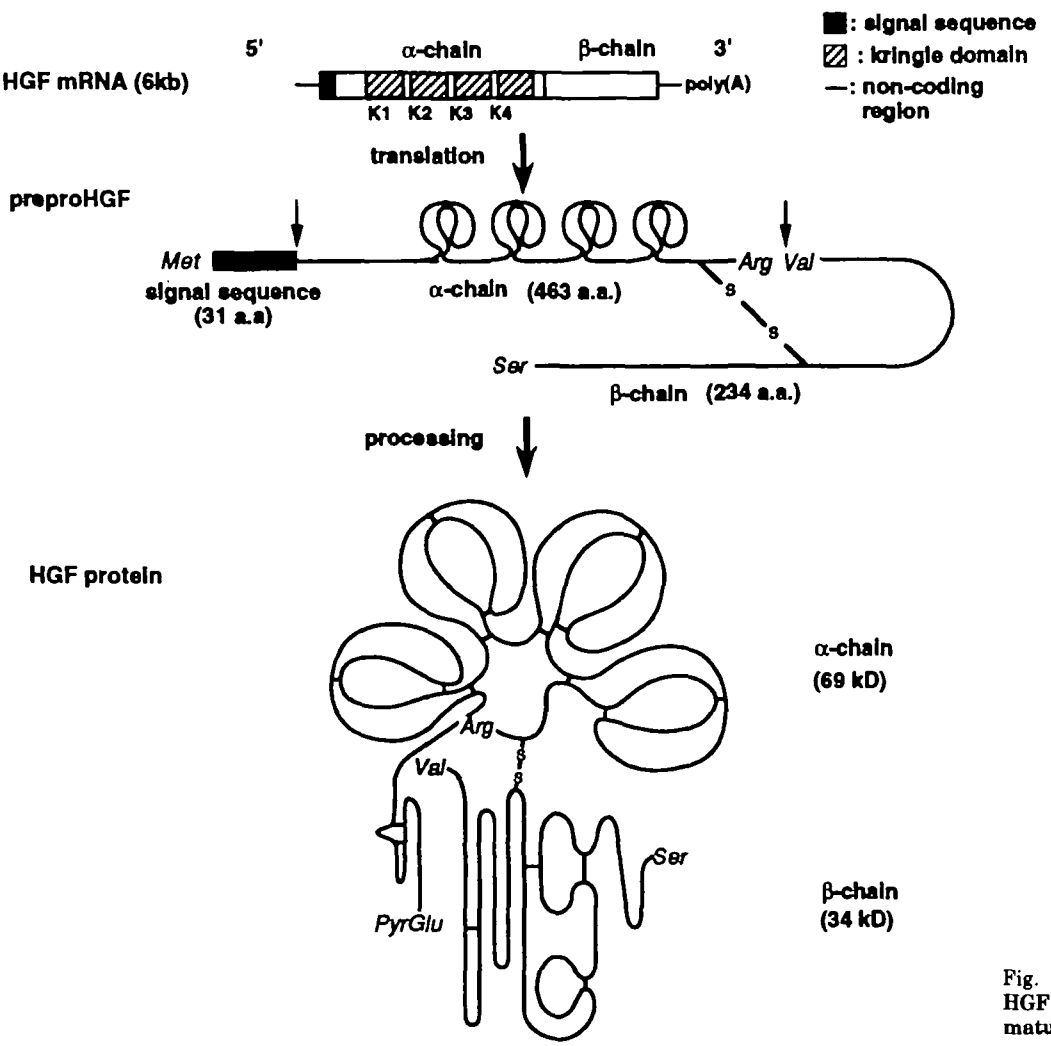

Fig. 1. Schematic structure of HGF mRNA, preproHGF, and mature HGF.

also has an angiogenic activity when implanted *in vivo* (*70, 71*). Recent studies revealed that HGF is also involved in hematopoiesis (*72, 74, 76*), chondrogenesis, and bone remodeling (*75, 77*). HGF stimulates proliferation of hematopoietic progenitor cells and enhances the formation of colonies toward erythroid lineage or granulocyte-erythroid-megakaryocyte lineage (*72-74, 76*). HGF enhances growth and differentiation of osteoclastic cells at the terminal stage (*77*). Articular chondrocytes are target cells of HGF and HGF mRNA is expressed at presumptive articular regions during development (*75*). *In vitro* and *in vivo* studies provided that HGF has anti-tumor activity for certain species of carcinoma cells, and in particular, growth of most hepatoma cells is inhibited by HGF (*14, 83-85*).

Cell movement is an important process during embryogenesis, wound healing, and tumor invasion. Although some growth factors are known to enhance cell motility, HGF is one of most potent motogens to induce dissociation and cell movement in various types of cells (Table I) (*13, 30, 59, 70, 78, 79, 81, 86-89*). The motogenic activity of HGF is mediated by activation of small GTP-binding proteins, Rho, Ras, and Rac (*90-93*). Disruption and regulation of cell-cell and cell-matrix interactions are related to the phosphorylation of E-cadherin-associated molecules (β-catenin, plakoglobin, and p120) (*94, 95*) and focal adhesion kinase ($p125^{FAK}$) (*88*), respectively. HGF also disrupts intercellular communications mediated by gap junctions (*96, 97*).

Among the multipotent characteristics of HGF, the morphogenic activity is notable and unique. This activity was initially noted in three-dimensional collagen gel cultures using MDCK cells derived from renal epithelium, wherein HGF induces branching tubular structures (*15*). Induction of similar branching tubules and gland-like structures in epithelial cells also occurs in other cells, including cell lines derived from hepatic duct and mammary gland (*29, 30, 80*). Therefore, HGF is an important factor regulating morphogenic processes during development and tissue reconstruction (see below).

Several ligands for receptor-tyrosine kinases have distinct neurotrophic actions in the brain, including members of the nerve growth factor family, basic fibroblast growth factor, and epidermal growth factor. HGF and c-Met/HGF receptor are expressed in various regions of the brain (*98, 99*). HGF activates Ras in neurons (*100*) and acts as a potent survival factor for primary cultured neurons and PC12 pheochromocytoma cells (*99, 101, 102*), all findings to support the thesis that HGF belongs to the family of neurotrophic factors. Likewise, HGF acts as a mitogen for Schwann cells (*103*).

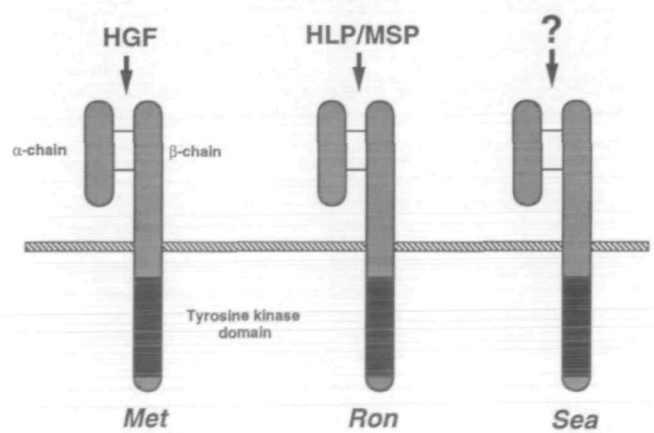

Fig. 2. Ligand-receptor relationship in molecules of HGF and c-Met/HGF receptor families.

HGF in epithelial-mesenchymal interactions and development

Interactions between epithelium and mesenchyme, *e.g.*, epithelial-mesenchymal interactions mediate crucial aspects of normal development, affecting tissue induction, organogenesis, and morphogenesis of specific multicellular structures. Development and morphogenesis of various organs and tissues, including kidney, lung, liver, pancreas, limb, tooth, mammary gland, hair follicle, *etc.* depend on epithelial-mesenchymal interactions. A conceptual frame-

TABLE I **Typical biological activities of HGF and target cells.**

Biological activity	Target cells
Mitogenic	
	Hepatocytes
	Hepatoblast-like cells
	Hepatic ductular epithelial cells
	Renal tubular cells
	Keratinocytes
	Hair cells
	Melanocytes
	Gastric epithelial cells
	Corneal epithelial cells
	Bronchial epithelial cells
	Alveolar type II epithelial cells
	Thyroid cells
	Mammary gland epithelial cells
	Schwann cells
	Pancreatic β cells
	Placental cytotrophoblasts
	Prostate epithelial cells
	Osteoclast-like cells
	Vascular endothelial cells
	Articular chondrocytes
	Hematopoietic progenitor cells
	Gallbladder cancer cells, *etc.*
Motogenic	
	Renal epithelial cells
	Hepatic ductular epithelial cells
	Keratinocytes
	Thyroid cell
	Mammary gland epithelial cells
	Vascular endothelial cells
	Articular chondrocytes
	Myogenic precursor cells
	Oral squamous carcinoma cells
	Gallbladder carcinoma cells
	A431 epidermoid carcinoma, *etc*
Morphogenic	
	Renal epithelial cells
	Hepatic epithelial cells
	Mammary gland epithelial cells
	Colon carcinoma cells, *etc.*
Promotion of cell survival	
	Neurons
	PC12 rat pheochromocytoma cells
Tumor inhibition	
	Hepatoma cells (HepG2, *etc*)
	B6/F1 melanoma cells
	KB squamous carcinoma cells, *etc.*

work of epithelial-mesenchymal interactions was established in the 1950s and 1960s, but molecular mechanisms responsible for these interactions have not been elucidated. Recent extensive works on HGF have established that HGF is a mesenchymal-derived mediator in epithelial-mesenchymal interactions.

During kidney development, the first interaction between epithelial ureteric bud and mesenchymal metanephric blastema is essential for the development of the kidney. Epithelial cells derived from ureteric bud form branching collecting tubules and mesenchymal cells at the tip of collecting tubules convert to epithelial cells that form the nephron. During organogenesis of the kidney, c-Met/HGF receptor mRNA is expressed in epithelial cells, while HGF mRNA is expressed in mesenchymal cells in close proximity to renal epithelial cells (*24, 26*). A specific antibody against HGF inhibits both morphogenesis of the kidney in organ culture system and differentiation of metanephric mesenchymal cells into epithelial precursors of the nephron (*25, 26*). Together with *in vitro* induction of branching tubulogenesis by HGF, this factor is a mesenchymal-derived morphogen for renal epithelial cells and is involved in transdifferentiation from mesenchymal to epithelial cells. Likewise, HGF and c-Met/HGF receptor mRNA are expressed in mammary gland tissue, and HGF potently promotes the formation of branching duct-like structures by mammary gland epithelial cells *in vitro* (*29-31*). Therefore, HGF may mediate inducing effects of mesenchyme (or stroma) on mammary gland development.

The potential participation of HGF in organogenesis was also demonstrated by disruption of the HGF gene (*27, 28*). In the homozygous mutant mice of HGF gene, embryos are lethal, due to defected development of the placenta (*28*) or both placenta and liver (*27*). Likewise, in c-*met* homozygous mutant mouse embryos, development of the liver and placenta was defected (*89*). These defects are in consistent with the finding that HGF is a potent mitogen for placental cytotrophoblasts (*64*), as well as hepatocytes. The essential role of HGF in liver development has recently been demonstrated using *in vivo* loss-of-function mutation in the *Xenopus* embryo. Overexpression of mutant c-Met/HGF receptor of tyrosine kinase-minus (TK^--Met) in *Xenopus* embryos resulted in liver defects and impaired development of pronephros, gut, and skeletal morphogenesis in tail regions (Aoki *et al.*, submitted). These results indicate that HGF and the c-Met/HGF receptor are highly conserved molecules, at least with regard to development of the liver, from amphibians to mammals. In contrast, in transgenic mice that express HGF specifically in the liver, a new population of small hepatocytes (presumably blastic hepatocytes) appears in the liver (*104*), thereby indicating that HGF may be involved in proliferation of hepatoblast-like cells (*61, 105*).

Localization of HGF and c-Met/HGF receptor mRNA in various tissues indicates that functional coupling between HGF and the c-Met/HGF receptor is important for development, morphogenesis, and migration of cells in other tissues, including limb, branchial arches, lung, tooth, and bone. Figure 3 shows the *in situ* localization of HGF and c-Met/HGF receptor mRNA in developing lung of day 13 of the rat embryo. The c-Met/HGF receptor mRNA is specifically localized in bronchial epithelial cells (Fig. 3, C and D), while HGF mRNA locates in surrounding mesenchymal cells (Fig. 3, A and B). Antisense HGF oligonucleotide specifically inhibits branching tubulogenesis of the developing lung *in vitro* (our unpublished data). Thus, HGF is a mesenchymal-derived factor for branching morphogenesis during lung development. Similarly, the functional coupling between HGF and c-Met/HGF receptor supports tooth development (*32*). The c-Met/HGF receptor is expressed in epithelial tissue while HGF is expressed in mesenchymal tissue in tooth germ, and antisense HGF oligonucleotide specifically induces abnormal tooth morphogenesis in organ culture system (*32*). Expression pattern of HGF and c-*met*, and biological activities of HGF implicate HGF in skeletal morphogenesis and chondrogenesis. HGF is mitogenic and motogenic for chondrocytes (*75*), and HGF and c-*met* are expressed in chondrogenic regions, including rib, limb joints, and branchial arches (*33, 34*). In $met^{-/-}$ embryos, migration of myogenic precursor cells into the limb bud, diaphragm, and tip of tongue is impaired, and as a consequence, skeletal muscles of the limb and diaphragm do not form (*89*). These observations mean that HGF is involved in migration of cells during development. In the chick embryo, HGF is involved in early steps of neural induction, presumably by inducing or maintaining

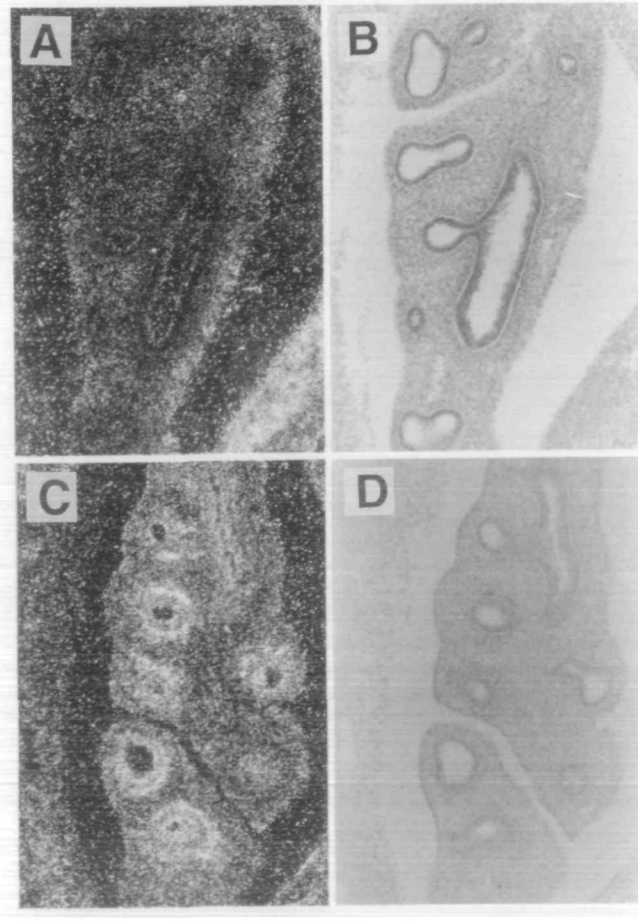

Fig 3 **Expression of HGF and c-Met/HGF receptor mRNA in developing rat lung.** Localization of HGF mRNA (A, B) and c-Met/HGF receptor mRNA (C, D) was analyzed by *in situ* hybridization using day 13 rat embryo. B and D indicate bright field views for A and C, respectively.

competence of the epiblast to respond to neural-inducing signals (*106-109*).

Organotrophic roles

Regeneration of the liver is one of the most dramatic phenomena in higher animals. When 70% of the liver is resected, the cells in the remaining liver rapidly proliferate and the original liver mass and functions are restored within a week. As partial purification of HGF was originally done using peripheral blood of partially hepatectomized rats, HGF was considered to be a humoral hepatotrophic factor which enhances liver regeneration. During the last 10 years, the hepatotrophic roles of HGF have been well-established. HGF is now seen to have the role of organotrophic factor for regeneration of other tissues and organs (*19-23*).

Liver injuries can be induced in rats or mice by means of partial hepatectomy, ischemia, liver crush, or administration of hepatotoxins such as CCl_4 and α-naphthyl-isothiocyanate. Expression of HGF mRNA rapidly increases following the onset of these injuries in the injured liver and distant intact organs such as the lung and spleen. The liver is composed of several types of cells, including parenchymal hepatocytes, sinusoidal endothelial cells, Kupffer cells (liver macrophages), Ito (fat-storing) cells, and bile duct epithelial cells. Cell fractionation and *in situ* hybridization revealed that HGF is expressed in non-parenchymal stromal cells such as Kupffer cells, sinusoidal endothelial cells, and Ito cells, but not in parenchymal hepatocytes, indicating that this factor acts through a paracrine mechanism. Additionally, up-regulation of HGF mRNA in intact organs, together with a marked increase in blood HGF levels, means that an endocrine-related mechanism is likely to be functioning in liver regeneration. Elevated levels of plasma HGF were also well-demonstrated in patients with hepatic diseases (*110, 111*).

Based on a wide spectrum in target cell specificity of HGF, the involvements of HGF in regeneration of other organs was noted. Expression of HGF is rapidly induced after injuries in the kidney and lung (*112, 113*). In analogy with the case of liver injury, non-epithelial stromal cells produce HGF. Taken together with *in vitro* and *in vivo* mitogenic actions of HGF for renal (*114, 115*) and lung epithelial cells (*60, 116*), HGF seems to trigger regeneration of these organs at least through a paracrine mechanism. Therefore HGF is a stromal-derived mediator responsible for organ regeneration. Changes in blood HGF levels were noted in patients with renal diseases (*117*) and in patients treated by renal transplantation (*118*).

Expression of HGF is regulated by various factors. Interleukin-1, platelet-derived growth factor, acidic and basic fibroblast growth factor, epidermal growth factor, prostaglandins, and heparin are potent inducers of HGF expression (*119-121*). In contrast, transforming growth factor-β1 and glucocorticoids suppress the gene expression of HGF (*122, 123*). Although these regulatory molecules are likely to have distinct roles, the regulatory network for expression of HGF may be involved not only in organ regeneration but also in epithelial-mesenchymal and tumor-stromal interactions during organogenesis and tumor progression (see below), respectively.

Direct evidence for the organotrophic roles of HGF has been obtained from *in vivo* studies and these studies suggested potential therapeutic strategies using recombinant HGF. Administration of HGF to experimental animals with liver injury strongly enhanced liver regeneration (*124-126*), and importantly, HGF suppressed the onset of hepatic dysfunction (*124, 127*). Likewise, HGF enhances renal regeneration and suppresses the onset of acute renal failure caused by renal toxins, renal ischemia, or unilateral nephrectomy (*114, 115*). More importantly, HGF prevented the onset of liver fibrosis/cirrhosis and abrogated lethal hepatic dysfunction due to chronic liver injury (*128*). Mitogenic, motogenic, and morphogenic activities, all of which are required for reconstruction of tissue architecture, no doubt are responsible for the organotrophic functions of HGF.

HGF in tumor-stromal interactions

Because of its profound effects on cell growth, motility, and angiogenesis, HGF is implicated in the growth, invasion, and metastasis of tumor cells. As establishment of an autocrine loop of growth factors and their receptors is involved in tumorigenic transformation of cells, gene transfer experiments indicate that autonomous activation of c-Met/HGF receptor results in tumorigenic transformation (*129-132*). Stable transfection of the HGF gene in *met*-expressing epithelial cells (*130-132*), and the c-*met* gene in HGF-producing fibroblasts (*129*) both confer *in vivo* tumorigenicity in these cells. Such an autocrine activation of the Met/HGF receptor is found in certain tumor cells derived from cancer patients (*87, 133*), however, most carcinoma cells derived from epithelial tissues express c-Met/HGF receptor but do not express the HGF gene. This may mean that autocrine activation of the Met/HGF receptor is restricted to certain species of tumor cells.

Studies indicate the particular importance of stromal-derived HGF in invasion and metastasis of carcinoma cells. Growth and invasive potentials of tumor cells are influenced by their interactions with normal stromal fibroblasts (*134-136*). *In vitro* invasion of carcinoma cells into the collagen gel matrix was induced in co-cultivation with stromal fibroblasts (*135*), and fibroblasts can produce migration-stimulating factor (*137*). Although molecular mechanisms underlying these tumor-stromal interactions are of current interest to tumor biologists, one fibroblast-derived invasion factor is known to be HGF (*88*) and HGF induces invasion of various types of carcinoma cells *in vitro* (*78, 79, 81, 86, 87*). In addition to stromal fibroblast-derived HGF, we recently found that carcinoma cells secrete inducing factors for HGF expression in fibroblasts (Matsumoto *et al.*, submitted) and the presence of such inducing factor(s) was also noted by other workers (*138, 139*). Therefore, HGF seems to be a predominant stromal-derived invasion factor for carcinoma cells. The mutual interaction between HGF-expressing stromal cells and Met-expressing carcinoma cells mediated by HGF and its inducers may result in an acquisition of invasive phenotype in tumor cells. The epithelial-mesenchymal (or -stromal) interactions mediated by HGF are likely to be functional in tumor-stromal interactions, as well as in tissue regeneration.

Perspective and future directions

The biological and physiological functions of HGF have been much greater than expected (Fig. 4). However, much

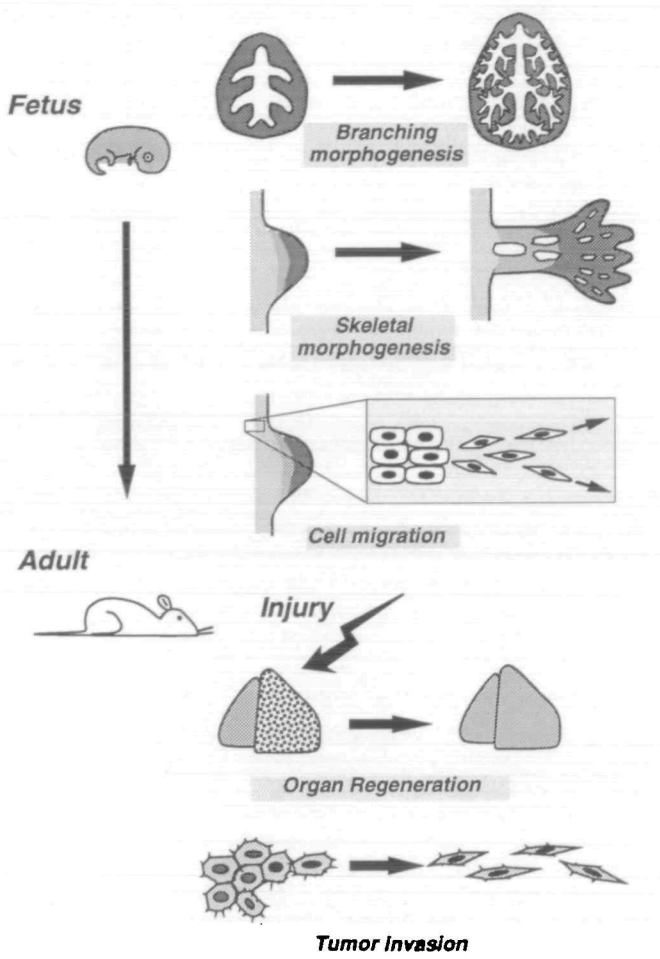

Fig. 4. **Pleiotropic roles of HGF during embryogenesis, organ regeneration, and tumor progression.**

work remains to be determined how HGF exerts its highly diversified activities and how HGF is involved in constructing an organized multicellular tissue structures (*e.g.*, branching tubules).

Target cells of HGF are distributed widely and specific biological roles of HGF for the development and homeostasis of each tissue need to be studied. Although localization and *in vitro* analysis indicate that HGF may well play a neurotrophic role in the brain, specific roles of HGF for the maintenance and regeneration of the central nervous system, and also for the inductive processes, development, and network formation of neural cells are of general interest.

Because of its organotrophic functions, HGF may well have therapeutic potential for disorders of the liver and kidney. HGF is highly effective for chronic and often incurable hepatic disease, *e.g.*, liver fibrosis/cirrhosis. Application of the HGF gene as a therapeutic for chronic diseases may be feasible. The generation and application of antagonistic molecules of HGF may prove to be therapeutic in inhibiting tumor invasion and metastasis.

The biological functions of HLP/MSP and Ron are still uncharacterized. Identification of novel members in HGF and the Met family, and elucidation of biological functions of HLP/MSP will shed light on the biological significance of HGF family molecules in embryogenesis, organogenesis, and tissue regeneration.

Due to space limitation, the papers of some scientists may not have been cited. Nevertheless, we are entirely grateful to all our colleagues for "working on HGF." Gratitude is extended to M. Ohara for helping us to write up this review.

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