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Invited Review

Hepatocyte growth factor/scatter factor, a cytokine playing multiple and converse roles

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Summary. Hepatocyte growth factor (HGF), otherwise known as scatter factor (SF), is a recently identified cytokine which exerts a wide spectrum of biological functions on a variety of cell types. Its receptor is encoded by the *c-met* proto-oncogene. HGF/SF has been implicated in the regulation of mitogenesis, motogenesis, and morphogenesis. Over the past few years, the structure, function and signal transduction pathways of HGF/SF and its receptor have become clearer. The cytokine is now know to play important roles in the regulation of both normal physiological processes as well as pathological ones. This review summarises recent progress involving HGF/SF and its receptor and discusses their role in cell biology, organ regeneration, cancer and other processes.

Hepatocyte growth factor (HGF) is a pleiotropic growth factor originally identified as a potent mitogen agent for rat hepatocytes. Subsequent studies have shown that it is mitogenic for a wide range of epithelial cells and not limited to hepatocytes. Its behaviour as a motogenic stimulator promoted its independent discovery and naming of scatter factor (SF). Analysis of cDNA and amino acid sequences have revealed that the two molecules are the same. A number of cytokine agents are known to stimulate cellular motility, however, it is the function of HGF/SF as a potent motogenic, mitogenic and morpho-regulatory agent on the diverse variety of cell types that makes the discovery of HGF/SF factor one of the most interesting stories in terms of identification of novel cytokines.

Key words: Hepatocyte growth factor, Scatter factor, C-*met* proto-oncogene, Cancer metastasis, Organ regeneration, Development

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HGF/SF

Discovery of HGF/SF

Hepatocyte growth factor (HGF) was first described as a powerful stimulatory agent for hepatocyte growth following liver resection or damage (Michalopoulos et al., 1984; Nakamura et al., 1984; Russell et al., 1984; Higashio et al., 1990). Subsequent cloning and sequencing of HGF showed it to be homologous to hepatopoietin A and tumour toxic factor (Miyazawa et al.,1989; Zarnegar et al., 1989, 1990; Higashio et al., 1990). In 1985, a fibroblast-derived protein was described by Stoker and Perryman that had the ability to scatter tightly-packed colonies of epithelial cells and was subsequently termed scatter factor (SF). Partial amino acid sequencing of SF revealed over 90% homology to both rat and human HGF (Gherardi and Stoker, 1990, 1991; Weidner et al., 1990; Furlong et al., 1991) and it has thus been generally accepted that the term HGF/SF should be used to describe that factor.

HGF/SF structure and synthesis

HGF/SF is synthesised as a single chain peptide of 728 amino acid residues containing a 29 amino acid signal sequence and a 25 amino acid pro sequence. Mature HGF/SF is formed by the extracellular hydrolysis of a pro-sequence Arg-Val bond by a unique serine protease resulting in the production of the active heterodimer (Nakamura et al., 1989, 1991; Zarnegar et al., 1989; Miyazawa et al., 1994; Naldini et al., 1995). This proteolytic conversion is required for HGF to function as a mitogenic stimulus. HGF remains as an inactive single chain form in the liver, kidney, lung and spleen (Miyazawa et al., 1994, Arakacki et al., 1995).

Activation of the pro-HGF/SF converting serine protease is itself activated by other proteases in response to tissue damage. Several enzymes possessing this ability have been described including hepatocyte growth-factor-converting enzyme (Mizuno et al., 1994),

thrombin (Shimomura et al., 1993), urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) (Mars et al., 1993; Naldini et al., 1995), blood coagulation factor XIIa (Shimomura et al., 1995) and a number of others (Arakaki et al., 1995).

The mature HGF/SF molecule consists of two peptide chains (α and ß) with apparent weights of 69kDa and 34kDa respectively. Studies of HGF/SF cDNA clones isolated from a liver cDNA library show the α-subunit to be 440 amino acids in length with a predicted molecular weight of 50,800 daltons whilst the ß-unit is comprised of 234 amino acids and has a predicted molecular weight of 26,000 daltons. Glycosylation of both subunits of HGF/SF account for the differences in observed and predicted molecular weights (Nakamura et al., 1989). The α-chain possesses four kringle domains and its N-terminal domain is homologous to plasminogen preactivation peptide (PAP) and is responsible for heparin and receptor binding (Lokker and Godowski, 1993; Lyon et al., 1994, Mizuno et al., 1994). The ß-unit has a domain similar to that of a serine protease, although no protease activity occurs due to amino acid substitution within the catalytic site (Strain, 1993). HGF/SF is a single copy gene located on chromosome 5 (mouse) and 7 at q21.1 (human) (Fukuyama et al., 1991; Weidner et al., 1991) and consists of 18 exons and 17 introns.

HGF/SF forms part of a family of plasminogen-related growth factors, along with hepatocyte growth factor-like/macrophage stimulating protein (HGFl/MSP), an effector of macrophage chemotaxis and phagocytosis (Shimamoto et al., 1993; Wang et al., 1993; Yoshimura et al., 1993; Li et al., 1995). Both proteins, along with plasminogen and apolipoprotein are thought to have evolved from the same ancestral gene (Donate et al., 1994).

Several variants of the HGF/SF protein have been observed, thought to arise via alternative splicing events. A fibroblast cell line, SK-LMS-1 secretes a truncated form of HGF/SF comprising only the N-terminal amino acid sequence and the first two kringle domains. This peptide has no biological activity and may therefore act as an inhibitor of HGF/SF-induced mitosis via competition with the wild type (Chan et al., 1991). A second form of the variant, designated as HGF/NK1 has been recently described (Cioce et al., 1996). This isoform consists of the HGF/SF amino-terminal sequence and first kringle domain only and possesses an angonist-antagonist property, which exerts weak mitogenic and motogenic effects at low concentrations but becomes inhibitory for DNA synthesis at excess. A naturally occurring splicing variant of hepatocyte growth factor (varHGF) described by Jeon et al., (1994) can induce gene expression and synthesis of osteonectin in aortic endothelial cells. HGF/SF binds to sulfoglycolipids including galactosylceramide sulfate (SM4), lactosylceramide sulfate (SM3), and gangliotriaosylceramide bis-sulfate, but not to gangliosides or neutral glycolipids (Kobayashi et al., 1994a,b), suggesting that the binding of HGF/SF to endogenous sulfaglycolipids may serve as a reservoir for HGF/SF.

HGF/SF metabolism

The liver plays a major role in the rapid clearance and subsequent deactivation of pro-recombinant human (rhu)HGF *in vivo* (Zioncheck et al., 1994). Studies have shown that following intravenous infusion, rhuHGF is rapidly distributed to the liver, kidney, adrenal gland and spleen.

The HGF/SF receptor

HGF/SF receptor structure and function

The various cellular responses that occur following stimulation by hepatocyte growth factor are mediated by the *c-met* protooncogene product (Bottaro et al., 1991; Naldini et al., 1991) first isolated as a transforming gene from chemically mutagenized human osteosarcoma cells (Cooper et al., 1984, 1992). The *met* gene has been mapped to chromosome 7 at q21-31 and encodes a 1408 amino acid glycoprotein lacking significant homology to any other growth factor receptor (Park et al., 1987). The mature *c-met* receptor is a 190kDa transmembrane tyrosine kinase, derived from a single chain precursor that undergoes extensive post-translational modification and is expressed predominantly on the surface of epithelial cells including those in the lung, pancreas and kidney (Gonzatti-Haces et al., 1988; Ishibashi et al., 1992; Igawa et al., 1993, Sonnenberg et al., 1993). It is comprised of a 50kDa α-chain and a 145kDa membrane-spanning ß-chain which possesses an intracellular tyrosine kinase domain (Park et al., 1987; Naldini et al.,1991; Bottaro et al., 1991). Two binding affinities for HGF/SF are known to exist on the surface of epithelial cells: high-affinity, low capacity sites and low-affinity, high capacity sites (Zarnegar et al., 1990; Tajima et al., 1992). Recent investigations imply that the former is likely to be the *c-met* receptor and the latter either heparin or heparin sulphate proteoglycans (Giordano et al., 1993; Weidner et al., 1993).

Two receptor tyrosine kinases related to *c-met* (*Ron* and *c-sea*) have been recently identified (Bardelli et al., 1994; Gaudino et al., 1994; Huff et al., 1994; Ponzetto et al., 1994). *Ron* is a heterodimeric tyrosine kinase receptor activated upon binding of the HGF/SF homologue, HGF1/MSP (Ronsin et al., 1993; Gaudino et al., 1994; Wang et al., 1994; Li et al., 1995). All three receptors share the novel heterodimeric structural motif of an extracellular α-unit and a transmembrane ß-unit possessing intrinsic tyrosine kinase activity.

Signal transduction in c-met mediated cellular response

The independent discoveries of HGF/SF as both a mitogenic agent (HGF) and a motogenic stimuli (SF) demonstrate that it is a factor which can elicit different

responses in target cells, although these activities are not mutually exclusive. The activation of different cellular response pathways may be regulated at the receptor itself, or at points downstream of it (Weidner et al., 1995).

HGF/SF binds to and induces tyrosine phosphorylation of the mature *c-met* receptor resulting in ligand-dependant receptor homodimerisation which allows cross-phosphorylation of tyrosine residues located on the intracellular portion of the *c-met* ß-chain (Faletto et al., 1993). Such events are thought to promote binding of intracellular signalling proteins containing *src* homology (SH) region 2 (phospholipase C (PLC) γ, Ras, GTPase-activating protein (GAP), phosphatidylinositol 3-kinase (PI-3 kinase), $pp^{60c\text{-}src}$ and the GRB-2-Sos complex) to the activated HGF/SF receptor (Koch et al., 1991; Pawson and Gish, 1992; Ponzetto et al., 1993, 1994). Work by Songyang et al. (1995) had indicated that the amino acid sequence that flanks the phosphorylated tyrosine in the HGF/SF receptor is the principal determinant of which SH2-containing protein will bind to that phosphotyrosine. Each SH2-containing protein may activate a different subset of signalling phosphopeptides thus eliciting different responses within the cell. Two tyrosine residues (Tyr 1349 and 1356) located towards the COOH-terminus and outside of the kinase domain in *c-met* have been reported to be critical in mediating the interaction of SH2-proteins with the receptor (Songyang et al., 1993; Ponzetto et al., 1994).

Following HGF/SF stimulation of *c-met*, phosphorylation of PLC-γ, both *in vitro* and *in vivo* has been detected (Bardelli et al., 1993; Okano et al., 1993). Experimentally introduced mutations in the tyrosine residues at positions 1349 and 1456 eliminates co-immuno-precipitation of PLC-γ and *c-met* whereas alteration of other tyrosine residues had no effect. Uptake of GTP by *ras* has also been shown to increase as a result of HGF/SF stimulation indicating activation of the Ras protein (Graziani et al., 1993). Stimulation of the MAP kinase pathway, a series of serine/threonine kinases, has been shown to occur as a consequence of $pp^{60c\text{-}src}$ activation by HGF/SF-*c-met* interaction (Ponzetto et al., 1994). The most well characterised example of intracellular signal activation by *c-met* stimulation is that of phosphatidylinositol 3 kinase (PI-3 kinase). PI-3 kinase is a cytosolic enzyme which catalyses the phosphorylation of phosphatidylinositol (PI) (Whitman and Cantley 1988). Cellular activation of PI-3 kinase results in the generation of a family of 3'-phosphorylated inositol phospholipids which may function as second messengers (Cantley et al., 1991; Royal and Park, 1995). The binding of PI-3 kinase to *c-met* is negatively regulated by the juxtamembrane domain of the receptor (Lee and Yamada, 1995) and by the phosphorylation of Ser985 (Gandino et al., 1994).

Rho, ras and rac are involved in c-met cell signalling

The three members of the *rho* p21 family, a sub-group of the *ras* p21-related small GTP-binding protein superfamily, are known to regulate numerous cellular functions, including motility and morphology by their interaction with the actomyosin system within the cell (Miura et al., 1993; Takaishi et al., 1993). Recent work by Takaishi and collegues (1994) has demonstrated that following HGF stimulation of cultured mouse keratinocytes, the inactive GDP-bound *rho* p21 is converted to the GTP-bound active form by GDP/GTP exchange proteins (GEP's). These regulatory proteins involved in *rho* p21 GDP-GTP interconversion are likely to be substrates for PKC, itself activated following stimulation of the PLC- pathway by *c-met*.

HGF/SF has been shown to stimulate the *ras*-guanine nucleotide exchanger thus promoting the GTP-bound active state of the Ras protein (Graziani et al., 1993). The Ras pathway has been implicated in mediation of HGF/SF-induced cell motility via its interaction with cell cytoskeleton components (Hartmann et al., 1994).

Isoforms of c-met

From the many responses elicited by HGF/SF in cells, it is tempting to speculate that there exist a number of different forms of HGF/SF receptor protein, each mediating a different cellular response by activating separate intracellular signalling pathways. Several protein isoforms have been described for many receptor tyrosine kinases, generated by a number of potential mechanisms including differential post-translational processing, alternative pre-mRNA splicing and the use of unique translational initiation sites. The major *c-met* protein product expressed in human cells is 190kDa in size. Truncated forms of this receptor have been described in several cell lines (Prat et al., 1991; Rodrigues et al., 1991). These truncated forms, one of which is a membrane-bound protein of 140kDa, the other of which is released into the culture supernatant and is 130kDa, are generated from the same 170kDa *c-met* precursory protein by post-translational proteolytic events. Recent work on these isoforms of *c-met* have shown them to lack the cytoplasmic kinase domain characteristic of the mature, full-length protein (Crepaldi et al., 1994). Gandino and coworkers (1994) have reported an isoform of the HGF/SF receptor present in a variety of mouse tissues. This receptor differs from normal *c-met* in that it has a deletion of 47 amino acids in its juxtamembrane domain, an alternatively-spliced cytoplasmic region adjacent to the transmembrane domain of the receptor (Lee and Yamada, 1995). The juxtamembrane domain has been implicated in the negative regulation of kinase activity and mitogenesis (Gandino et al., 1994; Zhen et al., 1994). The observation that loss of the juxtamembrane domain from the *c-met* receptor greatly enhances binding of the p85 subunit of IP3 kinase, whilst not affecting the binding of other intracellular signalling proteins, suggests that this form of the HGF/SF receptor expressed in mouse tissue

has biological significance by its ability to preferentially stimulate IP3-mediated signal transduction pathways.

Expression of HGF/SF and its receptor in cells and tissues

HGF/SF production has been shown in numerous tissues including fibroblasts, epithelial and endothelial cells, Kupffer's cells and fat-storing cells in the liver. Tumour cells, themselves, may also produce HGF, HGF transcripts and/or the ligand itself have been detected in fibrosarcoma cells (Stoker et al., 1987), lung cancer cells (Yoshinaga et al., 1992; Rygaard et al., 1993; Tsao et al., 1993), hepatoma cells (Miyazaki et al., 1991) and pancreatic cancer cells (Hirota et al., 1993). HGF/SF production by adipocytes plays a key role in the regulation of mammary tumour growth (Rahimi et al., 1994). Serum HGF/SF concentrations are reported to be elevated in patients with liver disease (Tsubouchi et al., 1991; Kaneko et al. 1992; Tomiya et al., 1992) and also some cancer patients (Yamashita et al., 1994; Taniguchi et al., 1995). The exact source of blood-borne HGF/SF is not clear; however, since HGF/SF is widely present in many tissues, these could contribute to blood-HGF/SF in an endocrine manner. In a study by Taniguchi et al. (1994), removal of malignant breast tumours resulted in a decrease in serum HGF/SF levels implying that the primary source of HGF/SF in these patients was the tumour cells themselves.

The HGF/SF receptor, *c-met*, is expressed in the normal epithelium of the majority of tissues where it is primarily located at intercellular junctions together with cell adhesion molecules such as E-cadherin (Crepaldi et al., 1994). *c-met* has also been reported to be produced by other cell types including melanocytes, endothelial cells, microglial cells, neurons and hematopoietic cells. The receptor status in a number of tumour tissues of various origins has been evaluated and expression has been reported in hepatomas and melanomas and malignant tumours of the thyroid, lung, pancreas, prostate and gastrointestinal tract (Di Renzo et al., 1991, 1992, 1995a,b; Jiang et al., 1993b).

Regulation of HGF/SF cellular production

Several factors are known to regulate the production of HGF/SF. HGF/SF gene expression is stimulated by the action of interleukin (IL)-1α, IL1ß, TNFα, a range of growth factors, and prostaglandins (Matsumoto et al., 1992a, 1995; Tamura et al., 1993; Gohda et al., 1994) and down regulation of HGF/SF occurs following TGF treatment (Gohda et al., 1992; Matsumoto et al., 1992b). Injurin, a humoral factor that is produced in non-injured distant organs following hepatic or renal injury, induces expression of HGF/SF mRNA in rat lungs (Matsumoto et al., 1992c, 1993). Activation of cAMP-mediated pathways by membrane-permeable cAMP analogues and agents that augment cAMP levels has been shown to result in regulation of HGF/SF expression (Matsunaga et al., 1994). Non HGF/SF-producing mammary carcinoma cells have been shown to produce soluble factors that promote HGF/SF gene and protein expression in fibroblasts. Rosen and co-workers (1994) have recently characterised one such HGF/SF-inducing protein of approximately 12 kD. Injurin like factor, a non-protein factor with an apparent MW of 8-15 kDa found in a number of tissue extracts including liver, kidney, brain and lung, has been shown to translationally enhance HGF production (Okazaki et al., 1994). Non contact co-culture of both carcinoma cells and fibroblasts results in HGF/SF down-regulation suggesting that a soluble inhibitor or inhibitors of HGF/SF production is/are released (Seslar et al., 1993).

Autocrine and paracrine action of HGF/SF

Paracrine regulation

Induction of hepatitis-like injuries in rat livers by administration of CCl_4 or D-galactosamine results in a marked increase of HGF/SF activity (up to 20 times higher than normal after 30 hours) (Lindroos et al., 1991; Ishiki et al., 1992). In addition to hepatotoxin-induced liver damage, hepatic levels of HGF/SF mRNA are also observed after other insults including ischemia and liver crush (Hamanoue et al., 1992). The mammalian liver is comprised of a number of different cell types: hepatocytes or parenchymal liver cells form approximately 70% of the total liver mass and are responsible for liver-specific functions. The rest of the cells are made up of non-parenchymal liver cells including sinusoidal endothelial cells, Kupffer cells, and fibroblasts. When both parenchymal and non-parenchymal liver cells are isolated from both normal and CCl_4-damaged rat livers, HGF/SF message expression was observed in the non-parenchymal cells only (Noji et al., 1990), suggesting that HGF/SF acts in a paracrine fashion to promote liver regeneration following liver damage.

HGF/SF appears to be produced in a paracrine fashion since studies have shown it to be produced by mesenchymal rather than epithelial cells both *in vitro* and *in vivo*. A recent study by Plaschke-Schlutter (1995) has shown that the promotor region for HGF/SF is active only in mesenchymal cells and not epithelial ones, further enforcing this observation. In a number of tumour tissues that over-express the HGF/SF receptor, message for HGF/SF itself is not detected (Sasaki et al., 1994; Di Renzo et al., 1995a,b; Hiscox et al., 1997). Localisation studies point to non-parenchymal cells as producers of this ligand providing further evidence for its role as a paracrine regulator.

Autocrine regulation

Although the evidence for the paracrine action of HGF/SF is convincing, autocrine circuits involving HGF/SF have been described in some cancer cell lines

(Di Renzo et al., 1991, 1992, 1995a,b). Fushida et al., (1993) showed that the gastric cancer cell line, MKN45, expresses both *c-met* and HGF/SF suggesting an autocrine regulatory pathway. There is simultaneous expression of a smaller HGF isoform and its receptor, *c-met*, in SBC-5 cells which induce autocrine stimulation of motility of this cell together with the development or progression of the lung carcinoma cells (Itakura et al., 1994). Ebert et al. (1994) show concomitant expression of both HGF/SF and its receptor in pancreatic cancer cells and excessive activation of the receptor in these patients, again suggesting autocrine regulation. It has been documented that transfection of the epithelial cell line, NBT-II, with HGF/SF DNA produces cells which express large quantities of bioactive HGF/SF and exert an autocrine regulation of cell invasion and tumorigenicity both in vitro and in vivo (Bellusci et al., 1994).

Paracrine and autocrine

In bone tumours, both autocrine and paracrine pathways have been proposed due to the variable expression of *c-met* and its ligand in these cells (Ferracini et al., 1995). In the vascular endothelium, HGF/SF is produced by both endothelial cells and vascular smooth muscle cells suggesting both paracrine and autocrine action (Hayashi et al., 1996).

Molecular and cellular functions of HGF/SF

Cell motility

Cell motility is an important component of many processes including embryogenesis, tissue repair, tumour invasion and angiogenesis. HGF/SF was originally identified by virtue of its ability to promote the scattering of epithelial cell colonies in culture (Gherardi et al., 1989). HGF/SF augments the motile nature of MDCK canine kidney epithelial cells (Pepper et al., 1992). Many other cell types including various tumour-derived cells respond to HGF/SF and demonstrate increased motility and scattering (Jiang et al., 1993a-c, 1994) (Fig. 1). On a tracking system (computer assisted or special coated matrix), cells stimulated with HGF/SF showed increased migration (Fig. 2).

Morphogenesis

The ruffling of free edges and the apical surface of cells is one of the earliest morphological events to occur

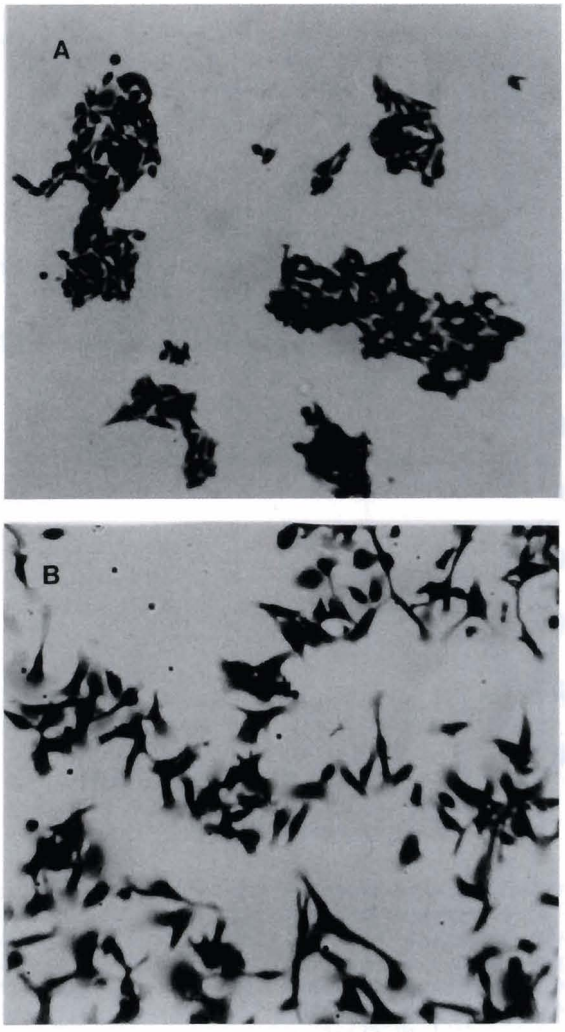


Fig. 1. Colony scattering induced by HGF/SF in a human colon epithelial cell line, HT115. **A.** Control cells. **B.** Cells stimulated with HGF/SF. HGF/SF induced a marked dissociation of cells and thus 'scattered' the colony. x 10. (Jiang et al., 1993a)

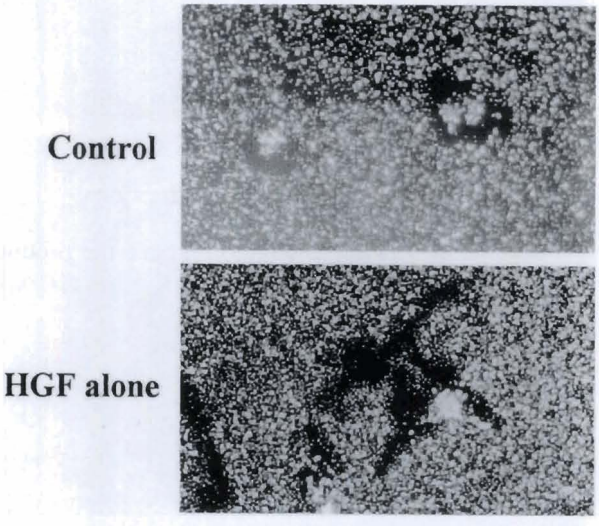
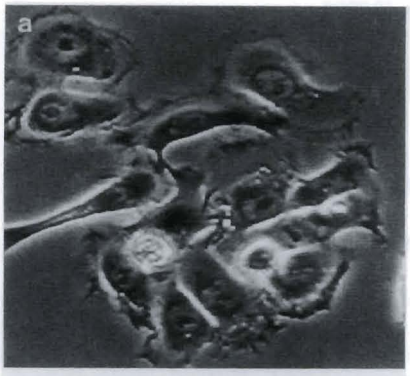
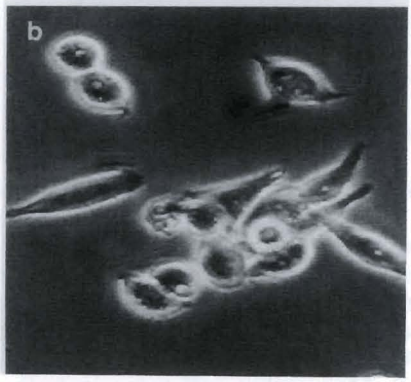
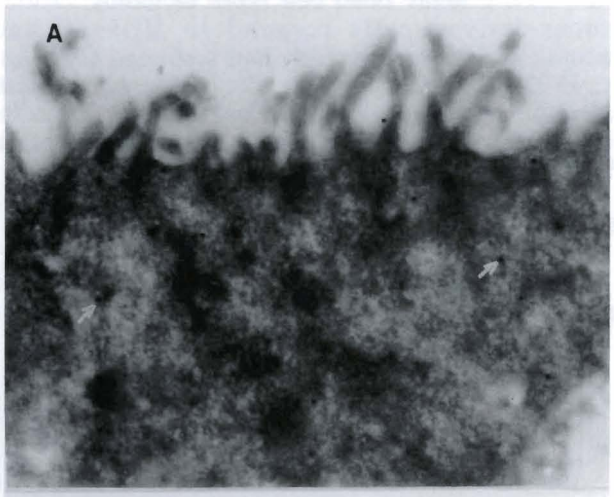
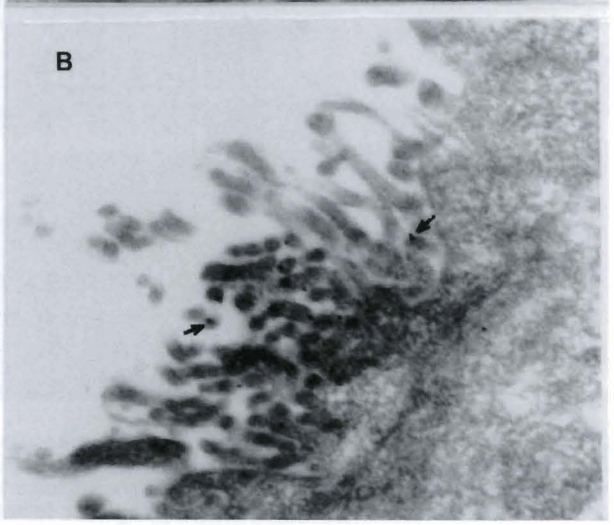


Fig. 2. HGF/SF stimulated phagokinetics of HT115. Slides were coated with colloidal gold (bright dots) before cells were added in medium **(A)** or with HGF/SF **(B)**. HGF/SF increased migration and phagokinetics of the cell, left a dark track after their movement. x 20. (Jiang et al., 1995a)









following HGF/SF stimulation (Dowrick et al., 1993; Jiang et al., 1995a) (Fig. 3), and involves activation of rho p21 (Nishiyama et al., 1994). Candidate molecule for HGF/SF induced ruffling has been recently reported as ezrin (Jiang et al., 1995b), whose translocation and tyrosine phosphorylation are responsible for the membrane changes (Fig. 3). HGF/SF acts via F-actin filaments, microtubules, intermediate filaments, focal contacts and cellular junctions resulting in a number of tissue specific, inductive programs in epithelial morphogenesis (Brinkmann et al., 1995). HGF/SF induces kidney epithelial cells to form branching ducts in collagen gels (Montesano et al., 1991; Clark 1994), SW1222 colon carcinoma cells to form crypt-like structures and Capan 2 pancreatic carcinoma cells to develop large hollow spheroids lined with a tight layer of polarized cells. Cultured prostate epithelial cells, when stimulated with HGF/SF, develop long ducts with

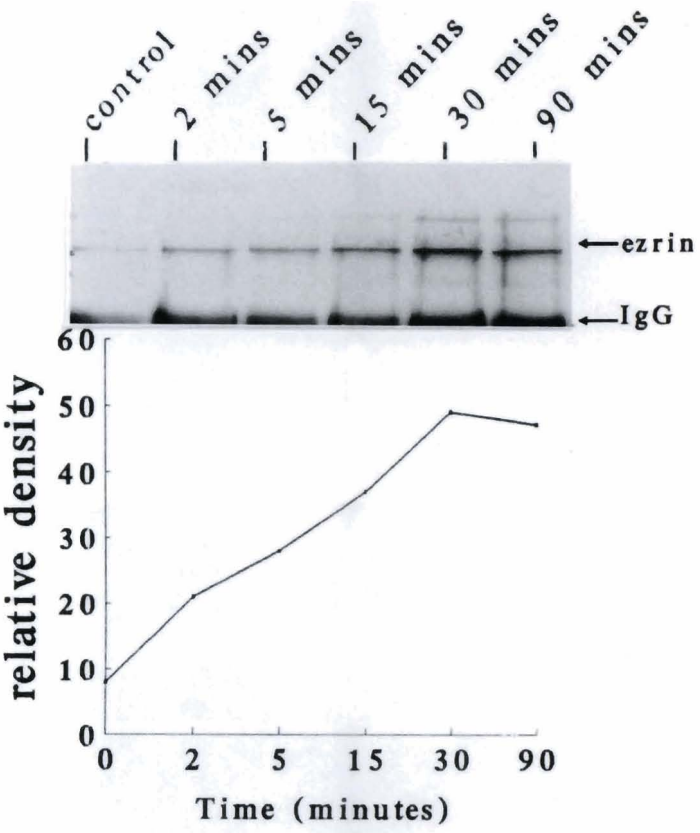


Fig. 3. HGF/SF induced membrane ruffling (a and b, taken at magnification x20 and printed with a video printer), ezrin translocation (A and B, magnification 13,000 on a transmission electron microscope) and tyrosine phosphorylation of ezrin (right) of HT115 cells. HGF/SF induced vigorous membrane ruffling (a) compared with control (b) (Jiang et al., 1995a-e). This is seen together with the translocation of ezrin, which is distributed generally in the cytoplasm in control cell (A) and moved toward the ruffled area and cell periphery in immunogold electron microscopy study (B, arrow indicated) (Jiang et al., 1995a). Ezrin at this stage becomes phosphorylated on tyrosine residue as shown in the right from a immunoprecipitation and Western blotting (Jiang et al., 1995b)

distal branching common to that found in prostate tissue whilst inducing alveolar differentiation in the lung carcinoma cell line, LX-1. This morphoregulatory action of HGF/SF is not produced by other growth factors such as EGF, bFGF, TGFß, IGF or PDGF so is a unique feature of this ligand.

Cell growth

HGF/SF is a growth factor for various types of cells originating from various tissues. It acts as a mitogen for renal epithelial cells, epidermal keratinocytes and melanocytes and numerous other epithelial cell lines. HGF/SF has been shown to promote the growth of both hepatopoietic and hematopietic cells in culture (Nishino et al., 1995; Zarnegar and Michalopoulos, 1995) depriving cultured hepatocytes of HGF/SF induces apoptosis (Revoltella et al., 1993, 1994). The receptor for HGF/SF is present in hematopoietic progenitor cells from human bone marrow and peripheral blood and, in the presence of erythropoietin, HGF/SF induces proliferation and differentiation of erythroid progenitors (Galimi et al., 1994). Whether HGF/SF-induced proliferation occurs via its cellular receptor or by the promotion of the release of other mitotic factors is not know. HGF/SF also stimulates DNA synthesis in alveolar epithelial type-II cell cultures (Mason et al., 1994; Shiratori et al.,1995). The regulation of cell growth by HGF/SF may represent part of a co-ordinated cell growth control state. Taipale and Keski-Oja (1996) have shown that TGF 1-induced growth arrest of epithelial and endothelial cells can be reversed by treatment with HGF/SF.

Contrary to it stimulatory effects on the proliferation of normal hepatocytes, it reduces growth of hepatoma cells such as HepG2 (Tajima et al., 1991, 1992; Shiota et al., 1992). Although the mechanism for this is unclear, a possible explanation is that the intracellular signalling pathways differ in the two cell types. HGF/SF activates PLCγ in normal hepatocytes but not in hepatoma cells (Okano et al., 1993; Shiota et al., 1994).

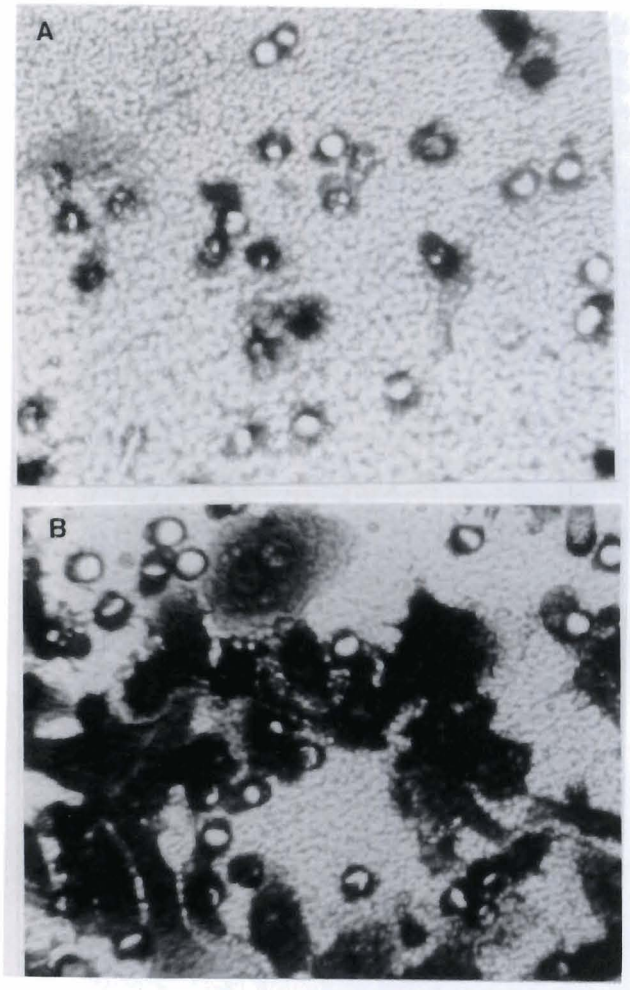


Fig. 4. Induction of in vitro invasion by HGF/SF. Transwell plate (with pore size 8.0 μm) was coated with Matrigel (a reconstituted basement membrane). Cell (HT115) was allowed for 72hours with either medium as control (A) or with HGF/SF (B). There was a markedly increased cells which invaded the matrix when stimulated with HGF/SF. x 40

Cell invasion

HGF/SF promotes the invasion of a number of cell types into collagen gels and artificial basement membranes (Jiang et al., 1993b, 1995c,d) (Fig. 4). Stimulation of a human small intestinal cell line by HGF/SF promotes their invasion across reconstituted matrices (Sunitha et al., 1994). Cellular release of basement membrane-degrading enzymes in response to HGF/SF stimulation may play a key role in the process of cellular invasion. HGF/SF specifically induces expression of gelatinase in KG-2 renal carcinoma cells with a resultant promotion of invasion in to the matrix (Gohji et al., 1994).

HGF/SF, cellular adhesion and communication

HGF/SF has the ability to dissociate epithelia and thus its effects on cellular adhesion molecules such as the cadherins has been studied. Cadherin function is modulated by intracellular proteins termed catenins that act as molecular linkers between the cytoplasmic domain of the cadherin protein and the cytoskeletal network within the cell (Jiang, 1996). It has been postulated that HGF/SF may inhibit cadherin function by altering the phosphorylation of these cadherin-associated proteins. HGF/SF induces tyrosine phosphorylation of ß-catenin, which may down-regulate cadherin-mediated cell-cell adhesion (Shibamoto et al., 1994; Tannapfel et al., 1994).

HGF reduces intercellular communication in hepatocytes and rat keratinocytes by down regulation of connexin 32 and 43 via a *c-met*-tyrosine-kinase-mediated pathway (Ikejima et al., 1995; Moorby et al., 1995; Jiang et al.,1996a). This may play a role in the

development of tumours by abolishing the regulation of cell growth by contact inhibition.

Motogenic effects of HGF/SF may be partially due to the initial recruiting of integrins, cytoskeletal proteins, pp125(FAK) and paxillin into focal adhesion complexes via the tyrosine kinase activity of *c-met* (Matsumoto et al., 1994, Jiang et al., 1996b) (Fig. 5). The results of these signalling events are increased cell matrix adhesions.

Angiogenesis

By stimulating endothelial cell proliferation and motility, it is plausible to implicate HGF/SF as a regulator of neovascularization *in vivo* (Bussolino et al., 1992; Comoglio et al., 1993; Grant et al., 1993). Recent studies have demonstrated HGF/SF as a powerful inducer of angiogenesis (Grant et al., 1993; Naidu et al., 1994). *In vivo* studies using HGF/SF implants have shown ingrowth of new blood vessels in mouse subcutaneous tissue and rat corneas (Bussolino et al., 1992; Rosen et al., 1993). Stimulation of HOME cells with HGF/SF in the presence of active tissue plasminogen activator (t-PA) results in the outgrowth of tubule-like structures suggesting a cooperative role of these factors in eliciting angiogenic responses (Morimoto et al., 1994). In vivo HGF/SF-induced angiogenesis has been shown to be amplified by a number of other factors including vascular endothelial growth factor (Silvagno et al., 1995). Regulation of neovasculature by HGF/SF may occur in both autocrine and paracrine mechanisms as both HGF/SF and its receptor are expressed in vascular tissue including vascular smooth muscle cells (VSMC), endothelial cells and neointimal VSMC cells and in intact aorta (Nakamura et al., 1995).

Embryogenesis

The majority of tissues express HGF/SF mRNA or at least contain the protein. These tissues include skin, spleen, placenta, liver, lung and various cells of the blood system including monocytes, leukocytes and platelets. In general, HGF/SF message is found in stromal cells rather than epithelial cells. HGF/SF receptor expression is, in contrast, found mainly in epithelial cells. This pattern of expression of receptor and ligand, along with the pleiotropic effects of HGF/SF suggest that HGF/SF is an important paracrine mediator

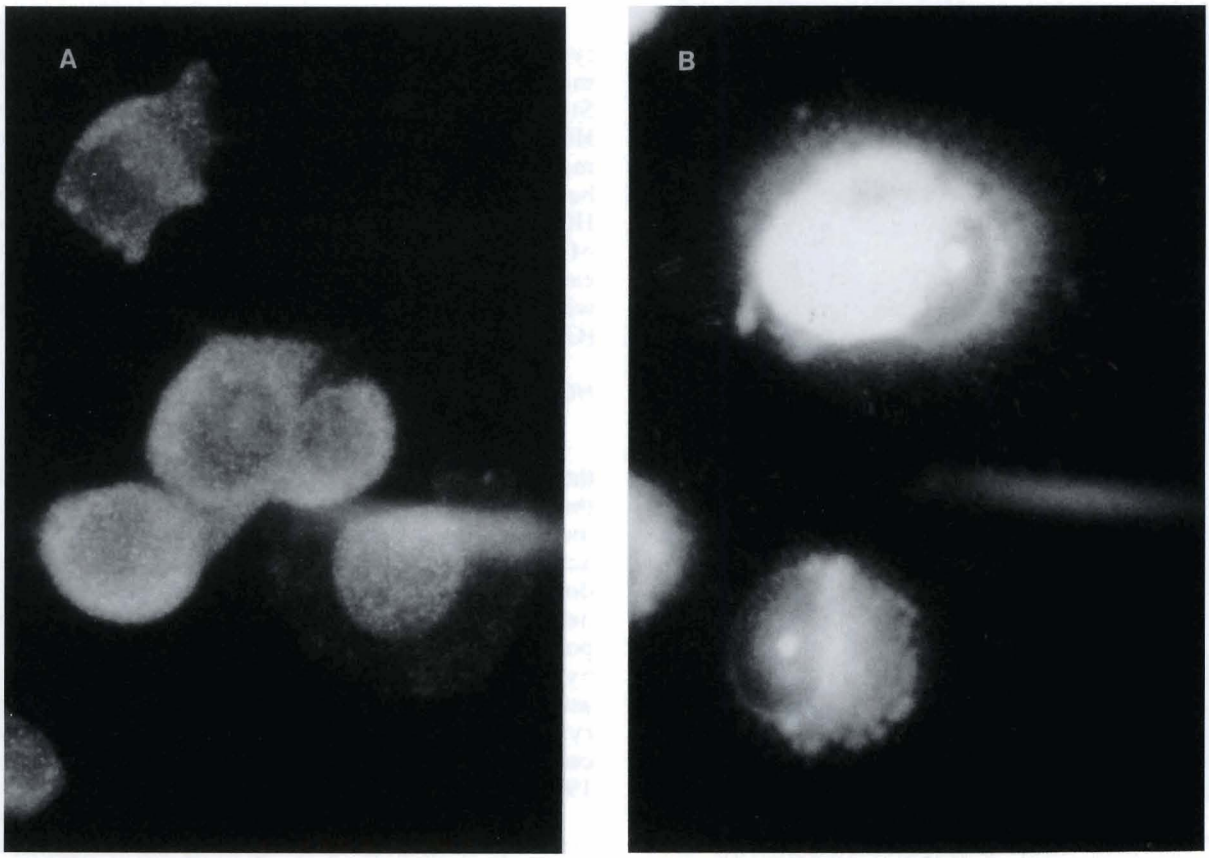


Fig. 5. Induction of focal adhesion complex (FAC) formation by HGF/SF. Cells were added to matrix either in medium (A) or with HGF/SF (B) for 60 minutes before they were stained with focal adhesion kinase (FAK) antibody. HGF/SF stimulated cells showed wider spreading as well as increased formation of FAC. x 10. (Jiang et al., 1996b).

of the interaction between epithelial and stromal cells during development (Sonnenberg et al., 1993; Rosen et al., 1994).

The interconversion of epithelia to mesenchyme and visa versa plays an important role in early development. HGF/SF mediates the transformation of epithelial sheets to cells displaying a fibroblastoid morphology and also their organisation into ordered tubular structures. Transfection of mouse fibroblasts with *c-met* and HGF/SF cDNA results in the formation of duct-like structures, expression of cytokeratins, HGF/SF and the formation of epithelial-like intercellular junctions (Tsarfaty et al., 1994). In the developing mouse kidney, HGF/SF and *c-met* are expressed maximally at day 11.5, which corresponds to the onset of tubulogenesis and branching morphogenesis (Santos et al., 1994). The role of HGF/SF in the early stages of development of the kidney has been further reported by Karp et al., (1994). Mutant mice with a targeted disruption of the HGF/SF gene shows severely impaired placentas with markedly reduced numbers of labyrinthine trophoblast cells, and die before birth, suggesting that HGF/SF is an essential mediator of allantoic mesenchyme-trophoblastic epithelia interaction required for placental organogenesis (Uehara et al., 1995). The mutation also affects the embryonic liver with reduced in size extensive loss of parenchymal cells (Schmidt et al., 1995). Co-expression of the HGF/SF and *met* genes in mesenchymal cells during embryonic development are essential in the survival of the renal mesenchyme and in the mesenchymal-epithelial transition that occurs during nephrogenesis (Woolf et al., 1995).

HGF/SF has been found to be markedly increased in maternal serum after 10 weeks of pregnancy and also exists in large quantity in amniotic fluid and placenta suggesting its role in fetal growth and the growth and differentiation of placenta (Horibe et al., 1995; Kurauchi et al., 1995). HGF/SF has also been postulated to play a role in the early steps of neural induction, probably by inducing or maintaining the competence of the epiblasts to respond to neural inducing signals (Bronnerfraser, 1995; Streit et al., 1995). The presence of HGF/SF and its receptor in specific regions of the developing and adult mammalian nervous system points to the fact that this ligand/receptor system may have a neurotrophic function (Jung et al., 1994).

Other cellular functions

Wound repair

Administration of HGF/SF to rabbits possessing artificially induced gastric wounds results in faster healing times (Watenabe et al., 1994). HGF/SF reduces transepithelial resistance to passive ion flow by specific regulation of paracellular tight junction resistance in intestinal epithelial cell monolayers (Nusrat et al., 1994). The closure of intestinal epithelial wounds is further enhanced by HGF/SF due to its stimulatory activity on cell motility and spreading.

Stimulation of protein synthesis

HGF/SF stimulates acute-phase protein gene expression in both rat hepatocytes and hepatoma cells (Pierzchalski et al., 1992; Baumann et al., 1993) together with the production of albumin and fibrinogen (Yamaoka et al., 1993). HGF/SF has also been shown to stimulate α-fetoprotein production in cultured human hepatocytes (Hatano et al., 1992). HGF/SF-induced increase of phospholipase A2 and cyclooxygenase activities in TMK-1 gastric cancer cells results in the increased production of prostaglandins (Hori et al., 1993). HGF/SF is also reported to prime human neutrophils (Jiang et al., 1992).

Inhibitory actions of HGF/SF

HGF/SF has been reported to exert growth inhibition of a number of cell types in contrast to its stimulatory activities. HGF/SF strongly inhibits the in vitro growth of the melanoma cell line, B6/F1, a squamous carcinoma cell line, KB and HepG2 hepatocellular carcinoma (HCC), and colon cancer cells (Tajima et al., 1991; Jiang et al., 1993a). Transfection of Fao HCC cells with HGF/SF cDNA results in a decreased growth rate both *in vitro* and *in vivo* suggesting that raised HGF/SF levels in the serum of HCC patients may be indicative of in vivo growth control of hepatic tumours (Shiota et al., 1992).

HGF/SF and cancer

HGF/SF has been implicated as a mediator of tumour metastatic progression because of its profound stimulatory effects on tumour cell functions that are central to the process of metastasis. Tumour cell motility and invasion are augmented by HGF/SF resulting in an enhanced metastatic phenotype (Rosen et al., 1990, 1994) transfection of cells that are *c-met* negative with *c-met* cDNA results in increased motility and tumorigenicity upon stimulation with HGF/SF (Rong et al., 1992). Release of matrix-degrading proteins by HGF/SF further promotes cellular invasion. HGF/SF is an inducer of angiogenesis (Grant et al., 1993), essential for tumour growth. Ingrowth of new blood vessels has been induced in mouse and rat *in vivo* models. HGF/SF is also detectable at sites of neovascularisation within human psoriatic plaques (Rosen et al., 1993).

HGF/SF may further play a role in tumour spread by enhancing tumour cell-matrix interactions. Binding to and degradation of the extracellular matrix is an essential stage in the metastatic spread of cancers and is regulated in part by a group of heterodimeric cell-surface proteins termed integrins. Integrin proteins bind to extracellular matrix components such as collagen and fibronectin, forming focal adhesion complexes (FAC's). It is now known that different integrins share a common

signal transduction pathway, regulated by focal adhesion kinase (FAK). Phosphorylation of FAK results in the activation of other downstream proteins such as paxillin and results in the assembly of actin stress fibres and FAC formation (Seufferlein et al., 1994). We have shown that HGF/SF phosphorylates both FAK and paxillin and enhances cell-matrix adhesion in tumour cells in vitro (Jiang et al., 1996b). Intercellular adhesion, responsible for the maintenance of tight cell-cell colonies, has also been implicated as a target for HGF/SF action. Dysfunction of cell surface cadherin molecules results in loss of cell-cell contact and a gain in invasiveness; such impairment of cellular adhesion may be facilitated by HGF/SF-induced phosphorylation of cadherin-associated proteins.

Both malignant and normal cells express the receptor for HGF/SF. In normal hepatocytes, levels of *c-met* are temporarily raised following liver damage suggesting that non-neoplastic cells are able to modulate their proliferative response to HGF/SF by receptor down-regulation. The *c-met* receptor is constantly over-expressed in most of tumour tissue types so far studied, including gastric, pancreatic, colorectal, prostatic and lung cancers (for review see Jiang et al., 1993b; Kuniyasu et al., 1993). Rusciano et al. (1995) has shown that in the metastatic melanoma cell line, B16, an increased level of *c-met* is observed which correlates with increased cell motilty and invasion. Thus inappropriate expression of the HGF/SF receptor protein may confer a selective advantage on neoplastic cells compared to the surrounding normal tissue cells. We have shown that the proto-oncogene, *c-met*, is over-expressed at both message and protein level in colorectal cancer (Hiscox et al., 1996) (Fig. 6) and it may be the case therefore that over-expression of the functional HGF/SF receptor in colon cancer tissue may play an important role in the initiation and/or promotion of tumour cell metastasis by enhancing these cells' response to the effects of HGF/SF.

Increased expression of HGF/SF in tumour tissues may arise from aberrant interactions between mesenchymal and epithelial tissue whereby tumour cells release factors stimulating the stromal production of HGF/SF (Seslar et al., 1993; Rosen et al., 1994). Several commonly occurring cytokines have also been shown to regulate the expression of HGF/SF receptor message in tumour cells (Hiscox and Jiang, 1996). A high level of HGF/SF in primary breast cancers is a strong, independent prognostic indicator (Yamashita et al., 1994); serum levels in these patients appears to have close relationship with disease progression and relapse (Taniguchi et al., 1994, 1995; Tominaga, 1995).

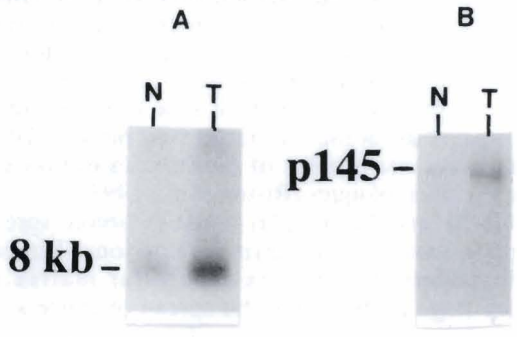


Fig. 6. Expression of *c-met* in human colon cancer tissue. mRNA **(A)** and protein **(B)** for the HGF/SF were detected with Northern and Western blotting, respectively. N: normal mucosa; T: colon tumour tissue. Tumour tissue expressed high level of *c-met* at both message and protein levels (Hiscox et al., 1997).

HGF/SF in tissue and organ regeneration

Liver regeneration

HGF is the most potent known stimulus for DNA synthesis by normal hepatocytes, a process which is essential for hepatocyte proliferation during liver regeneration. After liver resection, and in a variety of liver diseases, there is a marked increase in circulating HGF and increased expression of HGF mRNA in a variety of tissues (Kinoshita et al., 1989; Asami et al., 1991; Lindroos et al., 1991, 1992; Shimizu et al., 1991; Tsubouchi et al., 1991; Zarnegar et al., 1991; Janeko et al., 1992; Sakon et al., 1992; Tomiya et al., 1992). In liver regeneration, hepatocyte growth factor increases the expression of early response genes such as liver regeneration factor-1, jun-B, c-fos, early growth response gene-1 and insulin-like growth factor binding protein-1 (Weir et al., 1994). It appears that HGF/SF not only influences hepatocyte growth, but also induces hepatocytes to form acinar/ductular structures akin to bile duct morphology, a process that depends on the presence of collagen type I in the matrix (Block et al., 1996).

It has thus been suggested that HGF/SF is a key factor for triggering liver regeneration after liver resection or other damage to the liver. This is further strengthened by the fact that, following injection of labelled HGF/SF into hepatectomized rats, a marked increased HGF/SF binding to the remnant liver was seen (Ishiki et al., 1992, 1995). Furthermore, infusion of HGF both systemically and locally (Ishii et al., 1992, Kobayashi et al., 1996) accelerated liver regeneration and also modifies liver function. Similar changes were also seen in experiments in which liver cirrhosis was chemically induced. In these conditions, the lung may serve as the major contributor of HGF/SF for liver regeneration (Yanagita et al., 1992). In fulminant hepatitis patients, very high levels of circulating hepatocyte growth factor are associated with a poor prognosis. These high levels reflect both the extent of the decrease of functioning hepatocyte mass and also the decreased capacity of liver to remove HGF/SF (Tsubouchi et al., 1992). In damaged liver, *c-met* is also altered in order to facilitate the signals for regeneration. Expression of the *c-met* is enhanced in cells surrounding damaged areas in the liver, and also that the distribution of cells expressing *met* is in accordance with that of cells

expressing proliferating cells nuclear antigen. Following liver damage, the *met* protein undergoes intense tyrosine phosphorylation peaking at 12h post insult, an event that is a precursor to DNA synthesis. Phospholipase C-γ and phosphatidylinositol 3-kinase, Src-2 homology containing intracellular signalling molecules associate with the *MET* protein following tyrosine phosphorylation *in vivo* (Horimoto et al., 1995).

Several other factors are also modified in the damaged liver, which act to enhance HGF/SF action. These include the uPA receptor - a marked increased following liver resection is seen, occurring as early as 1 minute post-damage which enhances conversion of pro-HGF/SF to biologically functioning HGF/SF (Mars et al., 1995).

Kidney regeneration

Infusion of HGF/SF increases renal regeneration following ischemic kidney injury in rats (Igawa et al., 1993; Miller et al., 1994). In kidney regeneration, HGF induces renal collecting duct cell and renal tubular epithelial cell mitosis (Cantley et al., 1994; Sponsel et al., 1994) together with renal cyst formation (Okui et al., 1994). It has been suggested that cell motility enhancement by HGF/SF leads to tubule formation whereas the breakdown of cell-cell adhesion is required for tubule branching (Clark, 1994). Alpha 2 beta 1 (α2 ß1) integrins are also essential for the process of HGF/SF-induced branching (Saelman et al., 1995).

Other organs and tissues

HGF is produced in the lung after acute lung injury which may act to promote lung regeneration (Yanagita et al., 1993). HGF/SF may also be involved in muscle and hair growth (Jennische et al., 1993; Jindo et al., 1994) and hair follicle elongation (Shimaoka et al., 1995).

HGF/SF and other diseases

Synovial fluid concentrations of HGF/SF in patients with rheumatoid arthritis are known to be elevated compared to disease-free control patients. The elevated levels of HGF/SF are related to disease activity (Yukioka et al., 1994). Serum HGF/SF levels are raised in patients with acute pancreatitis and interstitial pneumonitis and bacterial pneumonia, which has been shown to correlate to disease course, and in patients with organ failure, infected pancreatic necrosis and sepsis. Successful intensive and surgical treatments have been shown to decrease circulatory HGF/SF levels thus it has been proposed that HGF/SF in circulation may be a useful prognostic indicator (Maeda et al., 1995; Ueda et al., 1996).

Inhibitory agents for HGF/SF action

Because HGF/SF has been implicated as playing a key role in the process of tumour cell metastasis, agents which block or reduce its stimulatory function in tumour cells may be valuable anti-metastatic agents. Several factors have shown promising results as inhibitors of HGF/SF-induced responses and are discussed below:

Gamma linolenic acid

Gamma linolenic acid (GLA) is an n-6 essential fatty acid which has been shown to be cytotoxic towards tumours *in vitro* and *in vivo* (Begin, 1986; Horrobin, 1990). We have shown that GLA exerts a potent inhibitory effect on HGF/SF-stimulated tumour cell motility, invasion, and membrane ruffling at concentrations that are non-toxic to the cells (Jiang et al., 1995c, 1996c) possibly by the regulation of cell-surface adhesion molecule, E-cadherin (Jiang et al., 1995b,c).

HGF antagonist

Chan et al. (1991) reported a naturally occurring HGF antagonist which specifically inhibits HGF induced mitogenesis. The antagonist has been found to be an alternative HGF transcript and may compete with HGF/SF for the receptor, *c-met*.

Increase in intercellular Ca^{2+}

HGF/SF-induced tumour cell membrane ruffling and motility have been shown to be inhibited by the addition of cytosolic calcium regulating agents such as ATP (Jiang et al., 1995a). Transient elevation of intracellular Ca^{2+} levels is thought to be part of the HGF/SF-inhibitory mechanism of ATP as inhibition of this Ca^{2+} raise by BAPTA abolished the inhibitory effects of ATP. Elevation of cytosolic free Ca2+ with other agents including ionomycin and ADP also resulted in HGF/SF inhibition.

Interleukin-12

We have also shown that the immunoregulatory cytokine, interleukin-12 (IL-12), inhibits tumour cell motility and basement membrane invasion stimulated by HGF/SF (Hiscox et al., 1995). These effects are thought to be mediated by alterations in cell-surface adhesion molecule levels.

Invasion inhibitory factor-2

Invasion inhibiting factors, are small protein extracted from the liver and exhibit anti-metastatic properties on melanoma and lung cancer cells in vivo (Isoai et al., 1992, 1993). Invasion inhibitory factor-2 (IIF-2, Isoai et al., 1994) has been shown to inhibit HGF/SF-stimulated motility and invasion of tumour cells in vitro (Jiang et al., 1995e; Han et al., 1996) however the mechanism by which this occurs is not

clear.

Retinoic acid

Retinoic acid, which belongs to a group of vitamin A metabolites, has been shown to exert opposite effect on the same cell (Koj et al., 1995), including regulation of cytokine production and acute phase response which appears at transcription level. RA has been widely reported involved in the regulation of other motility factor receptor functions, cell-matrix interaction and proteolytic enzymes (Edward et al., 1989; Hendrix et al., 1990; Lotan et al., 1992).

In summary, HGF/SF and its receptor have over the past few years attracted much attention in many areas including cell biology, oncology, development, physiology, pathology. It effects, via its specific receptor *c-met*, can perhaps be broadly summarised as regulation of cell movement, cell/tissue morphology, cell growth and therefore can be nicely described by the terms mogoten, morphogen and mitogen. It is a key regulator of many cellular behaviours in a range of cell types which express HGF/SF receptor. It participates in a number physiological processes including liver and kidney regeneration, angiogenesis, embryogenesis, tissue repair, haematopoiesis, etc. HGF/SF is also a key mediator in certain diseases such as carcinogenesis, tumour spread, rheumatoid arthritis.

The importance of this factor is not only these physiological and pathological roles in normal as well as disease conditions, but also opens a new area to explore common pathways/factors in mitosis, motogenesis, and morphogenesis. As we understand more about the factor, strategies aimed at using modern technologies to modify HGF/SF and its receptor in favour of combating disorders where HGF/SF may be involved will be possible. Indeed, progress has been made in enhancing liver regeneration by using recombinant HGF/SF. We anticipate therefore that various strategies may be designed to counter attack the unwanted effects of HGF/SF in other diseases, particular in cancer.

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