Hepatocyte Growth Factor

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About this review

The default animal model context used in this review is *Mus musculus*. Consistent with currently accepted practice, the following nomenclature for hepatocyte growth factor and its cell surface receptor (Met) is used: Hgf and Met denote the mouse proteins, HGF and Met (in context) denote the human proteins and all other species as indicated, *hgf* and *met* denote the mouse genes, and *HGF* and *MET* denote the human genes and those of all other species as indicated.

This review is focused on Hgf *per se*, not Met, although by necessity very basic information about Met is included. In addition to its vital roles in development, maturation and homeostasis, the Hgf/Met pathway contributes to oncogenesis through several mechanisms, including *MET* gene mutation, rearrangement and/or amplification, defects in receptor attenuation or downregulation systems, or other means of pathway activation that may be ligand-independent or exhibit reduced ligand dependency. These mechanisms are covered in greater depth in reviews on Met, indicated in the text. We focus here specifically on those instances where evidence suggests that Hgf is a critical contributor to oncogenesis or disease progression.

This review was completed and reviewed by three colleagues with expert knowledge of the field in 2011. Updates intended to bring the review current to 2022 are in progress and will be submitted as new versions, per the Zenodo DOI versioning policy (https://help.zenodo.org). Reader comments intended to aid the update process are welcome.

Historic alternative names for Hepatocyte Growth Factor

F-TCF; Fibroblast-derived tumor cytotoxic factor; Hepatocyte growth factor; Hepatocyte growth factor alpha chain; Hepatocyte growth factor beta chain; Hepatocyte growth factor precursor; Hepatopoeitin-A; Hepatopoietin A; HGF; Hgf; HGF/SF; HGFB; HPTA; Lung fibroblast-derived mitogen; NK1; NK2; PRGF (Plasminogen related growth factor); Scatter factor; SF; SF/HGF

Abstract

Polypeptide growth factors have been intensively studied since their initial discovery as pivotal regulators of cell proliferation and differentiation in multicellular organisms more than 70 years ago. Despite their name, many elicit multiple cellular responses during embryogenesis and throughout adulthood; dysregulated signaling can also contribute to disease. Few factors illustrate these principles as thoroughly as hepatocyte growth factor (Hgf), also known as scatter factor (SF). As evident from its pseudonyms, Hgf pleiotropism has been a striking feature from its initial discovery more than two decades ago by several groups with interests in liver regeneration, cell growth control, motility and morphogenesis. Thousands of scientific publications now document the critical contributions of Hgf signaling to normal development, adult homeostasis and several forms of cancer.

Hgf protein and the related macrophage stimulating protein (MSP; also known as Hgf-like protein) comprise a small but distinct growth factor subfamily related to plasminogen serine proteinases, though they are devoid of proteolytic activity. In humans, a single gene encodes five HGF isoforms produced through mRNA splicing: two full-length forms that differ by only five residues and three substantially shorter forms. The more abundant full-length forms are secreted as inactive single chain polypeptides that are proteolytically converted to biologically active disulfide-linked heterodimers at the target cell surface. All isoforms bind strongly to heparan sulfate proteoglycan, a feature that profoundly influences their local and systemic distribution, receptor binding, and biological impact. Hgf signaling is primarily paracrine: it is secreted by mesenchymal cells in many tissues and acts on a broad spectrum of cellular targets that express the receptor tyrosine kinase known as Met. Hgf-related research has identified molecular pathways important for tissue protection, tissue regeneration and oncogenesis, with the promise to advance tissue engineering, regenerative medicine as well as cancer diagnosis and treatment.

1. Hgf Function in Development and Adulthood

In their succinct and comprehensive reviews of Hgf/Met signaling, Rosario and Birchmeier (2003; 2004) parallel the late evolutionary appearance of *hgf* and *met* genes and the processes of placentation, liver development and long-range muscle progenitor cell migration. Accordingly, we have emphasized Hgf signaling in these vertebrate processes, as well as in nervous system development, in the following summary. In most of these developmental processes, throughout adulthood, and in disease, Hgf stimulates cell proliferation and/or survival, motility, and morphogenesis encompassing shape change and extracellular matrix turnover. Hgf was discovered on the basis of these activities during liver regeneration (Nakamura et al., 1984; Thaler and Michalopoulos, 1985; Nakamura et al., 1989; Miyazawa et al., 1989; Zarnegar and Michalopoulos, 1989) and independently in the context of cultured epithelial cell growth and motility (Stoker and Perryman, 1985; Stoker et al., 1987; Gherardi et al., 1989; Gherardi and Stoker, 1990; Rubin et al., 1991; Montesano et al., 1991; Weidner et al., 1991; Chan et al., 1991). cDNA cloning of the *HGF* gene, first reported in 1989, made the identity of hepatocyte growth factor, scatter factor, and a lung fibroblast-derived epithelial cell mitogen unambiguous and merged diverse research efforts that have grown to advance the fields of signal transduction, cancer biology and regenerative medicine.

1.1 Embryonic Development

1.1.1 Embryonic Development in Rodents

The genes encoding Hgf and its cell-surface receptor, Met, are expressed during gastrulation and throughout subsequent phases of vertebrate embryonic development (Stern et al., 1990; Sonnenberg et al., 1993; Andermarcher et al., 1996). Early in mouse gastrulation, both genes are expressed in the endoderm and in the mesoderm along the rostro-intermediate part of the primitive streak and later, in the node and in the notochord. Neither gene is expressed in the ectodermal layer during gastrulation (Andermarcher et al., 1996). This overlapping expression of *hgf* and *met* genes persists into the earliest phases of organogenesis in the heart, condensing somites and neural crest cells (Andermarcher et al., 1996). Thereafter, a distinct pattern of expression, characterized by the presence of Hgf protein in mesenchymal tissues and Met protein in the surrounding ectoderm, begins in the branchial arches and in the limb buds. By E13 (13 days postcoitum) in the developing mouse, only this second pattern of expression is observed in differentiated somites and several major organs such as lungs, liver, placenta, muscle and gut (Sonnenberg et al., 1993; Andermarcher et al., 1996; Birchmeier and Gherardi, 1998; Ishikawa et al., 2001). These observations suggest that a shift from autocrine to paracrine signaling takes place in early organogenesis and predominates throughout the remainder of development and maturation. Andermacher et al. (1996) proposed that during gastrulation, Hgf affects the fate of migrating mesodermal cells and may play a role in axis determination, whereas during organogenesis and thereafter, the expression patterns of *hgf* and *met* are consistent with the signaling exchange between mesenchymal and epithelial cell compartments that regulates the morphogenesis and differentiation of a variety of embryonic organs. At these later stages of development, *hgf* is expressed within somites, neural crest cells, branchial

arches, liver, heart, nervous system, and mesenchyme surrounding the olfactory canal, kidney, gut, limb bud, lung, and liver; met transcripts are found in neural, endothelial and muscle cells, and a variety of epithelia (Sonnenberg et al., 1993; Woolf et al., 1995; Andermarcher et al., 1996; Thewkes and Seeds, 1996; Birchmeier and Gherardi, 1998; Ishikawa et al., 2001). Functional studies using tissue explants and cultured cells confirm the suspected role of Hgf in epithelial branching morphogenesis (Santos et al., 1994; Woolf et al., 1995; Ohmichi et al., 1998). For example, *hgf* and *met* are expressed in the mesenchyme and epithelium, respectively, of the developing lung, where Hgf and fibroblast growth factors synergize to promote epithelial proliferation, branching and tubulogenesis (Ohmichi et al., 1998).

The expression of *met* and *hgf* genes in ventral motor neurons of the mouse and rat embryonic spinal cord is also consistent with a role in tissue patterning through the regulation of migratory and morphogenic processes, such as axon guidance (Sonnenberg et al., 1993; Ebens et al., 1996; Wong et al., 1997). Functional studies provide evidence that Hgf guides axons of spinal motor neurons to their distant muscle targets in the limbs (Ebens et al., 1996; Wong et al., 1997; Yamamoto et al., 1997) and acts as an essential survival factor for a subpopulation of limb-innervating motoneurons (Wong et al., 1997; Yamamoto et al., 1997). Both *hgf* and *met* are also expressed in the brain and retina during development (E12 - 13) and in the adult, where signaling supports neuron survival and maturation (Jung et al., 1994; Honda et al., 1995; Yamagata et al., 1995; Hamanoue et al., 1996; Achim et al., 1997; Sun et al., 1999; Thewkes and Seeds, 1999). In neocortical explants, Hgf induced neurite outgrowth, and in mesencephalic cultures, Hgf increased the number and development of tyrosine hydroxylase-positive neurons and enhanced dopamine uptake (Hamanoue et al., 1996). In the developed brain, *hgf* is expressed in neurons, primarily in the hippocampus, cortex, and the granule cell layer of the cerebellum, as well as in ependymal cells, the chorioid plexus, and the pineal body. *met* is expressed in neurons, preferentially in the CA-1 area of the hippocampus, the cortex, and the septum, as well as in the pons (Jung et al., 1994; Honda et al., 1995; Yamagata et al., 1995; Thewkes and Seeds, 1999). Evidence suggests a neurotrophic function for Hgf in the CNS, supporting the survival and reconstruction of specific neurons in response to cerebral injury (Honda et al., 1995). Hgf attracts and promotes the growth of cranial motor axons (Caton et al., 2000). Various types of glial cells and neurons have been shown to respond to Hgf *in vitro*. Hgf induces c-Fos expression and activates the Ras pathway in brain neurons (Streit et al, 1997), stimulates Schwann cell growth (Krasnoselsky et al., 1994) and promotes axon outgrowth of embryonal carcinoma cells (Yang and Park, 1993). Hgf stimulates neurite outgrowth in sensory and sympathogenic neurons, as well as enhanced survival and differentiation from progenitors (Maina et al., 1997; 1998).

Loss of *hgf* or *met* function in mice with homozygous gene deletion is embryonic lethal between days E12.5 and E15.5 (Schmidt et al., 1995; Uehara et al., 1995; Bladt et al., 1995). *hgf* and *met* null mice exhibit very similar phenotypes, further supporting the concept that Met is the only receptor for Hgf, and Hgf the only ligand for Met (Birchmeier et al., 2003). Defects in the proliferation and survival of cells in the liver and placenta result in arrested organogenesis of these and other tissues, highlighting the importance of Hgf stimulated mitogenicity and survival in target cells. These animal models also consistently underscore the importance of Hgf as a potent and critical regulator of cell migration. Skeletal muscle progenitor cells that form limb, tongue, and diaphragm musculature

normally delaminate from the epithelial dermomyotome of the somites by an epithelial-to-mesenchymal transition and migrate to their final destination where they complete differentiation. Loss of Hgf signaling in mice homozygous for *met* deletion results in defective delamination and migration of muscle progenitors from the dermomyotome and failure to form the skeletal muscles of the limb and diaphragm (Bladt et al., 1995; Maina et al., 1996; Dietrich et al., 1999; Birchmeier et al., 2003; Christ and Brand-Saberi, 2002). Conversely, *hgf* overexpression in transgenic mouse embryos induces the inappropriate formation of skeletal muscle in the CNS through dysregulated migration of Met containing myogenic precursor cells to the neural tube (Takayama et al., 1996). Melanoblasts were also aberrantly localized to inappropriate sites within the E12.5 transgenic embryo, including the neural tube, and melanocytes were found within the transgenic adult in a number of abnormal ectopic sites, including the CNS (Takayama et al., 1996). Mice bearing conditional deletions of *hgf* or *met* have been used to demonstrate the functional relevance of pathway activation at later developmental stages and in adulthood. For example, Met and epidermal growth factor receptor jointly regulate final nephron number and collecting duct morphology (Ishibe et al., 2009). Mice with a targeted mutation of the gene encoding urokinase plasminogen activator receptor, an important Hgf activator, have decreased Hgf levels and a substantial reduction in neocortical GABAergic interneurons at embryonic and perinatal ages, leading to changes in circuit organization and behavior (Powell et al., 2001; 2003). Mice with targeted mutation of two critical carboxylterminal tyrosine residues in Met were found to be phenotypically similar to met null animals. In contrast, targeting one of those sites and thereby disrupting the consensus for Grb2 binding allowed development to proceed to term, but caused a striking reduction in limb muscle mass coupled to a generalized deficit of secondary fibers, revealing a role for Hgf signaling in late myogenesis (Maina et al., 1996). Hgf signaling in maturation and adulthood are discussed further below.

1.1.2 Embryonic Development in Other Vertebrates

Developmental studies in other vertebrates confirm and extend results found using mice. Exogenous HGF applied to chick embryos generated supernumerary axial structures resembling the primitive streak and/or neural plate, suggesting that it may participate in the induction of these structures (Stern et al., 1990). Chick embryos express *HGF* in Hensens's node, the limb buds, and intermediate and lateral plate mesoderm, whereas Met is detectable in the spinal cord and somites; both genes are expressed in the branchial arches, hindbrain rhombomere boundaries and circulatory system (Théry et al., 1995) HGF supports the growth and survival of sensory neurons in the dorsal root ganglion (Funakoshi and Nakamura, 2001).

In Xenopus embryos, *HGF* is expressed in mesoderm starting at late gastrulation and increases thereafter, especially in the ventral mesoderm, which primarily gives rise to mesenchymal cells (Nakamura et al., 1995). Basic fibroblast growth factor, and to a lesser extent, Activin A, can stimulate *HGF* expression in blastula animal cap cells, suggesting that signals known to induce the ventral mesoderm also drive early *HGF* expression there (Nakamura et al., 1995). *MET* expression is found in Xenopus foregut, neural tube, and tailbud mesenchymal tissue (Aoki et al., 1996). Overexpression of mRNAs encoding a

truncated *MET* transcript lacking the tyrosine kinase domain causes defects in liver, gut, and kidney development (Aoki et al., 1997).

Consistent with other animal models, work using zebrafish has also demonstrated that HGF/Met signaling is required for liver development and the long-distance migration of muscle progenitor cells from the somites to form fin hypaxial muscle (Haines et al., 2004; Latimer and Jessen, 2008). These studies also further illustrate the importance of HGF/Met signaling in neural development. Met is necessary for deposition of pro-neuromasts by the migrating posterior lateral line primordia (Haines et al., 2004; Latimer and Jessen, 2008), various types of spinal cord primary motor neurons and many secondary motor neurons express Met (Tallafuss and Eisen, 2008; Latimer and Jessen, 2008), and this is required for secondary motor neuron formation and proper primary motor neuron axon development (Tallafuss and Eisen, 2008).

1.2 Maturity and Homeostasis

1.2.1 Postnatal Nervous System Development and Homeostasis

Both *hgf* and *met* are expressed in the adult brain, retina and olfactory bulb (Jung et al., 1994; Honda et al., 1995; Yamagata et al., 1995; Hamanoue et al., 1996; Achim et al., 1997; Thewkes and Seeds, 1996, 1999). At the cellular level, *HGF* mRNA expression has been found in the microglia of the rat brain, while *MET* mRNA is expressed in neurons as well as astrocytes and microglia (Yamagata et al., 1995). Most of the neurons were Met positive, and HGF stimulated activation of Met and Ras in these cells (Yamagata et al., 1995). Layer specific expression of *hgf* and *met* mRNA and protein occurs in the adult cerebral cortex: *hgf* is expressed in layers IV and V and Met in layers II-III, IV, V and the hippocampus (Thewkes and Seeds, 1999). Hgf treatment of primary hippocampal cell cultures modulated the expression of presynaptic and scaffolding proteins of the N-methyl-d-aspartate (NMDA) receptor complex, suggesting that Hgf promotes the maturation of excitatory synapses in young hippocampal neurons (Nakano et al., 2007).

Cerebellar development is primarily postnatal and requires extensive cell proliferation and migration. *hgf* and *met* are both expressed in the cerebellum: Met is localized in granule cell precursors and cultures of these cells proliferate in response to Hgf (Ieraci et al., 2002). Hgf function in postnatal cerebellar development was further explored using genetically engineered mice where one met allele harbored a hypomorphic met mutation at the Grb2-binding site (Ieraci et al., 2002). These mice display reduced cerebellar size, foliation defects and balance impairments, suggesting that normal cerebellar development and function require Hgf signaling (Ieraci et al., 2002). These and other reports reinforce the concept that Hgf is neurotrophic in postnatal development and may help maintain CNS, visual and olfactory system homeostasis. HGF also promotes oligodendrocyte progenitor cell proliferation and delays their differentiation into myelinating oligodendrocytes during early postnatal development in the rat; subsequent down-regulation of *HGF* mRNA in the striatum observed between postnatal days 7 to 14 presumably permits differentiation and myelination to proceed (Ohya et al., 2007). Schwann cells, responsible for nerve myelination in the peripheral nervous system, also express met mRNA (Krasnoselsky et al., 1994). Although Schwann cells are normally quiescent in adulthood, nerve injury and certain diseases such as type 1 neurofibromatosis

trigger proliferation through several mitogenic pathways, including that of HGF (Krasnoselsky et al., 1994).

Other evidence indicates roles for Hgf in the natural reconstruction of central and peripheral neuronal networks in response to injury, and/or as a potential therapeutic agent to facilitate wound repair. Both *hgf* and *met* expression are increased in reactive astrocytes in the subacute to chronic stage of spinal cord injury in rats (Shimamura et al., 2007). *HGF* gene transfer attenuated brain ischemic injury in rats, without cerebral edema, through angiogenic, neuroprotective and neuriotogenic activities, as well as prevention of gliosis (Shimamura et al., 2004; 2006). Intrastriatal administration of HGF protein also potently protected hippocampal neurons against postischemic delayed neuronal death (Miyazawa et al., 1998).

1.2.2 Mammary Gland Development

The mammary gland undergoes morphogenetic differentiation cyclically during the menstrual cycle, pregnancy and lactation. *hgf* and *met* are expressed and *hgf* is regulated temporally during mouse mammary development and differentiation (Niranjan et al., 1995; Yang et al., 1995). Hgf secreted by fibroblasts acts on mammary myoepithelial and luminal epithelial cells expressing Met, promoting tubulogenesis in underlying myoepithelial cells, branching of the epithelial ductal tree and motogenesis in both cell types (Niranjan et al., 1995; Yang et al., 1995; Niemann et al., 1998). Neuregulin, another important regulator of mammary gland differentiation produced by fibroblasts and acting on the epithelium, stimulates lobulo-alveolar budding and milk protein production (Yang et al., 1995, Niemann et al., 1998). In organ culture, branching morphogenesis and lobulo-alveolar differentiation of the mammary gland was abolished by blocking expression of endogenous Hgf and neuregulin, and morphogenesis was rescued by the addition of recombinant Hgf and neuregulin (Yang et al., 1995). Experimental *hgf* overexpression induces a range of alterations in virgin mouse mammary gland architecture, including enhanced of ductal end bud size and numbers and hyperplastic branching morphogenesis (Yant et al., 1998). Hgf is a significant contributor to oncogenesis and disease progression in breast cancer, as detailed below.

1.2.3 Renal and Pulmonary Homeostasis

Tissue fibrosis is a common pathological consequence of chronic injury to kidneys and lungs. Initial responses to injury in both systems include signaling cascades associated with tissue repair and regeneration that include the production and secretion of growth factors (including Hgf), chemokines and cytokines, inflammatory cell recruitment, extracellular matrix (ECM) production, cell proliferation and differentiation, and matrix remodeling. With chronic injury these carefully orchestrated events are not properly regulated, leading to ECM overproduction, abnormal ECM organization, fibrotic lesions and tissue scarring. Mice with conditional knockout of met in the collecting duct of the kidney were more susceptible to interstitial fibrosis and tubular necrosis after unilateral ureteral obstruction, and had diminished capacity for tubular cell regeneration after release of the obstruction (Ma et al., 2009). When conditional met knockout was targeted to renal podocytes, mice developed more severe podocyte apoptosis and albuminurea than control

littermates when subjected to nephrotoxic renal damage (Dai et al., 2010). In addition to these insights into the cellular basis of Hgf antifibrotic effects, our understanding of its molecular basis has also progressed substantially. Hgf produced in response to injury antagonizes the actions of transforming growth factor-beta (TGF-β), a critical profibrotic agent, thereby inhibiting fibrosis and preserving normal organ architecture and function (reviewed in Liu, 2004; Mizuno et al., 2008; Crosby and Waters, 2010; Panganiban and Day, 2010). The reciprocal effects of the Hgf and TGF-β signaling pathways are well documented, and occur via direct modulation of intracellular effectors downstream of TGF-β and Hgf receptors in common target cells as well as by eliciting opposing activities in cells targeted independently (Yo et al., 1998; Gao et al., 2002; Mizuno et al., 2004). TGF-β induced apoptosis of podocyte, endothelial and tubular epithelial cells, epithelial-to-mesenchymal transition by tubular epithelial cells, and myofibroblastic activation, are key pathogenic events that are opposed by Hgf signaling (reviewed by Bottinger and Bitzer, 2002). An abundance of findings support the therapeutic use of exogenous HGF, the *HGF* gene, or the induction of endogenous *HGF* expression, for the treatment of a wide range of chronic fibrotic disorders in both kidney (Mizuno et al., 2001, 1998; Dworkin et al., 2004; Dai et al., 2004; Herrero-Fresneda et al., 2006; reviewed in Liu and Yang, 2006; Mizuno et al., 2008) and lung (Dohi et al., 2000; Mizuno et al., 2005; Watanabe et al., 2005).

1.2.4 Vascular System Homeostasis

Hgf production in the vascular system is positively regulated by prostaglandins and Hgf itself, and negatively regulated by angiotensin II, TGF-β, glucose and hypoxia (reviewed in Morishita et al., 2002). *hgf* is induced in cardiac and skeletal muscle in animal models of ischemic injury (Aoki et al., 2000) and serum Hgf levels are increased with hypertension, peripheral artery disease and myocardial infarction (reviewed in Morishita et al., 2002). Exogenous administration of the Hgf protein or gene promotes angiogenesis without the increased permeability often observed with vascular endothelial cell growth factor (VEGF) treatment (Aoki et al., 2000; Taniyama et al., 2001; Morishita et al., 2004). Hgf promotes angiogenesis directly (Sengupta et al., 2003) but also by inducing VEGF expression (Wojta et al., 1999; Gille et al., 1998), and the two factors appear to act synergistically on the vasculature (Van Belle et al., 1998; Xin et al., 2001). These and other findings support the use of Hgf for therapeutic angiogenesis to treat peripheral artery disease, myocardial infarction and restenosis after angioplasty. Recent clinical trials indicate that *HGF* gene therapy is safe and effective for the treatment of critical limb ischemia (Powell et al., 2008; Shigematsu et al., 2010).

1.2.5 Liver Regeneration

HGF signaling is well established as a primary driver of liver regeneration (Nakamura et al., 1984; Thaler and Michalopoulos, 1985; Zarnegar and Michalopoulos, 1989; Nakamura et al., 1989; Miyazawa et al., 1989; Okajima et al., 1991; and others). Comprehensive studies of tissue selective *hgf* overexpression or *met* suppression in genetically engineered animal models confirm and extend earlier studies (Borowiak et al., 2004; Huh et al., 2004; Paranjpe et al., 2007; Shiota and Kawasaki, 1998). In addition to demonstrating that Hgf was essential for liver regeneration, these reports showed that Hgf

was critical for liver cell transition from G1 to S-phase via the MAPK/Erk pathway and protection against apoptosis. A more recent study using *met* suppression engineered selectively in hepatocytes, as opposed to all liver cell types, further revealed that Hgf signaling was also critical for progression from G2 to M phase via Erk-mediated activation of the immediate early genes c-Fos and Egr-1, among others known for orchestrating G2/M transition (Factor et al., 2010). In addition to stimulating the proliferation of mature hepatocytes, emerging evidence indicates that Hgf contributes to the differentiation and maturation of hepatic progenitor cells (Kamiya et al., 2001). Treatment of animals with exogenous HGF protein or the *HGF* gene promotes survival in various experimental animal models of acute hepatic failure (Kosai et al., 1998; Nomi et al., 2000) and prevents fibrosis associated with liver cirrhosis (Kaibori et al., 1997; Matsuda et al., 1997). Clinical trials of recombinant human HGF for treatment of patients with fulminant hepatic failure are in progress (Ido and Tsubouchi, 2009).

1.2.6 Skin Repair

Damage to the epidermis and dermis of the skin requires reepithelialization of the epidermis and the transient formation of dermal granulation tissue. During reepithelialization, keratinocytes from the wound edge form the hyperproliferative epithelium, which proliferates and migrates over the injured dermis and the granulation tissue. In addition to other important soluble regulators of skin repair such as epidermal and fibroblast growth factor family ligands and transforming growth factor-β, locally secreted Hgf is involved in granulation tissue formation and reepithelialization (Yoshida et al., 2003, Chmielowiec et al., 2007). Engineered overexpression or exogenous application of Hgf protein, or exogenous *hgf* gene transfer, to treat full-thickness skin wounds accelerates both processes, as well as vascularization, in rodent models (Toyoda et al., 2001; Yoshida et al., 2003; Bevan et al., 2004; Kunugiza et al., 2006). In conditional met mutant mice, skin wound closure occurred only though a small population of keratinocytes that had escaped conditional mutation designed to inactivate kinase activity, i.e. in those keratinocytes with wild type met, reinforcing the conclusion that Hgf/Met signaling is required for full-thickness skin wound repair (Chmielowiec et al., 2007).

2. Hgf Function in Disease

2.1 Cancer

The Hgf/Met signaling axis has been implicated in a broad spectrum of human cancers. Met contributes to oncogenesis through several mechanisms, including gene mutation, rearrangement and/or amplification, other active signaling networks, defects in receptor attenuation or downregulation systems, as well as paracrine or autocrine ligand-driven activation. Some of these mechanisms are covered in greater depth in reviews on Met. We focus here on instances where evidence suggests that Hgf is a potentially critical contributor to oncogenesis or disease progression. Evidence of oncogenesis specifically associated with the phenotypes of genetically engineered mice can be found in the Phenotypes section, below.

2.1.1 Hepatocellular Carcinoma

Gains in human chromosome 7q, where both *HGF* and *MET* genes are located, occur in approximately 16% of hepatocellular carcinoma (HCC) cases (Moinzadeh et al., 2005; growth factor signaling in HCC is reviewed in Breuhahn et al., 2006). HGF signaling drives the transcriptional activation of *MET* in HCC (Seol et al., 2000), and *HGF* is overexpressed in the HCC microenvironment relative to normal adult liver levels (Selden et al., 1994; Noguchi et al., 1996). Secretion by stellate cells and myofibroblasts is apparently induced by tumor cell signals; HGF, in turn, stimulates tumor cell invasiveness (D'Errico et al., 1996; Neaud et al., 1997; Guirouilh et al., 2000, 2001). The criticality of HGF in human HCC oncogenesis remains unclear; *HGF* expression levels did not correlate with patient survival or clinicopathological parameters in at least one study (Ueki et al., 1997), whereas later reports show that higher HGF serum levels negatively correlate with patient survival time (Vejchapipat et al., 2004) and positively correlate with tumor size (Yamagamim et al., 2002). Similarly, there are conflicting reports regarding the role of Hgf in HCC animal models. Transgenic *hgf* expression in mice accelerated chemically induced hepatocarcinogenesis, suggesting an oncogenic effect (Bell et al., 1999; Horiguchi et al., 2002), yet conditional *met* knockout also accelerated chemically induced hepatocarcinogenesis, suggesting a suppressor effect (Takami et al., 2007; Marx-Stoetling et al., 2009). Consistent with the latter, HCC cell lines injected into the portal veins of *hgf* transgenic mice displayed significantly lower rates of experimental liver metastasis than control littermates (Shiota et al., 1996), and recombinant HGF treatment of rats on carcinogenic diets did not increase HCC incidence (Nakanishi et al., 2006).

2.1.2 Head and Neck Squamous Cell Carcinoma

Human head and neck squamous cell carcinoma (HNSCC) show significantly increased HGF levels relative to normal mucosa, which correlated a poorly differentiated tumor type and decreased survival rates (Takada et al., 1995). Locally increased HGF production is likely to be due, at least in part, to SCC cell secretion of interleukin-1 (Hasina et al., 1999). Squamous cell carcinoma cells are responsive to esophageal submucosal fibroblast-derived HGF with increased invasiveness (Matsumoto et al., 1994; Iwazawa et al., 1996). Additional information on HGF in HNSCC is available in a comprehensive recent review (De Herdt and Baatenburg de Jong, 2008).

2.1.3 Papillary Thyroid Carcinoma

Overexpression of both human *HGF* and *MET* is found in most papillary thyroid carcinomas (PTC), but not other thyroid tumor types. Although paracrine HGF sources have been identified, at least one study reported that the majority of these cases appear to possess autocrine HGF/Met signaling (Trovato et al., 1998); this latter point is controversial (Oyama et al., 1998). Increased MET and HGF expression is associated with a high risk for metastasis and recurrence in children and young adults with PTC (Ramirez et al., 2000). Cell lines established from thyroid carcinomas are responsive to HGF with increased motility and invasiveness, increased chemokine and VEGF production involved in

the recruitment of dendritic cells and new blood vessels, respectively (de Luca et al., 1999; Scarpino et al., 1999, 2000, 2003).

2.1.4 Lung Cancer

Early studies demonstrated the presence of HGF in pleural effusion fluid obtained from patients with metastatic spread to the pleura (Kenworthy et al., 1992) and that HGF was an autocrine factor for normal bronchial epithelial cells as well as lung carcinoma cells (Tsao et al., 1993). These findings have been confirmed and extended by dozens of other reports (e.g. Olivero et al., 1996; Eagles et al., 1996), including those demonstrating significantly increased serum HGF levels and tissue levels in lung cancer patients (Takigawa et al., 1997; Yamashita et al., 1998) and one report that surgery exacerbates this condition (Uchiyama et al., 1999). *MET* is well expressed in normal bronchial epithelium and both small cell and non-small cell lung cancers. Somatic *MET* mutations in these tumor types are relatively frequent (5 - 13%), occurring primarily in the juxtamembrane and extracellular domains (reviewed in Ma et al., 2008). These do not appear to confer ligand independence, but rather defects in ligand-induced receptor degradation and/or other mechanisms that result in aberrantly sustained signaling or increase ligand sensitivity (Ma et al., 2008; Kong-Beltran et al., 2006; Peschard and Park, 2003). Evidence of autocrine HGF signaling in normal bronchiolar epithelium and in non-small cell lung cancer, also has been reported (Tsao et al., 2001). Cigarette smoking induced overexpression of *HGF* in type II pneumocytes and lung cancer cells (Chen et al., 2006), and HGF inhibited cigarette smoke extract induced apoptosis in human bronchial epithelial cells (Togo et al., 2010). Consistent with these findings, a neutralizing monoclonal antibody directed against HGF significantly reduced tumor burden in mice treated with a tobacco carcinogen (Stabile et al., 2008). Sustained HGF treatment of lung adenocarcinoma cells harboring activating EGFR mutations conferred resistance to EGFR-directed TK inhibitors, foreboding yet another route to oncogenic HGF signaling in this disease, and suggesting that inhibition of both EGF and HGF pathways might offer greater therapeutic efficacy for its treatment (Yano et al., 2008; Turke et al., 2010).

2.1.5 Breast Cancer

Analysis of breast tumor HGF levels in a large cohort revealed a wide range of concentrations, but breast cancer patients with high values had a significantly shorter relapse-free survival and overall survival when compared to those with low values; in fact, HGF levels were a better independent predictor of relapse-free and overall survival than lymph node involvement (Yamashita et al., 1994; Nagy et al., 1996). Serum HGF levels were also significantly higher than those of healthy controls in about one-third of breast cancer patients, a finding significantly associated with node status, tumor size and histological evidence of venous invasion (Taniguchi et al., 1995; Toi et al., 1998; Sheen-Chen et al., 2005). Removal of the primary tumor decreased the serum HGF levels, suggesting that the elevation was tumor-related (Taniguchi et al., 1995). Almost all patients with recurrent breast cancer also had increased serum HGF level, and patients with liver metastases had higher levels compared to those with other sites of metastases (Taniguchi et al., 1995; Maemura et al., 1998; Eichbaum et al., 2007). Consistent with these findings, the expression

of HGF activator is increased in breast cancer specimens, while the cognate inhibitors HAI-1 and HAI-2 are expressed to a significantly lower level in poorly differentiated breast tumors; HAI-2 expression was also inversely correlated with nodal involvement and tumor spread (Parr et al., 2004; Parr and Jiang, 2006). Somatic mutations and functional polymorphisms in the HGF gene promoter cause increased HGF production in breast cancer; 51% of African Americans and 15% of individuals of mixed European descent with breast cancer harbor a promoter truncation variant in their breast tumors that which is associated with increased cancer incidence and a substantially younger age of disease onset than those with a wild-type genotype (Ma et al., 2009).

2.1.6 Genitourinary Malignancies

Inherited missense mutations in the human HGF receptor gene, *MET*, were first found in individuals with hereditary papillary renal carcinoma (HPRC) type 1; similar somatic mutations were also found in a small subset (13%) of sporadic papillary renal carcinoma (PRC) tumor samples (reviewed in Dharmawardana et al., 2004). Trisomy of human chromosome 7, which contains both *MET* and *HGF* genes, occurs in 95% of sporadic papillary renal carcinoma and virtually all HPRC cases, where there is always non-random duplication of the mutant *MET* allele (Dharmawardana et al., 2004). The biochemical and biological impact of HPRC-associated *MET* mutations have been investigated in several model systems, confirming their suspected oncogenic potential (Dharmawardana et al., 2004). Although the role of HGF binding in the oncogenicity of HPRC and PRC-associated *MET* mutations was initially perceived as minimal, a study specifically addressing this issue indicated that ligand binding may contribute significantly to oncogenic potential (Michieli et al., 1999). Several lines of evidence suggest a role for HGF in human prostate cancer (reviewed in Knudsen and Edlund, 2004; Hurle et al., 2005). *MET* is expressed in normal human prostatic epithelium and *HGF* in the underlying normal stroma. Here again, a reciprocal relationship appears to exist between HGF and TGF-β in terms of biological activity on prostate epithelium (HGF pro-survival and proliferation vs TGF-β pro-apoptosis) and regulation of local expression (Knudsen and Edlund, 2004; Hurle et al., 2005). *MET* expression was frequently (~50%) found in localized prostate tumor samples and virtually all prostate cancer metastases (Knudsen and Edlund, 2004). The increased frequency of *MET* expression and loss of androgen responsiveness in advanced disease is consistent with the finding that androgen receptor negatively regulates *MET* expression (Verras et al., 2007). Plasma HGF level was found to be an independent predictor of metastasis to lymph nodes and disease recurrence following surgery in patients treated for localized prostate cancer (Gupta et al., 2008), and higher plasma HGF levels in hormone refractory patients were associated with a decreased patient survival (Humphrey et al., 2006). Moreover, among 174 cytokines analyzed in a collection of prostatic fluid samples, HGF was the most increased in patients with extensive disease compared to those with minimal disease (Fujita et al., 2008).

2.1.7 Brain Tumors

HGF and *MET* are expressed in human glioma and medulloblastoma, where increased relative abundance frequently correlate with tumor grade, tumor blood vessel

density, and poor prognosis. Overexpression of *HGF* and/or *MET* in brain tumor-derived cells enhances their tumorigenicity and growth, while inhibition of HGF or Met in experimental tumor xenografts suppresses tumor growth and angiogenesis (Li et al., 2005; Kim et al., 2006; reviewed in Abounader and Laterra, 2005). A recent pilot study reported that elevated levels of HGF in human cerebrospinal fluid were associated with mortality and recurrence of glioblastoma, suggesting that cerebrospinal fluid HGF level could be of prognostic value for this disease (Garcia-Navarrete et al., 2010). Consistent with the suspected role of Hgf in glioma progression, a potent, highly selective, orally bioavailable Met ATP binding antagonist significantly inhibited intracranial brain tumor malignancy and growth in mice (Guessous et al., 2010). Early results from human clinical trials are, unfortunately, not as promising. A recent phase II study evaluated the efficacy and safety of AMG 102 (rilotumumab), a fully human monoclonal antibody against HGF, in 60 patients with recurrent glioblastoma. The study showed that AMG 102 monotherapy at doses up to 20 mg/kg was not associated with significant antitumor activity in this heavily pretreated patient group, although one objective response was observed per investigator assessment but not central assessment (Wen et al., 2011). Trials with other HGF or Met targeted agents are underway.

2.1.8 Colorectal and Gastric Carcinomas

Overexpression of Met protein and/or amplification of *MET* was found in 50% of primary human colorectal carcinomas and 70% of liver metastases, suggesting that Met abundance contributes to disease progression (Di Renzo et al., 1995). *MET* gene amplification also occurs with 10-13% frequency in human gastric cancer (Smolen et al., 2006) via the breakage-fusion-bridge mechanism, wherein recurrent breaks occur in chromosomal common fragile sites upon replication stress (Hellman et al., 2002). Studies of human cultured colorectal tumor cells and tumor tissue samples indicated increased activation of pro-HGF, coincident with modestly increased HGF activator abundance and dramatically decreased levels of HGF activator inhibitor-1 (Kataoka et al., 2000). Several selective Met kinase inhibitors show potent anti-tumor activity in gastric tumor-derived xenografts (Christensen et al., 2003; Smolen et al., 2006; Zhou et al., 2007; Buchanan et al., 2009) and colon derived xenografts (Zhang et al., 2010). A genome-wide expression analysis of colon tumor specimens identified MACC1 as an independent prognostic indicator of metastasis; interestingly, *MET* is a transcriptional target downstream of MACC1, and expression of the latter promoted HGF-induced colon tumor cell proliferation, invasion as well as tumor growth and metastasis in xenograft models (Stein et al., 2009).

2.1.9 Other Malignancies

MET is normally expressed in melanocytes and the acquisition of *HGF* expression has been reported in melanoma (Halaban et al., 1993; Natali et al., 1993; Saito et al., 1994). *hgf* transgenic mice display a high frequency of metastatic melanoma in increased sensitivity to UV radiation induced carcinogenesis, as noted in the Phenotypes section, in fact, several mouse models of melanoma indicate the prevalence of Hgf pathway involvement (reviewed in Walker et al., 2002). In some sarcomas, *MET* is overexpressed in malignancy similar to many carcinomas, where Hgf is delivered locally in a paracrine

manner. However, many sarcomas naturally express *HGF* and acquire *MET* expression, resulting in autocrine pathway activation and enhanced oncogenesis. Sarcomas where the Hgf pathway has been strongly implicated include rhabdomyosarcoma (Chen et al., 2007; Rees et al., 2006; Taulli et al., 2006; Jankowski et al., 2003), leiomyosarcoma (Gao et al., 2009), and clear cell sarcoma (Davis et al., 2010) and osteosarcoma (MacEwan et al., 2003; Coltella et al., 2003).

2.2 Other Diseases

In some cases, enhanced Hgf signaling in response to a pathologic condition may contribute to disease progression; this may be a common mechanism of paracrine Hgf enhancement of tumorigenesis and cancer progression. Glial cells in the neuroretinas and epiretinal membranes of patients with proliferative vitreoretinopathy (PVR) and proliferative diabetic retinopathy respectively show increased HGF levels, and both glial and pigmented retinal epithelial cells express Met, suggestive of autocrine and/or paracrine roles of HGF in glial cell responses during proliferative vitreoretinal disorders as well as in retinal neovascularization, by stimulating of VEGF release (Hollborn et al., 2004; Cui et al., 2007).

3. Critical Hgf Interactions

3.1 Activation of pro-Hgf

Full-length single chain Hgf isoforms undergo proteolytic cleavage at Arg495-Val496 to become biologically active heterodimers consisting of a 69 kDa alpha (or heavy) chain disulfide-linked to a 34 kDa beta (or light) chain (Miyazawa et al., 1989; Nakamura et al., 1989). This conversion is essential for Hgf signaling via its cognate receptor Met on target cell surfaces (Gak et al., 1992; Hartmann et al., 1992; Lokker et al., 1992; Naka et al., 1992, Naldini et al., 1992). The inability of single chain Hgf to signal is not due to poor receptor binding, as both single and two chain Hgf forms have similar receptor binding affinities (Lokker et al., 1992; Kirchhofer et al., 2004). Rather, it is most likely attributable to structural changes that occur upon proteolytic activation: like the activation of plasminogen and related serine proteases, the activation loop of Hgf undergoes conformational changes that are characteristic of the protein family (reviewed in Maun et al., 2010). For plasminogen and other proteases, these changes result in a catalytically active state, while for Hgf, they allow binding interactions between the nascent Hgf light chain aminoterminus and the Met sema domain that are critical for Met kinase activation and signaling (Kirchhofer et al., 2004; Maun et al., 2010).

Several serine proteases are capable of proper cleavage and activation of Hgf in vitro including Hgf activator (HGFA) (Shimomura et al., 1992; Miyazawa et al., 1993; Shimomura et al., 1995), matriptase (Lee et al., 2000), hepsin (Herter et al., 2005; Kirchhofer et al., 2005), urokinasetype plasminogen activator (uPa; Mars et al., 1993), tissue plasminogen activator (tPA; Mars et al., 1993), plasma kallikrein (Peek et al., 2002), factor XIa (Peek et al., 2002), and factor XIIa (Shimomura et al., 1995). Of note, cleavage by uPA occurs stoichiometrically following the formation of a stable complex between uPA

and pro-Hgf while each is bound to their respective receptor on the cell surface (Naldini et al., 1995). In addition, cleavage of pro-Hgf by plasma kallikrein and factor XIa occurs at both Arg495 as well as within the K4 domain of the alpha chain at Arg425-His426 with no apparent impact on HGF function (Peek et al., 2002). Demonstration of Hgf activation in vivo has been limited to HGFA (Miyazawa et al., 1996) and uPA (Mars et al., 1995; Shimizu et al., 2001), thus the physiologic relevance of many of these Hgf activators is yet to be established.

Proteolytic conversion of full-length pro-Hgf to the active, two chain form is further controlled by the Kunitz-type inhibitors Hgf activator inhibitor-1 (HAI-1), HAI-1B (a splice variant of HAI-1) and HAI-2 (also known as placental bikunin). Each of these inhibitors consists of two Kunitz domains, the first of which (KD1) is responsible for the inhibition of Hgf activators (Denda et al., 2002; Kirchhofer et al., 2003). HAI-1 and HAI-1B inhibit HGFA, matriptase, and hepsin potently (Kirchhofer et al., 2003; Shia et al., 2005), while HAI-2 additionally inhibits a broader spectrum of serine proteases including plasma kallikrein and factor XIa (Delaria et al., 1997). In addition to protease inhibition, HAI-1 promotes localized activation of pro-Hgf through reversible binding and sequestration of HGFA on the target cell surface for concentrated release under the appropriate circumstances, such as tissue injury or local inflammation (Kataoka et al. 2000). Several groups have demonstrated that an increased ratio of Hgf activators to HAI-1 or HAI-2 correlates with malignant progression and poor prognosis in a variety of carcinomas (Betsunoh et al., 2007; Kataoka et al., 2000; Oberst et al., 2002; Vogel et al., 2006), emphasizing the important balance between Hgf activators and their cognate inhibitors for normal Hgf pathway activation in tissue homeostasis. A recently reported crystallographic structural analysis of HGFA and HAI-1 further refines our understanding of this remarkably complex system of regulating Hgf activity, and sheds new light on the structural basis for the restricted substrate specificity of HGFA toward Hgf and the highly related family member macrophage stimulating protein (Eigenbrot et al., 2010).

3.2 Cell-surface Heparan Sulfate Proteoglycans

The interaction between Hgf and heparan sulfate (HS) proteoglycans is broadly relevant to Hgf biology and was discovered in early Hgf studies. Hgf was observed to be bound to the extracellular matrix of isolates from normal adult rat liver (Masumoto and Yamamoto, 1991) and low affinity (relative to Met) Hgf binding sites (Kd = 250 - 400 pM) observed on a variety of cultured target cell types were sensitive to displacement by exogenously added soluble heparin (Naldini et al., 1991). Many affinity chromatography purification schemes exploited this strong heparin binding to efficiently isolate Hgf from low-abundance sources (Nakamura et al., 1987; Gohda et al., 1988; Zarnegar et al., 1989; Rosen et al., 1989; Gherardi et al., 1989; Selden and Hodgson, 1989; Weidner et al., 1990; Rubin et al., 1991). Several later studies demonstrated the broader functional relevance of HS in Hgf binding, Met activation and cellular responses (Weidner et al., 1993; Kato et al., 1994; Strain et al., 1994; Zioncheck et la., 1995; Schwall et al., 1996; Hartmann et al., 1998; Sakakura et al., 1999; Day et al., 1999; Sergeant et al., 2000; Seidel et al., 2000; Willians and Clark, 2003; Karihaloo et al., 2004). When injected intravenously, Hgf has an early phase half-life of 4 min (Liu et al., 1997); however, when administered as a complex with heparin, plasma disappearance is much slower, consistent with clearance by hepatic uptake (Kato et

al., 1994). Moreover, intravenous injection of soluble heparin into normal humans results in a significant and immediate increase in serum Hgf concentration (Seidel et al., 1999). These and other observations suggest that circulating Hgf is rapidly sequestered by HS present on luminal vascular surfaces, which may constitute a widely distributed reservoir of Hgf. Similar to fibroblast growth factor (FGF) signaling, which requires not only FGF-HS binding, but also FGF receptor-HS interaction (Mohammadi et al., 2005), evidence suggests that HS may facilitate Hgf signaling through interactions with both Hgf and Met (Rubin et al., 2001).

Substantial progress has been made in identifying HS binding sites in Hgf. Early studies of deletion mutants implicated the HGF N domain (Okigaki et al., 1992), and particularly its hairpin loop region, in HS binding (Matsumoto et al., 1991; Mizuno et al., 1994). The demonstration that recombinantly expressed HGF N domain retained the HS binding properties of full-length HGF directly established that the primary determinants of HS binding resided there (Sakata et al., 1997; Lyon et al., 2004). Putative HS binding residues in N domain, selected on the basis of similarity to consensus HS binding motifs, were investigated by using site-directed replacement with alanine with only modest biological impact (Sakata et al., 1997; Kinosaki et al., 1998). Candidate selection based on structural modeling, combined with functional analysis of opposite charge amino acid substitution mutants, more strongly implicated residues R74 and R77 (human residues R73 and R76) in HS binding over earlier studies of alanine substitutions at these positions (Hartmann et al., 1998).

Efforts to identify HS binding residues were considerably refined upon solving high resolution three-dimensional structures of N domain and NK1 proteins. Using the solution structure of N domain, residues K61, K63, and R74 (human K60, K62 and R73) were proposed as a primary HS binding site (Zhou et al., 1998). Crystallographic analysis of NK1 reinforced this concept and distinguished a secondary site at R77 and R79 (human R76 and R78) with potential contributions from R36 and R37 (human R35 and R36; Ultsch et al., 1998). A second NK1 crystallography study identified R74 and R77 as most important for HS binding (Chirgadzi et al., 1999). Combined NMR spectral analysis and fluorescence binding studies provided functional evidence of primary HS binding by K61, K63, and R74, and secondary binding by R36, R37, R77, and K79 (Zhou et al., 1999). Subsequent co-crystallographic structural analysis of NK1 and HS supported a pivotal role for R74 in HS binding, with contributions from main chain atoms of T62, K64 and G80 and the side chains of K59, K61, T62, K63, and R77 (Lietha et al., 2001). HS and dermatan sulfate (DS) bind to the same sites on NK1, NK2 and full-length Hgf, which have identical glycosaminoglycan (GAG) binding properties (Sakata et al., 1997; Lyon et al., 2004).

Both heparan sulfate (HS), which is a component of proteoglycans present on most cell surfaces, and the closely related GAG heparin, which is produced by mast cells, display a wide range of fine structural variability. These GAGs are composed of a linear chain of 10-200 disaccharide units of N-acetyl-D-glucosamine linked to D-glucuronic acid. The disaccharide repeat unit can be modified to include N- and O-sulfation (6-O and 3-O sulfation of the glucosamine and 2-O sulfation of the uronic acid) and epimerization of beta-D-glucuronic acid to alpha-L-iduronic acid. Together, these five modifications give rise to 32 combinations, thereby exceeding the complexity of proteins, which are made up of 20 typical amino acids. On this basis, HS-GAGs may be the most information-dense biopolymers in nature (reviewed in Sasisekharan and Venkataraman, 2000). This

structural variety can confer a high degree of selectivity in protein binding, with significant impact on processes such as signal transduction.

Substantial progress has also been made in identifying the compositional and structural determinants within heparin and HS-containing proteoglycans that define selectivity for Hgf binding. Hgf binds to syndecans -1, -2 and -4; high affinity binding sites are contained within the N-sulfated domains of HS, although the N-sulfates themselves contribute far less than nonsulfated alpha-L-iduronic acid residues (Lyon et al., 1994; Ashikari et al., 1995). Disaccharide analyses indicated that affinity is more closely associated with 6-0-sulfation of alpha-D-N-sulfoglucosamine residues than with sulfation at any other position, implying that the structural specificity of Hgf-HS interaction is significantly different from that of the fibroblast growth factor family (Lyon et al., 1994, Ashikari et al., 1995). Another feature that distinguishes Hgf from other known HS-binding growth factors is the ability to bind DS, which is found on decorin and biglycan (Lyon et al., 1998). The minimum oligosaccharide chain length for high affinity Hgf binding is a tetrasaccharide for HS but a hexasaccharide for DS (Lyon et al., 2004). DS is synthetically and compositionally distinct from HS, and although both contain idurate domains of variable length, the sulfation of HS occurs primarily within these domains, whereas DS sulfation is more uniformly distributed. DS is an abundant matrix component of the stromal compartment of many organs, implying that retention there must be overcome for Hgf delivery to target epithelial and endothelial cells, where HS predominates over DS in basement membranes. This compositional gradient of Hgf-binding GAGs is thought to control Hgf diffusion from source to target, and act as a reservoir from which relatively high Hgf concentrations could be released in a spatially and temporally restricted manner through matrix turnover under various physiological and pathological conditions (Lyon et al., 1998).

HS and DS interactions with Hgf and Met may promote receptor activation and downstream signaling through several mechanisms. Hgf binding to cell-surface HS increase local Hgf concentrations and promote an intrinsic tendency for Hgf to self-associate, which may in turn facilitate and stabilize receptor clustering, kinase activation and potentially the recruitment of intracellular effectors (Schwall et al., 1996; Sakata et al., 1997; Hartmann et al., 1998; Lietha et al., 2001; Kemp et al., 2006; Tolbert et al., 2007). However, many details as to how these GAGs promote receptor activation and signaling remain unclear. HS-Met interactions are substantially weaker than HS- or DS-Hgf interactions, and their contribution to the stability a ternary Hgf-HS-Met complex may not be critical for all Hgf responses (Lyon et al., 2002). Small HS or DS oligosaccharides thought to capable of binding only Hgf alone appear to be sufficient for Met and Erk activation, and subsequent migration (Lyon et al., 2002). These questions illustrate the complexity of Hgf signaling regulation and highlight the need for further investigation into the roles of GAGs in this process.

3.3 The Met Receptor Tyrosine Kinase

Hgf shares several structural motifs and approximately 38% amino acid sequence identity with plasminogen. Each is synthesized as a single polypeptide chain which is cleaved at a conserved site to generate a biologically active disulfide-linked heterodimer. The heavy chain of the dimer (~60 kDa in Hgf) is derived from the amino-terminus of the

precursor and contains multiple kringle domains (K; four in Hgf, five in plasminogen). Kringle domains (~80 amino acids) have a characteristic folding pattern determined by three internal disulfide bonds and additional conserved sequences (Patthy et al., 1984). The Hgf light chain (~34 kDa), like that of plasminogen, has the structure of a serine protease, but two non-conservative substitutions within the catalytic triad render Hgf devoid of proteolytic activity (reviewed in Matsumoto and Nakamura, 1996).

The human *HGF* gene encodes full-length HGF and two truncated isoforms (NK1 and NK2) which consist of the amino-terminal domain (N) linked in tandem with the first one (K1) or two (K1+K2) kringle domains, respectively. All three isoforms bind to Met (Bottaro et al., 1991; Chan et al., 1991; Lokker et al., 1992); like full-length HGF, NK1 stimulates mitogenesis, motogenesis and morphogenesis, though at reduced potency and with greater HS dependence, suggesting that the primary Met binding site is contained within this fragment (Montesano et al., 1998; Stahl et al., 1997). NK2 can competitively antagonize mitogenicity stimulated by HGF or NK1, but retains motogenic activity, activating the Met kinase and a subset of those intracellular signaling pathways activated by either HGF or NK1 (Day et al., 1999). Within NK1, the N domain contains the HS binding site (as described in detail above; Okigaki et al., 1992; Mizuno et al., 1994; Sakata et al., 1997; Zhou et al., 1998; Kinosaki et al., 1998; Hartmann et al., 1998; Zhou et al., 1999; Lietha et al., 2001) and K1 contains the primary site of Met interaction (Lokker et al., 1994; Rubin et al., 2001).

Although a high-resolution structure of the NK1-Met complex has not yet been obtained, several crystallographic studies of NK1 have refined the basic principles of HGF-Met interaction obtained from functional studies (Ultsch et al., 1998; Chirgadze et al., 1999; Watanabe et al., 2002). In addition to the relatively high affinity Met binding site within NK1, full-length HGF has a lower affinity Met binding site in the light chain (serine protease-like domain) that binds to the Met Sema domain; high-resolution structures have been obtained for this intreaction (Stamos et al., 2004; Kirchhofer et al., 2004; Kirchhofer et al., 2007; Gherardi et al., 2006). As noted in section 3.1, single chain pro-Hgf binds with high affinity to Met, but upon conversion of pro-Hgf to the active two-chain heterodimeric form, it undergoes a structural change from a compact, closed conformation to an elongated, open conformation which, through interaction with the Met Sema domain, results in Met kinase activation (Stamos et al., 2004; Kirchhofer et al., 2004; Kirchhofer et al., 2007; Gherardi et al., 2006). There are conflicting reports regarding the localization of the high affinity Hgf binding site within the Met ectodomain. Gherardi and colleagues (2006) reported the structure of a complex between two-chain Hgf and the Met ectodomain in which the NK1 portion of Hgf contacted the one face of the seven-blade beta-propeller Sema domain of Met (that harboring the loops connecting the beta-strands b-c and d-a), whereas the light chain bound the opposite ("b") face. In contrast, Basilico and colleagues (2008) reported that the NK1 region of Hgf bound to the more carboxyl terminal Met Ig-like loops (the so-called Met "stalk" region), specifically loops 3 and 4. Ultimately, further structural and functional analysis will help clarify this apparent discrepancy. Despite remaining uncertainties regarding the structure of the Hgf-Met signaling complex, the existing structural studies have provided significant insights into strategies to artificially modulate Hgf-driven Met kinase activation. As mentioned above, by altering a secondary HS binding site in K1, Lietha and colleagues (2001) engineered a potent competitive antagonist of Met activation. Kirchhofer and colleagues (2007) altered residues in the amino-terminus of the Hgf light chain that impaired the conformational

change accompanying Hgf activation, and similarly generated a potent competitive antagonist of native Hgf-Met interaction and signaling. More recently, Tolbert and colleagues (2010) reported on the structural basis of competitive mitogenic antagonism by NK2, and generated mutant forms that acquired mitogenic activity.

4. Major Sites of Hgf Expression

4.1 Tissues and Organs

hgf is expressed in many organs throughout the body from early embryonic development through adulthood. As noted above, a large collection of work suggests that Hgf is typically produced in the tissue stroma and acts in a paracrine manner on epithelial and endothelial cells, and other cell types as noted below (reviewed in Zarnegar, 1995).

Early tissue extraction and immunohistochemical staining of rabbit specimens demonstrated HGF in the pancreas, small intestine, salivary glands, thyroid and brain (Zarnegar et al., 1990). Subsequent immunolocalization studies of human and rat tissues confirmed and extended these findings, revealing significant staining of surface epithelia, prostatic and seminal vesicle epithelia, distal renal tubules and collecting ducts, megakaryocytes, granulocytes and placental tissues, and more moderate staining of respiratory, gastrointestinal, biliary and uterine epithelium and in macrophages and vascular endothelium (Wolf et al., 1991; Defrances et al., 1992; Tsuda et al., 1992). Because Hgf binds strongly to heparan sulfate proteoglycans found in abundance in most extracellular matrices, immunohistochemical localization studies must be interpreted carefully, preferably in the company of independent experimental methods, where the question of the cellular origin of Hgf is concerned. In the absence of other independent experimental means, immunohistochemical studies have provided reliable information concerning the relative spatial and temporal abundance of Hgf on a tissue and organ level. In the aforementioned studies, protein staining patterns may be as much an indication of Hgf's targets as its site of synthesis. This presumably accounts for the strong immunostaining of epithelia, as there is little evidence of Hgf expression by isolated normal epithelial cells. Northern analysis of rat tissue specimens revealed a diverse pattern of expression generally consistent with protein staining results, with some differences in relative signal intensities (Tashiro et al., 1990). In particular, lung had the highest level of *hgf* transcript, though only a moderate level of protein staining, suggesting that lung-derived Hgf is released into the circulation for systemic distribution, consistent with reports of *hgf* induction in the lung following injury in distant organs (Yanagita et al., 1992; 1993). Many tissues that show modest levels of Hgf production under normal conditions can display significantly increased production during wound healing, tissue repair and regeneration. For example, Hgf production is dramatically elevated during skeletal muscle regeneration, where it promotes myoblast proliferation and inhibits myotube formation (Hayashi et al., 2004).

hgf mRNA transcript and/or protein has been detected in cultured fibroblasts derived from many organs, including the lung, stomach, colon, breast, prostate and skin (Rubin et al., 1991). The mRNA transcript also has been observed in other cells such as alveolar macrophages (Wolf et al., 1991; Yanagita et al., 1992), peripheral leukocytes (Seki

et al., 1990) and the HL-60 promyelocyte leukemic cell line (Nishino et al., 1991). There is a consensus that Hgf is synthesized in the liver by non-parenchymal cells (Kinoshita et al., 1989); in situ hybridization revealed *hgf* mRNA transcript in Kupfer and endothelial cells (Noji et al., 1990). However, cell fractionation followed by Northern blot analysis indicated that the fat-storing, Ito cell is responsible for expression in the normal liver (Schirmacher et al., 1992; Ramadori et al., 1992; reviewed in Schirmacher et al., 1993).

4.2 Subcellular Localization

Full-length Hgf isoforms are each synthesized as a single polypeptide chain, pre-pro-Hgf, containing an amino-terminal signal peptide sequence for insertion into the rough endoplasmic reticulum (RER) and ultimately, secretion. Maturation of pre-pro-Hgf is presumed to follow a conventional subcellular pathway for secreted proteins, i.e. from RER to the Golgi apparatus to secretory vesicles that ultimately fuse with the plasma membrane allowing protein release into the extracellular environment. There is evidence for both N-linked (Hara et al., 1993) and Olinked glycosylation (Shimizu et al., 1992) of Hgf during maturation, and presumably removal amino-terminal 31 amino acid signal peptide occurs prior to secretion (Miyazawa et al., 1991). The secreted single chain Hgf precursor (pro-Hgf) is biologically inactive and later converted in the active two-chain disulfide-linked heterodimer by proteolytic cleavage (as described in detail above) in the extracellular space, in plasma, or on target cell surfaces.

5. Regulation of Hgf Production

Several exogenous agents alter the magnitude of Hgf production. Protein kinase C-activating phorbol esters stimulate Hgf secretion by fibroblasts in culture, and this is reversed by concomitant administration of dexamethasone (Gohda et al., 1992). Other tumor promoters which induce liver hyperplasia also increase the plasma Hgf concentration (Lindroos et al., 1992). Hepatotoxins such as carbon tetrachloride and D-galactosamine induce a rapid and transient rise in hgf transcript level in the liver and other tissues (Yanagita et al., 1992; Okajima et al., 1990; Zarnegar et al., 1991; Kinoshita et al., 1991), accompanied by an increase of circulating Hgf protein (Zarnegar et al., 1991; Kinoshita et al., 1991).

Profound liver damage dramatically also stimulates *hgf* expression, and *hgf* transcript levels rise substantially soon after partial hepatectomy (Yanagita et al., 1992; Zarnegar et al., 1991; Kinoshita et al., 1991) or unilateral nephrectomy (Nagaike et al., 1991). Normally, both singlechain and active two-chain Hgf are present in liver, the former being in greatest abundance. Following partial hepatectomy the liver displays two phases with regard to Hgf production, activation and metabolism (Pediaditakis et al., 2001). During the first three hours, Hgf is rapidly consumed, in part from hepatic stores, with a decrease in overall abundance of both single-chain and active two-chain Hgf species; only active Hgf is seen in the plasma during this period (Pediaditakis et al., 2001). During the second phase, there is a pronounced reappearance of both single-chain and two-chain Hgf, and the level of Hgf activation (proteolytic conversion from single to two-chain form) increases 5-fold (Pediaditakis et al., 2001). The factors responsible for the dramatic

cessation of liver growth following partial hepatectomy, once the correct liver mass has been reached, remain unknown. One early study showed that an initial rise in *hgf* expression was followed by a period of active cell proliferation, then an increase in a ~ 1.5 kb transcript that may correspond to the Hgf/NK2 isoform (Zarnegar et al., 1991). Production of this competitive Hgf mitogenic antagonist after a wave of hepatocyte proliferation could provide a mechanism for attenuating liver regeneration as it nears completion, although other mechanisms for attenuating growth, such as increased integrin signaling via integrin linked kinase, are clearly involved (Apte et al., 2009).

Transient increases in plasma Hgf levels are rapidly regulated by blood clearance, organ uptake and biliary excretion (Appasamy et al., 1993). For example, plasma concentrations of radiolabeled HGF injected into rats peaked within 15 minutes; HGF was distributed primarily to the liver and kidneys, and it appeared in the bile within 3 minutes, peaking in 50 minutes (Appasamy et al., 1993). Consistent with a critical role in HGF uptake and clearance, the short-term impact of partial hepatectomy was significantly decreased blood clearance (Appasamy et al., 1993), and patients with fulminant hepatic failure display chronically elevated plasma levels of HGF (Gohda et al., 1986; Tsubouchi et al., 1991).

The induction of *hgf* expression at locations distant from sites of injury suggest that systemic factor(s) might regulate in this process (Yanagita et al., 1992; Kono et al., 1992). Nakamura and colleagues have referred to such a systemic regulator as 'injurin' and proposed that it recruits Hgf production by distant tissues which release it into the circulation in response to injury. An apparently novel protein isolated from the serum of rats subjected to partial hepatectomy or ischemic insult has been reported to stimulate HGF synthesis in other rats or in cell lines in vitro (Matsumoto et al, 1992). Interleukin 1 (IL-1), tumor necrosis factor-α, the phorbol ester, tetradecanoylphorbol 13-acetate (TPA), cAMP-elevating agents, PKA-activating agents, growth factors, 1,25-dihydroxyvitamin D3 and inflammatory cytokines can independently increase hgf expression, and the combination of IL-1 and TPA exerts a synergistic effect (Matsumoto et al., 1992; Li et al., 2005). TGF-β and glucocorticoids can block *hgf* induction elicited by IL-1 and TPA as well as by other stimuli (Ramadori et al., 1992; Gohda et al., 1992; Matsumoto et al., 1992). Co-culture of Hgf-producing fibroblasts with epithelial cells can inhibit Hgf expression (Kamalati et al., 1992). Thus, a variety of factors act locally and systemically to regulate Hgf production.

HGF expression is also regulated upon infection of mammalian hepatocytes by Plasmodium, the causative agent of malaria (Carrolo et al., 2003). Plasmodium sporozoites migrate through several hepatocytes, breaching plasma membranes and effectively injuring the liver, before infection is finally established. This injury induces Hgf production, and the ensuing activation of Met renders hepatocytes susceptible to infection by induces rearrangements of the host-cell actin cytoskeleton that are required for the early development of the parasites, and protects infected cells from apoptosis (Carrolo et al., 2003; Leiriao et al., 2005).

6. Phenotypes Associated with *hgf* or *met* Alteration

As indicated earlier, loss of *hgf* or *met* function in mice with homozygous gene deletion is embryonic lethal between days E12.5 and E15.5 (Schmidt et al., 1995; Uehara et al., 1995; Bladt et al., 1995). *hgf* and *met* null mice exhibit very similar phenotypes, further supporting the concept that Met is the only receptor for Hgf, and Hgf the only ligand for Met (Rosario and Birchmeier, 2003). Defects in the proliferation and survival of cells in the liver and placenta result in arrested organogenesis of these and other tissues, highlighting the importance of Hgf stimulated mitogenicity and survival in target cells. These animal models also consistently underscore the importance of Hgf as a potent and critical regulator of cell migration. Skeletal muscle progenitor cells that form limb, tongue, and diaphragm musculature normally delaminate from the epithelial dermomyotome of the somites by an epithelial-to-mesenchymal transition and migrate to their final destination where they complete differentiation. Loss of Hgf signaling in mice homozygous for *met* deletion results in defective delamination and migration of muscle progenitors from the dermomyotome and failure to form the skeletal muscles of the limb and diaphragm (Bladt et al., 1995; Maina et al., 1996; Dietrich et al., 1999; Birchmeier et al., 2003; Christ and Brand-Saberi, 2002).

Conversely, *hgf* overexpression in transgenic mouse embryos induces the inappropriate formation of skeletal muscle in the CNS through dysregulated migration of Met-containing myogenic precursor cells to the neural tube (Takayama et al., 1996). Melanoblasts were also aberrantly localized to inappropriate sites within the E12.5 transgenic embryo, including the neural tube, and melanocytes were found within the transgenic adult in a number of abnormal ectopic sites, including the CNS (Takayama et al., 1996).

Mice bearing conditional deletions of *hgf* and *met* have been used to demonstrate the functional relevance of pathway activation at later developmental stages and in adulthood. For example, Met and epidermal growth factor receptor jointly regulate final nephron number and collecting duct morphology (Ishibe et al., 2009). Mice with conditional knockout of *met* in the collecting duct of the kidney were more susceptible to interstitial fibrosis and tubular necrosis after unilateral ureteral obstruction, and had diminished capacity for tubular cell regeneration after release of the obstruction (Ma et al., 2009). When conditional *met* knockout was targeted to renal podocytes, mice developed more severe podocyte apoptosis and albuminurea than control littermates when subjected to nephrotoxic renal damage (Dai et al., 2010). Mice with a targeted mutation of the gene encoding urokinase plasminogen activator receptor, an important Hgf activator, have decreased Hgf levels and a substantial reduction in neocortical GABAergic interneurons at embryonic and perinatal ages, leading to changes in circuit organization and behavior (Powell et al., 2001; 2003). Mice with targeted mutation of two critical carboxylterminal tyrosine residues in *met* were found to be phenotypically similar to met null animals. In contrast, targeting one of those sites and thereby disrupting the consensus for Grb2 binding allowed development to proceed to term, but caused a striking reduction in limb muscle mass coupled to a generalized deficit of secondary fibers, revealing a role for Hgf signaling in late myogenesis (Maina et al., 1996).

Hgf function in postnatal cerebellar development was explored using genetically engineered mice where one met allele harbored a hypomorphic met mutation at the Grb2-

binding site (Ieraci et al., 2002). These mice display reduced cerebellar size, foliation defects and balance impairments, suggesting that normal cerebellar development and function require Hgf signaling (Ieraci et al., 2002).

Tissue selective, conditional *hgf* overexpression or *met* gene suppression in mice also established that Hgf is essential for liver regeneration (Borowiak et al., 2004; Huh et al., 2004; Paranjpe et al., 2007; Shiota and Kawasaki, 1998). These reports further showed that Hgf was critical for liver cell transition from G1 to S-phase via the MAPK/Erk pathway and protection against apoptosis. A more recent study using *met* suppression engineered selectively in hepatocytes, as opposed to all liver cell types during liver regeneration, further revealed that Hgf signaling was also critical for progression from G2 to M phase via Erk-mediated activation of the immediate early genes c-Fos and Egr-1, among others known for orchestrating G2/M transition (Factor et al., 2010).

Genetically engineered animal models have also revealed that Hgf is involved in granulation tissue formation and reepithelialization in skin wound repair (Yoshida et al., 2003, Chmielowiec et al., 2007). Engineered overexpression or exogenous application of Hgf protein, or exogenous *hgf* gene transfer, to treat full-thickness skin wounds accelerates both processes, as well as vascularization, in rodent models (Toyoda et al., 2001; Yoshida et al., 2003; Bevan et al., 2004; Kunugiza et al., 2006). In conditional *met* mutant mice, skin wound closure occurred only though a small population of keratinocytes that had escaped conditional mutation designed to inactivate kinase activity, i.e. in those keratinocytes with wild type met, reinforcing the conclusion that Hgf/Met signaling is required for full-thickness skin wound repair (Chmielowiec et al., 2007).

Chronic, ubiquitous overexpression of *hgf*, including truncated Hgf isoforms, results in tumorigenesis and tumor metastasis in a variety of tissues and organs, particularly malignant melanoma with liver metastasis (Takayama et al., 1997; Otsuka et al., 1998, 2000; Horiguchi et al., 2002; Sharp et al., 2002), significantly increases the frequency of environmentally driven skin and liver carcinogenesis (Noonan et al., 2000; Horiguchi et al., 2002), as well as the frequency of renal tubular hyperplasia, polycystic disease and glomerulosclerosis, vascularization and granulation tissue formation (Takayama et al., 1997; Toyoda et al., 2001), and chemicallyinduced liver fibrosis (Hagiwara et al., 2008). These studies, as well as the studies of HPRC Type 1 in humans (see section 2.1.6), provide clear evidence of the oncogenic and pro-metastatic potential of aberrant Hgf signaling at the organismal level. On the other hand, studies of transgenic *hgf* mice have also shown that Hgf ameliorates high-fat diet-induced fatty liver (Kosone et al., 2007) inhibits chemically-induced acute liver injury (Otsuka et al., 2002), and that NK2 overexpression inhibits liver regeneration after partial hepatectomy (Otsuka et al., 2005).

7. mRNA Splice Variants

Five splice variants of the human *HGF* gene have been identified.

Transcript variant 1 (NCBI Accession: NM_000601) encodes the longest isoform (isoform 1; NP_000592) with 728 amino acids.

Transcript variant 2 (NM_001010931) lacks multiple 3' exons but includes an alternate 3' exon relative to variant 1. The encoded protein (isoform 2; NP_001010931; also known as NK2; Chan et al., 1991) is truncated after the second kringle domain,

contains 290 amino acids and has a distinct carboxyl-terminus relative to isoform 1. NK2 protein binds Met (Bottaro et al., 1991; Chan et al., 1991) and has intrinsic motogenic activity of modestly lower potency than mature HGF isoform 1 (Stahl et al., 1997). However, NK2 can competitively antagonize mitogenicity and morphogenicity stimulated by mature HGF isoform 1 through Met (Chan et al., 1991; Stahl et al., 1997; Montesano et al., 1998). These in vitro observations are consistent with the phenotype of transgenic mice expressing NK2 (Otsuka et al., 2000; Otsuka et al., 2005).

Transcript variant 3 (NM_001010932) lacks an in-frame coding segment present in isoform 1. The encoded protein isoform 3 contains 723 amino acids but lacks the sequence "FLPSS" at positions 162 - 166 (163 - 167 in mouse) within the first kringle domain of isoform 1.

Transcript variant 4 (NM_001010933) combines the the 3' truncation of variant 2 and internal deletion of isoform 3. The encoded protein (isoform 4; NP_001010933) contains 285 amino acids and is identical to NK2 except it lacks the sequence "FLPSS" at positions 162 - 166 in isoforms 1 and 2.

Transcript variant 5 (NM_001010934) lacks multiple 3' exons and has an alternate 3' segment that is distinct from either isoform 1 or 2. The encoded protein isoform 5 (NP_001010934; also known as NK1; Lokker et al., 1992; Hartmann et al., 1992; Cioce et al., 1996; Stahl et al., 1997; Montesano et al., 1998) contains 210 amino acids with a unique carboxyl terminal sequence immediately following kringle 1. Isoform 5/NK1 binds Met and has intrinsic motogenic activity of modestly lower potency than mature isoform 1. The mitogenic and morphogenic activities of this isoform are controversial. Early reports found that NK1 had mixed agonist/antagonist activities relative to isoform 1 (Lokker et al., 1992, 1993; Hartmann et al., 1992; Cioce et al., 1996). Later reports, where recombinantly expressed protein was more thoroughly characterized both physically and biologically, suggest that NK1 is a better agonist than previously thought, with mitogenic and morphogenic potency approximately 30-fold lower than mature isoform 1 in cultured cell models (Stahl et al., 1997; Montesano et al., 1998; Ultsch et al., 1998). The conclusions of these latter in vitro studies are also consistent with the phenotype of transgenic mice expressing NK1 (Otsuka et al., 1998; Jakubczak et al., 1998).

Splice variants murine *hgf* are less well characterized. The NCBI lists NM_010427 as the reference sequence for the *M musculus hgf* mRNA and NP_034557 as its encoded protein, which contains 728 amino acids and presumably corresponds to the longest human variant encoding isoform 1. At least three murine isoform sequences have been identified: isoform CRA_a (NCBI Accession EDL03238), encoding 211 amino acids; isoform CRA_b (EDL03239), encoding 728 amino acids; and isoform CRA_c (EDL03240), encoding 723 amino acids. Thus CRA_a, CRA_b and CRA_c appear to correspond most closely to human isoforms 5, 1 and 3, respectively.

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