

# The Many Faces of Hepatocyte Growth Factor: from Hepatopoiesis to Hematopoiesis

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RESEARCH performed over the past few years, in particular, has made it clear that, in addition to the liver, hepatocyte growth factor (HGF)<sup>1</sup> affects virtually every tissue in the body ranging from the nervous system to the immune and reticuloendothelial systems. Recent findings have also revealed that the biological responses of target cells to HGF are not confined to the induction of cell proliferation and motility per se but include a plethora of effects such as inhibition of cell growth, induction of morphogenesis, stimulation of T cell adhesion to endothelium and migration, enhancement of neuron survival, and regulation of erythroid differentiation. Furthermore, the discoveries of the HGF receptor as Met, of an HGF-related factor, called HGF-like protein, and of HGF-like's receptor as Ron, a transmembrane tyrosine kinase similar to the HGF receptor, have added yet more levels of complexity to the nature of HGF and its now growing family.

### Structural Properties of HGF

Hepatocyte growth factor is a mesenchymally derived heparin-binding glycoprotein that is secreted as a single-chain (pro-HGF), biologically inert precursor. Under appropriate conditions such as tissue damage (21), pro-HGF is converted to its bioactive form by proteolytic digestion at a specific site within the molecule. This proteolytic digestion may be mediated by urokinase plasminogen activator (uPA) (27) or by a protease homologous to factor XII (21). Mature HGF is a heterodimer, consisting of a 60,000  $M_r$  alpha and a 30,000  $M_r$  beta chain held together by a single disulfide bond. The nucleotide sequences of human, rat, and mouse HGF cDNAs also predict that both chains of HGF are encoded by a single open reading frame resulting in a 728-amino acid polypeptide. The alpha chain of HGF contains a hairpin loop (of ~27 amino acids) at its amino terminus and four unique domains known as kringles, while its beta chain contains a serine protease-like structure (26). (For in depth review, see references 20 and 30.) The kringle motif, an 80-amino acid double-looped struc-

ture formed by three internal disulfide bridges, was first described for many of the enzymes involved in coagulation and fibrinolysis. Understandably, HGF resembles several coagulation/fibrinolytic related proteins such as plasminogen, but these proteins have no known growth potentiating activity comparable to HGF. Conversely, HGF has no known protease activity, since the characteristic amino acids normally present in the catalytic site of serine proteases have been mutated in HGF, while the consensus sequences which normally surround them still remain (26). These unique structural features of HGF have led to the assignment of HGF as the prototype of a new family of growth factors.

### The HGF Receptor

Recent studies have shown that HGF transduces its multiple biological effects such as mitogenesis, motogenesis, metastogenesis and morphogenesis via activation of a transmembrane tyrosine kinase cell surface receptor known as Met (2, 40). The *met* protooncogene was cloned and sequenced before HGF itself had been cloned and was initially discovered as an activated oncogene based on its ability to transform normal fibroblast cell lines (4). The mature Met receptor is a heterodimer held together by disulfide bonds and consists of an alpha chain that is ~50,000 Da which remains entirely extracellular, and a large polypeptide chain with a molecular mass of 145,000 (named the beta chain) which traverses the plasma membrane and contains the intracellular tyrosine kinase domain. Both polypeptide chains of the Met receptor are derived posttranslationally from a single chain precursor by proteolytic cleavage at a specific site within the precursor molecule. (For review see reference 9). The HGF receptor (HGFR) is expressed in normal epithelium of almost every tissue; however, other cell types such as melanocytes, endothelial cells, microglial cells, neurons, hematopoietic cells, and a variety of tumor cell lines of various origins also express this receptor.

### HGF, the Hepatocyte and Liver Regeneration

HGF's existence was originally postulated based on studies in which liver regeneration was surgically stimulated by removal of two-thirds of the liver in rats resulting in the appearance of a hepatocyte mitogen in the peripheral blood. Following two-thirds partial hepatectomy, plasma HGF levels are found to be 15- to 25-fold greater than

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1. *Abbreviations used in this paper:* HGF, hepatocyte growth factor; HGFR, hepatocyte growth factor receptor (Met); Ks, Kaposi's sarcoma.

those of the control animal. A similar rise in HGF also occurs sharply after acute liver injury after administration of chemicals such as carbon tetrachloride. The levels of HGF then decline within 24 h but remain elevated for the duration of the regenerative response. Analogous changes in plasma HGF levels have also been described after administration of chemicals to rats that augment liver DNA synthesis and liver weight (19), such as phenobarbital, dilantin, valium, and others that, in long term administration, function as liver tumor promoters, as well as in human liver disease whenever a massive loss of hepatocytes occurs such as in a condition known as acute fulminant hepatitis (37). These findings, as well as several other direct and indirect pieces of evidence, implicate HGF as an important paracrine and perhaps endocrine regulator of liver growth. (For review see reference 20).

The HGF/HGFR system may also influence other aspects of liver growth and development. In addition to its ability to stimulate proliferation and morphogenesis of mature hepatocytes, HGF is linked to hepatocyte stem cell proliferation and differentiation (8). As stem cells in the liver proliferate, nearby Ito cells also undergo cell division. These neighboring cells express HGF pointing to a possible paracrine effect of HGF on the growth of stem cells which express HGFR (8). Several studies also strongly suggest a role for HGF in liver embryogenesis. In situ hybridization studies reveal that HGF and HGFR expression is highest in the liver as compared to other tissues (Katyal and Michalopoulos, unpublished observations). Additionally, HGF protein is also present in the developing liver, especially in the hematopoietic cells (5), which may implicate HGF not only in liver formation but also in hematopoiesis (see below). Other supportive evidence includes the finding that HGF may be involved in the transformation of apolar embryonic hepatocytes into acinar structures prior to the appearance of the mature hepatocyte plate (34) which are the same morphological changes seen during liver regeneration and in hepatocytes cultured in type I collagen gels in the presence of HGF. Direct evidence on the role of HGF in liver growth and development comes from very recent investigations on transgenic mice homozygous for a null mutation in the HGF gene (knock-out mice). These studies have revealed that such animals do not survive beyond day 15 of embryonic development with most notable defects seen in liver formation and architecture primarily due to an extensive loss of hepatic parenchyma (31). Moreover, lack of HGF expression also affected the development of the placenta as was evidenced by a severe reduction in the number of trophoblasts (31, 38).

Other investigations have defined a fundamental role for HGF in mediating responses to tissue injury in other organs in adults. In animal models in which kidney (16) or lung (42) has been damaged experimentally, HGF expression is induced markedly. This increase in HGF mRNA is followed by increases in the level of pro-HGF and in its subsequent activation by proteolytic cleavage to the bioactive heterodimeric form in the damaged tissue (21). Additionally, when exogenous HGF is administered to these animals, it remarkably enhances the regeneration of the injured organ (20). These findings indicate that HGF is activated locally which may in part explain the lack of response to the biological effects of HGF in uninjured tis-

sues. The discovery that the mRNAs for HGF (20) and the HGF receptor (23) are induced in stromal and epithelial cells, respectively, by inflammatory cytokines such as IL-1, IL-6, and TNF $\alpha$  also supports the idea that this ligand/receptor system is involved in mediating inflammatory responses to tissue injury. These studies have defined HGF as a major mediator of tissue repair and organ regeneration and underscores its potential use as a therapeutic agent for treating diseases such as acute liver or renal failure.

### *Biological Effects of HGF on Other Cell Types*

The growth regulating effects of HGF on various cell types, other than hepatocytes, is now well-documented. (For review see references 20 and 30). One of the hallmark in vitro responses to HGF is the induction of cell motility and dissociation (scattering) of various normal and malignant epithelial cells. Based on this property, HGF was independently purified and characterized from the culture medium of fibroblast cell lines such as MRC-5, and was named scatter factor (35). Subsequent investigations, however, revealed that this molecule is identical to HGF (39). A third type of biological activity associated with HGF is its remarkable morphogenic effects on epithelial tissues. HGF is now believed to be most potent epithelial morphogen inducing formation of branching tubules and gland-like structures in epithelial cells derived from kidney or mammary tissue in vitro (24, 33).

Based on these properties, it has been postulated that HGF is a mediator of epithelial-mesenchymal interaction and interconversion. (For a review see reference 29). Most tissues either express HGF mRNA or contain HGF protein. Among these are blood (megakaryocytes, monocytes, leukocytes, and platelets), brain, bone marrow, liver, lung, kidney, placenta, spleen, and skin. The highest levels of HGF mRNA are detected in the adult lung, liver, skin, and spleen although the other tissues mentioned all contain detectable levels of HGF mRNA and/or protein. In general, HGF mRNA is expressed in stromal cells such as fibroblasts, smooth muscle cells, mast cells, macrophages, endothelial cells, leukocytes, and megakaryocytes of various tissues but not in epithelial cells. HGF receptor expression, on the other hand, is mainly detected in epithelial cells. This unique expression pattern in combination with the mitogenic, motogenic, and morphogenic properties of HGF support the idea that this ligand is an important paracrine mediator of the interaction between the epithelial and stromal compartments of various tissues during development and in the maintenance of homeostasis in adult tissues (29, 32).

HGF has also been shown to induce mesenchymal to epithelial conversion in fibroblasts overexpressing HGF and HGFR when these cells are injected into nude mice (36). In another investigation using cell lines derived from metanephric ridge cells of mouse embryos, it was shown that HGF stimulates epithelial differentiation of these mesenchymal cells suggesting that this cytokine may be involved in the early commitment of cells in the kidney (15). The recent findings by Woolf et al. (41) show that simultaneous expression of HGF and HGFR occurs in the kidney mesenchyme during the early development of the mouse kidney and that anti-HGF antibody inhibits the differentiation of metanephric mesenchymal cells into the epithelial

precursors and subsequent nephrogenesis when added to metanephric organ cultures. Other studies have also implicated HGF in early embryological processes such as the formation of the primitive streak and induction of neural tissues as demonstrated by studying HGF and HGFR expression in *Xenopus* and chick during early stages of development and by ectopic application of HGF in a chick embryo model. (For review see reference 20.)

The potential participation of HGF in organogenesis and the later stages of embryonic development has also been well documented by studying HGF and HGFR expression in rodents (5, 32). As stated, recent studies have shown that the disruption of the HGF gene results in embryonic lethality, primarily due to defects in proper development of the placenta and liver (31, 38). In these studies, however, other organs and tissues where HGF and HGFR are reportedly expressed during embryogenesis (such as lung, kidney, and the central nervous system), appeared normal at the time of death (day 15 of gestation). This may indicate that either HGF is not essential for the early stages of embryogenesis or that compensation or redundancy exists in the HGF signaling network. It should be noted that further analysis of these animals has been hampered due to their death in utero preventing additional investigations on the functions of HGF in other processes such as terminal differentiation and maturation or regeneration of other tissues (31).

It should be emphasized that although epithelial cells are one of the major targets of HGF, as more investigations are conducted, it is becoming clear that nonepithelial cell types such as hematopoietic, lymphoid, neural, and skeletal muscle cells also respond to the multifaceted actions of HGF. The first clue indicating that HGF may be involved in hematopoiesis came from studies on progenitor-enriched murine bone marrow cells and on several murine myeloid progenitor tumor cell lines blocked in the early stages of myeloid differentiation. Such investigations revealed, first, that these cells express the HGFR, and second, that HGF synergizes with IL-3 or GM-CSF to support the growth of these cells in culture (17, 22). Conflicting results, however, were obtained by these two investigations with regard to whether HGF alone stimulates mitogenesis in myeloid progenitor cell lines. Although HGF synergized with other factors to stimulate growth of progenitor cells, it apparently did not influence the pattern of myeloid differentiation since the ratio of macrophages to granulocytes in resultant colonies remained similar to those obtained with IL-3 or GM-CSF alone (17).

Galimi et al. (10) recently reported that the HGF receptor is present in a small fraction of highly-enriched hematopoietic progenitor cells from human bone marrow and peripheral blood and showed that, in the presence of erythropoietin, HGF induces the formation of colonies along the erythroid lineage when cultured in vitro. However, in the presence of erythropoietin and stem cell factor, it was demonstrated that HGF supports the growth of multipotent colonies (granulocyte-erythroid-megakaryocyte) rather than recruiting erythroid precursors.

The differences in the results of the experiments described above may be due to variations in technique such as culture conditions (i.e., presence or absence of particular cytokines and doses), purity of cells, or simply because

so few studies have addressed HGF's involvement in hematopoiesis. Additionally, whether HGF's mitogenic/differentiation effects on hematopoietic stem cells are mediated through the HGFR directly or whether HGF through its receptor causes secretion of other modulating cytokines has not been addressed in studies thus far completed. Regardless of how HGF elicits such responses, the fact that hematopoiesis is altered at all in the presence of HGF deserves further study.

The role of the HGF family in hematopoiesis and reticuloendothelial cell function is further underscored by other findings. It has been shown that the HGF-like receptor (Ron) is highly expressed in hematopoietic stem cells (12) and monocytes (11). Moreover, HGF-like protein (also known as macrophage stimulating protein) was demonstrated to elicit monocyte migration through Ron activation (11). Biological activities affecting reticuloendothelial cells have also been described for HGF and the HGFR using in vitro models. These include activation of the oxidative response of human neutrophils (13), promotion of adhesion and migration of a subset of human T cells (1), and enhancement of humoral immune responses in murine B cells (6).

Recently, in vivo studies in which HGF was implanted into rabbits have demonstrated that HGF has angiogenic activities (3). Interestingly, HGF has also been linked to Kaposi's sarcoma (KS), a form of human neoplasm in which the cellular origin has not been defined, but is believed to be an endothelial derivative. Several lines of evidence support this possibility. First, HGF is secreted by HTLV-II-infected T lymphocytes; secondly, HGF induces endothelial cells to convert to a Kaposi sarcoma tumor cell-like phenotype; thirdly, antibody against HGF inhibits the growth of KS cells in culture; and lastly, HGF is present in KS lesions (25).

The presence of HGF and its receptor in specific regions of the developing and adult mammalian nervous system points to the fact that this ligand/receptor system may have a neurotrophic function (14). Recently, HGF was shown to promote the survival of motor neurons and enhance the neurotrophic function of ciliary neurotrophic factor. In other studies, Krasnoselsky and colleagues reported that rat sciatic nerve Schwann cells express the HGF receptor and strongly respond to the mitogenic effects of HGF in culture (18).

HGF has also been examined in the context of endocrine function. Studies on the effects of HGF on the endocrine system show that HGF may contribute to the formation and maintenance of organs involved in hormone secretion such as the pancreas and the thyroid. Using primary organ cultures of human fetal pancreas, Otonkoski et al. have recently reported that HGF is the most potent inducer of  $\beta$ -cell proliferation and formation of islet-like cell clusters subsequently resulting in insulin production in vitro (28). HGF also seems to regulate the growth and function of the thyroid gland as revealed by in vitro studies (7).

Although the early work on HGF was confined almost exclusively to one organ, the liver, researchers with wide-ranging scientific interests have helped over the years to define the multifaceted functions and target cells of HGF. Clearly, however, much remains to be learned about HGF, and more biological and physiological roles for this growth factor will undoubtedly be revealed.

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