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Gene Section

Review

HGF (hepatocyte growth factor (hepapoietin A; scatter factor))

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Identity

Other names: DFNB39; F-TCF; HGFB; HPTA; SF

HGNC (Hugo): HGF

Location: 7q21.11

Local order: 5'- 81237388 - 81169380 -3'; strand: (-). The human HGF gene is centromeric to CACNA2D1 (calcium channel, voltage-dependent, alpha 2/delta subunit 1) and telomeric to LOC100128317 (similar to hCG2036731) and SEMA3C (sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C).

DNA/RNA

Description

Total length: 68009 bases; mRNA product length: 2820, processed length: 2805.

Transcription

The HGF gene structure consists of 18 exons and 16 introns spanning 68 Mb. Five human mRNA transcript variants arise from alternative splicing. Transcript variant 1 (NCBI Accession NM_000601) encodes the longest isoform (isoform 1; NP_000592) comprised of 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) is truncated after the second kringle domain, contains 290 amino acids and has a distinct carboxyl-terminus relative to isoform 1. 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 within the first kringle domain of isoform 1. Transcript variant 4 (NM_001010933) combines 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 isoform 2 except it lacks the sequence "FLPSS" present 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) contains 210 amino acids with a unique carboxyl terminal sequence immediately following kringle 1.

Pseudogene

There are no known pseudogenes.

Protein

Description

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.

A schematic representation of the domain structure of pre-pro-HGF protein isoform 1 (728 amino acids total), which consists of a signal peptide for secretion (residues 1-31), an amino-terminal heparin binding domain (N), 4 kringle domains, and a serine protease-like domain. Gray areas between named domains represent structurally undefined regions. The lengths of all regions are directly proportional to their sequence length.

All three isoforms bind to the receptor tyrosine kinase Met (Bottaro et al., 1991; Chan et al., 1991; Lokker et al., 1992; Cioce et al., 1996); 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 below) and K1 contains the primary site of Met interaction (Lokker et al., 1993; Rubin et al., 2001).

All HGF isoforms are synthesized as pre-pro-peptides that undergo proteolytic cleavage at or near residue 31 prior to secretion as pro-HGF. Full-length single chain pro-HGF (isoforms 1 and 3) undergo proteolytic cleavage at R494-V495 to become biologically active heterodimers consisting of a ~69 kDa alpha (or heavy) chain disulfide-linked to a ~34 kDa beta (or light) chain; this conversion is essential for biological activity (Miyazawa et al., 1989; Nakamura et al., 1989; Gak et al., 1992; Hartmann et al., 1992; Lokker et al., 1992; Naka et al., 1992; Naldini et al., 1992). Several serine proteases are capable of HGF activation in vitro, including HGF activator (HGFA) (Shimomura et al., 1992; Miyazawa et al., 1993; Shimomura et al., 1995; Shimomura et al., 1997), matriptase (Lee et al., 2000), hepsin (Herter et al., 2005; Kirchhofer et al., 2005), certain plasminogen activator family members (Mars et al., 1993; Mars et al., 1995; Mars et al., 1996), and blood factors XIa and XIIa (Miyazawa et al., 1993; Shimomura et al., 1995; Peek et al., 2002). Conversion from single chain to 2-chain HGF is further regulated by the Kunitz-type inhibitors HGF activator inhibitor-1 (HAI-1), HAI-1B (a splice variant of HAI-1) and HAI-2 (Kawaguchi et al., 1997; Kataoka et al., 2000b; Delaria et al., 1997; Denda et al., 2002; Kirchhofer et al., 2003; Shia et al., 2005; Eigenbrot et al., 2010). The truncated HGF isoforms (2, 4 and 5) do not contain R494 and do not require this processing step for biological activity, which are generally less potent and/or less pleiotropic than that of the full-length HGF isoforms (Stahl et al., 1997; Montesano et al., 1998).

The interaction between HGF and heparan sulfate (HS) proteoglycans is also profoundly relevant to HGF biology. HGF was shown to be bound to the extracellular matrix of normal adult rat liver isolates (Masumoto and Yamamoto, 1991) and HGF binding sites with Kd in the range of 250-400 pM observed on a variety of cultured target cell types were sensitive to displacement by soluble heparin (Naldini et al., 1991). 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 and Michalopoulos, 1989; Rosen et al., 1989; Gherardi et al., 1989; Selden and Hodgson, 1989; Weidner et al., 1990; Rubin et al., 1991). Later studies demonstrated the biological 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 al., 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; Rubin et al., 2001; Williams and Clark, 2003; Karihaloo et al., 2004). When injected intravenously, HGF has a relatively short half-life (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 observations suggest that circulating HGF is rapidly sequestered by HS present on luminal vascular surfaces, which may constitute a widely distributed reservoir of HGF.

HS binding sites are contained primarily in the HGF amino terminal (N) domain (Matsumoto et al., 1991; Okigaki et al., 1992; Mizuno et al., 1994; Sakata et al., 1997; Kinosaki et al., 1998; Hartmann et al., 1998; Zhou et al., 1998; Ultsch et al., 1998; Chirgadze et al., 1999; Zhou et al., 1999; Lyon et al., 1994), but secondary sites are also in the first kringle domain (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., 1998; Deakin et al., 2009). HGF binds to syndecan-1, syndecan-2 and syndecan-4; high affinity binding sites are contained within the N-sulfated domains of HS, although the N-sulfates themselves contribute less to binding than nonsulfated alpha-L-iduronic acid residues (Lyon et al., 1994; Ashikari et al., 1995). 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). 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).

Together with GAG binding, HGF signaling is mediated by the cell surface receptor tyrosine kinase Met (Bottaro et al., 1991; Naldini et al., 1991). Although a high-resolution structure of an HGF-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 that binds to the Met Sema domain; high-resolution structures have been obtained for this interaction (Stamos et al., 2004; Kirchhofer et al., 2004; Kirchhofer et al., 2007; Gherardi et al., 2006). Upon proteolytic conversion of single chain pro-HGF to the mature 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). Conflicting reports localize the high affinity HGF binding site within the Met ectodomain to the Sema domain (Gherardi et al., 2006), or alternatively, to the more carboxyl terminal Met Ig-like loops 3 and 4 (Basilico et al., 2008). Despite remaining uncertainties, strategies to artificially modulate HGF-driven Met kinase activation have been advanced. Potent competitive antagonists of Met activation have been engineered by altering a secondary HS binding site in K1 (Lietha et al., 2001) and by altering residues in the amino-terminus of the HGF light chain that impair the conformational change accompanying HGF activation (Kirchhofer et al., 2007).

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). Yet, 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 (Delehedde et al., 2002).

Expression

HGF expression has been reported in many tissues throughout the body, including skin, lungs, liver, muscle, pancreas, gastrointestinal tract, salivary glands, thyroid, brain, prostate and seminal vesicles, breast, uterus, placenta, kidney, as well as megakaryocytes and granulocytes (Kinoshita et al., 1989; Noji et al., 1990; Seki et al., 1990; Zarnegar et al., 1990; Nishino et al., 1991; Rubin et al., 1991; Wolf et al., 1991; Defrances et al., 1992; Tsuda et al., 1992; Yanagita et al., 1992; Schirmacher et al., 1993). As a secreted, soluble growth factor that binds strongly to heparan sulfate proteoglycan present in most extracellular matrices and on target cell surfaces, protein staining patterns may indicate target tissue as well as sites of synthesis. This may account for observed immunostaining of epithelia, since there is little evidence of HGF expression by isolated normal epithelial cells. In contrast, normal fibroblasts from many tissues secrete HGF in culture.

Localisation

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 O-linked 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 above) in the extracellular space, in plasma, or on target cell surfaces.

Function

In most developmental processes and throughout adulthood HGF stimulates cell proliferation, survival, motility, and morphogenesis. These activities were the basis for its discovery as a promoter of liver regeneration (Nakamura et al., 1984; Thaler and Michalopoulos, 1985; Gohda et al., 1986; Nakamura et

al., 1989; Miyazawa et al., 1989; Zarnegar and Michalopoulos, 1989) and independently, 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, ultimately clarified the identity of hepatocyte growth factor, scatter factor, and a lung fibroblast-derived epithelial cell mitogen concurrently under investigation by researchers around the world.

Embryonic development. HGF and its receptor, Met, are expressed during gastrulation and throughout later phases of vertebrate embryogenesis (Stern et al., 1990; Sonnenberg et al., 1993; Andermarcher et al., 1996). Overlapping expression of both genes persists into the earliest phases of organogenesis in the heart, condensing somites and neural crest cells (Andermarcher et al., 1996), but thereafter HGF is expressed in mesenchymal tissues and Met in the surrounding ectoderm in differentiated somites as well as lungs, liver, placenta, muscle, gut, heart and nervous system (Sonnenberg et al., 1993; Woolf et al., 1995; Andermarcher et al., 1996; Thewke and Seeds, 1996; Birchmeier and Gherardi, 1998; Ishikawa et al., 2001). Studies using tissue explants and cultured cells confirm the suspected role of HGF in epithelial branching morphogenesis, e.g. in the developing lung (Santos et al., 1994; Woolf et al., 1995; Ohmichi et al., 1998).

The expression of HGF and Met genes in ventral motor neurons of the 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 indicate 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; Thewke and Seeds, 1999).

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). Defects in the proliferation and survival of cells in the liver and placenta result in arrested organogenesis of these and other tissues, underscoring the importance of HGF stimulated mitogenicity and survival in target cells. These models also highlight 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. Homozygous deletion of Met 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; Rosário and Birchmeier, 2003; Christ and Brand-Saberi, 2002). Conversely, HGF overexpression in transgenic mouse embryos induces the inappropriate formation of skeletal muscle in the central nervous system (CNS) through dysregulated migration of Met containing myogenic precursor cells to the neural tube (Takayama et al., 1996).

Mice bearing conditional deletions of HGF or Met also have been used to demonstrate relevance of pathway activation at later developmental stages and in adulthood. 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, considered 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; Powell et al., 2003a). Mice with targeted mutation of two critical carboxyl terminal 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 and a generalized deficit of secondary fibers, indicating the importance of HGF signaling in late myogenesis (Maina et al., 1996).

Maturity and adult homeostasis. 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 (Streit et al., 1995). 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; Streit et al., 1995; Honda et al., 1995; Yamagata et al., 1995; Thewke and Seeds, 1999). HGF is though to provide a neurotrophic function 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), 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; Maina et al., 1998).
HGF and Met are expressed in the cerebellum, where development is primarily postnatal and requires extensive cell proliferation and migration. Met is localized in granule cell precursors and cultures of these cells proliferate in response to HGF (Ieraci et al., 2002). HGF also promotes oligodendrocyte progenitor cell proliferation and delays their differentiation into myelinating oligodendrocytes during early postnatal development; 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).
The mammary gland undergoes cyclic morphogenic differentiation 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; Yant et al., 1998; Niemann et al., 1998).
HGF production in the adult vascular system is positively regulated by prostaglandins and HGF itself, and negatively regulated by angiotensin II, TGF-beta, 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, consistent with homeostatic and repair functions (reviewed in Morishita et al., 2002).
Wound repair and tissue regeneration. 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).
HGF signaling supports 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; Shimamura et al., 2006). Intrastriatal administration of HGF protein also potently protected hippocampal neurons against postischemic delayed neuronal death (Miyazawa et al., 1996).
Tissue fibrosis is a common pathological consequence of chronic injury to kidneys and lungs. With chronic injury to these organs, the normal production and secretion of growth factors, including HGF, inflammatory cell recruitment, cell proliferation and differentiation, and matrix production and remodeling become increasingly aberrant, leading to matrix overproduction, abnormal organization, fibrotic lesions and scarring. Mice with conditional knockout of Met in the collecting duct of the kidney are more susceptible to interstitial fibrosis and tubular necrosis after unilateral ureteral obstruction, and show a diminished capacity for tubular cell regeneration after release of the obstruction (Ma et al., 2009). Conditional Met knockout targeted to renal podocytes was associated with more severe podocyte apoptosis and albuminurea than in control littermates subjected to nephrotoxic renal damage (Dai et al., 2010). HGF produced in response to injury antagonizes the actions of transforming growth factor-beta (TGF-beta), 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, 2011). The reciprocal effects of the HGF and TGF-beta signaling pathways occur via direct modulation of intracellular effectors downstream of TGF-beta 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., 2005). TGF-beta induced apoptosis of podocyte, endothelial and tubular epithelial cells, epithelial-to-mesenchymal transition by tubular epithelial cells, and myofibroblastic activation, are critical pathogenic events that are opposed by HGF signaling (reviewed by Böttinger 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 variety of chronic fibrotic disorders in kidney (Mizuno et al.,1998; Mizuno et al., 2001; 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 (Yanagita et al., 1993; Dohi et al., 2000; Mizuno et al., 2005).
HGF signaling is required for 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., 1990). Studies of tissue selective HGF overexpression or Met suppression in genetically engineered animal models confirm and extend earlier studies (Shiota and Kawasaki, 1998; Borowiak et al., 2004; Huh et al., 2004; Paranjpe et al., 2007; Factor et al., 2010). In addition to stimulating the proliferation of mature hepatocytes, 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).
HGF/Met signaling is required for full-thickness skin wound 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-beta, locally secreted HGF promotes 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).

Homology

Human HGF is highly conserved among mammals but (99.9% amino acid identity between human and chimp, to 91% between human and rat), however, homologs rapidly diverge in birds (75% between human and chicken) and bony fish (50% between human and zebra fish). Structural homology beyond teleosts is partial. More generally, HGF resembles members of the plasminogen family (~38% amino acid identity), in that the mature 2-chain protein contains multiple kringle domains in the amino terminal alpha (or heavy) chain and a serine protease like domain in the carboxyl terminal beta (or light) chain. Unlike the canonical plasminogen family members, HGF is devoid of proteolytic activity (reviewed in Matsumoto and Nakamura, 1996). Of plasminogen family members, HGF is most closely related to macrophage stimulating protein (MSP; 44% amino acid identity; also known as MST1 or HGF-like protein).

Mutations

Note
Polymorphisms in the HGF promoter region affect HGF transcription levels and have been linked to breast cancer (Ma et al., 2009). Noncoding mutations of HGF are associated with nonsyndromic hearing loss, DFNB39 (Schultz et al., 2009).

Implicated in

Hepatocellular carcinoma (HCC)

Note
HGF signaling has been implicated in a broad spectrum of human cancers. Gains in human chromosome 7q, where both HGF and MET genes are located, occur in approximately 16% of hepatocellular carcinoma (HCC) cases (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; Guirouilh et al., 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).

Head and neck squamous cell carcinoma (HNSCC)

Note
Analysis of head and neck squamous cell carcinoma samples revealed 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). The role of HGF in HNSCC was recently reviewed by De Herdt and Baatenburg de Jong, 2008).

Papillary thyroid carcinomas (PTC)

Note

Overexpression of both human HGF and MET is found in most papillary thyroid carcinomas, but not other thyroid tumor types. At least one study reported that the majority of these cases appear to possess autocrine HGF/Met signaling (Trovato et al., 1998) although this 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 respond to HGF with increased motility and invasiveness, increased chemokine and VEGF production, and the recruitment of dendritic cells and new blood vessels (de Luca et al., 1999; Scarpino et al., 1999; Scarpino et al., 2000; Scarpino et al., 2003).

Lung cancers

Note

HGF has been found in pleural effusion fluid obtained from patients with metastatic lung cancer (Kenworthy et al., 1992); serum HGF levels and tissue levels are also frequently elevated in lung cancer patients (Takigawa et al., 1997; Yamashita et al., 1998). HGF stimulates normal bronchial epithelial cells as well as lung carcinoma cells (Tsao et al., 1993; Olivero et al., 1996; Eagles et al., 1996). 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 sustain 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).

Breast cancer

Note

Analysis of breast tumor HGF levels in a large cohort revealed that 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). 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).

Renal cell carcinoma

Note

Inherited missense mutations in the human HGF receptor gene were first found in individuals with hereditary papillary renal carcinoma (HPRC) type 1; similar somatic mutations were also found in a small subset of {CC:XT: sporadic papillary renal carcinoma ID: 5003} (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 nearly all HPRC cases, where there is always non-random duplication of the mutant allele. Although the role of HGF in the oncogenicity of HPRC and PRC-associated Met mutations is not yet defined, ligand binding clearly promotes cell transformation (Michieli et al., 1999).

Prostate cancer

Note

HGF signaling is implicated in prostate cancer (reviewed in 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). 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).

Brain tumors

Note

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 of AMG 102 (rilotumumab), a fully human monoclonal antibody against HGF, in patients with recurrent glioblastoma showed that treatment was not associated with significant antitumor activity (Wen et al., 2011).

Digestive tract tumors

Note

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). Studies of human cultured colorectal tumor cells and tumor tissue samples indicated increased activation of pro-HGF, coincident with increased HGF activator abundance and decreased levels of HGF activator inhibitor-1 (Kataoka et al., 2000a). Several Met kinase inhibitors show potent anti-tumor activity in gastric tumor-derived xenografts (Christensen et al., 2003; Smolen et al., 2006; Zou 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).

Melanoma

Note

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; Saitoh et al., 1994). HGF transgenic mice display a high frequency of metastatic melanoma in increased sensitivity to UV radiation induced carcinogenesis; indeed, several mouse models of melanoma indicate the prevalence of HGF pathway involvement (reviewed in Walker and Hayward, 2002).

Sarcomas

Note

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, including rhabdomyosarcoma (Chen et al., 2007; Rees et al., 2006; Taulli et al., 2006; Jankowski et al., 2003), leiomyosarcoma (Gao et al., 2009), clear cell sarcoma (Davis et al., 2010) and osteosarcoma (MacEwen et al., 2003; Coltella et al., 2003).

Other diseases

Note

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 for 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). Both HGF and its receptor are required for malarial infection (Carrolo et al., 2003).

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