Histol Histopathol (2005) 20: 1339-1349
DOI: 10.14670/HH-20.1339

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Review

Hepatocyte growth factor/scatter factor and prostate cancer: a review

R.A. Hurle[1], G. Davies[1], C. Parr[1], M.D. Mason[2], S.A. Jenkins[3], H.G. Kynaston[3] and W.G. Jiang[1]

[1]Metastasis and Angiogenesis Research Group, Department of Surgery, Wales College of Medicine, Heath Park, Cardiff,
[2]Department of Clinical Oncology, Wales College of Medicine, Heath Park, Cardiff and
[3]Department of Urology, University Hospital of Wales, Heath Park, Cardiff, UK

Summary. Men who die from prostate cancer do so from uncontrolled metastatic disease. A better understanding of the mechanisms involved in the progression and metastasis of prostate cancer may lead to novel therapeutic approaches to prevent its natural progression. Hepatocyte Growth Factor / Scatter factor (HGF/SF) has been demonstrated to elicit a number of key functions in numerous tissues that are important in the progression, invasion and metastasis of cancer. Studies have demonstrated that the activity of HGF/SF and its receptor c-Met are linked to disease progression in numerous cancers. However, research into these functions, which include activities as a mitogen, a motogen and an anti-apoptotic and angiogenic factor in prostate cancer are limited. This article reviews the published evidence of the roles HGF/SF plays in prostate cancer progression and highlights the clinical and therapeutic potential of research into this pleiomorphic cytokine.

Key words: Hepatocyte growth factor, scatter factor, c-Met, Prostate cancer

Introduction

Cancer is the cause of a quarter of all deaths in the UK. Excluding non melanoma skin cancers prostate cancer is the second most frequently diagnosed cancer in men. The UK incidence of prostate cancer in 2000 was reported as 27,150 which accounted for 10% of all cancers and 20% of male cancers. Prostate cancer resulted in 9,940 deaths in the UK during 2002 and accounted for 6% of all cancer deaths and 12% of male cancer deaths (Office for National Statistics, 2000; Cancer Research UK 2002).

The prevalence of histologically confirmed cancer of the prostate at autopsy greatly exceeds the incidence of clinically evident disease (Breslow et al., 1977). Furthermore, the incidence of histologically confirmed cancer of the prostate has been shown to be similar throughout the world although the prevalence of clinical disease varies widely (Shiraishi et al., 1994; Shimizu et al., 1991). Similarly, prostate cancer is not always life threatening and frequently follows an indolent course which does not require immediate treatment and in some patients, may never require treatment. These observations suggest that the biological behaviour and natural history of cancer of the prostate is very variable. At present it is not possible to distinguish between those patients in whom prostate cancer will progress from those in whom the disease will follow a non-progressive course. Not surprisingly therefore, the optimum management of early organ confined prostate cancer has not been established. Current therapies for men with metastatic disease are palliative and those men with advanced hormone refractory prostate cancer continue to have a very limited life expectancy. An improved understanding of the cellular pathways and mechanisms involved in the growth, progression and metastasis of cancer of the prostate may suggest new therapeutic approaches to the management of this malignancy. In particular, therapeutic strategies to prevent the development of metastases have the potential to make a huge impact on the morbidity and mortality from prostate cancer.

A number of factors are known to play a role in the complex cascade of events leading to metastases, a process which involves numerous complex interactions between tumour and host cells. Cell adhesion, motility and invasion are key components in the dynamic multi-step process of metastasic disease and Hepatocyte Growth Factor /Scatter factor (HGF/SF), a pleiotropic

Offprint requests to: Dr. R.A. Hurle, Metastasis and Angiogenesis Research Group, Department of Surgery, Wales College of Medicine, Heath Park, Cardiff, UK. e-mail: rhidian.hurle@cardiffandvale.wales.nhs.uk

cytokine possesses activity at all of these steps (Parr and Jiang, 2001). Therefore, the aim of this review was to critically examine the evidence implicating HGF/SF in the progression and metastasis of prostate cancer.

Discovery of HGF/SF

Hepatocyte growth factor (HGF) initially isolated from the serum of partially hepatectomised animals and from the lysate of rat platelets was shown to be a powerful hepatotrophic factor that stimulated DNA synthesis and growth of hepatocytes (Michalopoulos et al., 1984; Nakamura et al., 1984; Russell et al., 1984). A year later scatter factor (SF), a fibroblast-derived protein that had the ability to scatter tightly packed colonies of epithelial cells was discovered (Stoker and Perryman, 1985). Subsequent structural studies indicated that HGF and SF were identical molecules (Gherardi and Stoker, 1990; Weidner et al., 1990) and that their biological and immunochemical properties were indistinguishable (Furlong et al., 1991). HGF and SF were therefore renamed HGF/SF and later shown to be homologous to hepatopoietin A, a protein that stimulates hepatocyte growth and tumour toxic factor (Zarnegar et al., 1989; Higashio et al., 1990). Amino acid sequencing of HGF/SF confirmed over 90% homology between rat and human HGF/SF (Weidner, 1990; Gherardi and Stoker, 1990). The gene encoding HGF/SF has now been isolated on chromosome 7 at q21.1 (Fukuyama et al., 1991; Laguda et al., 1991).

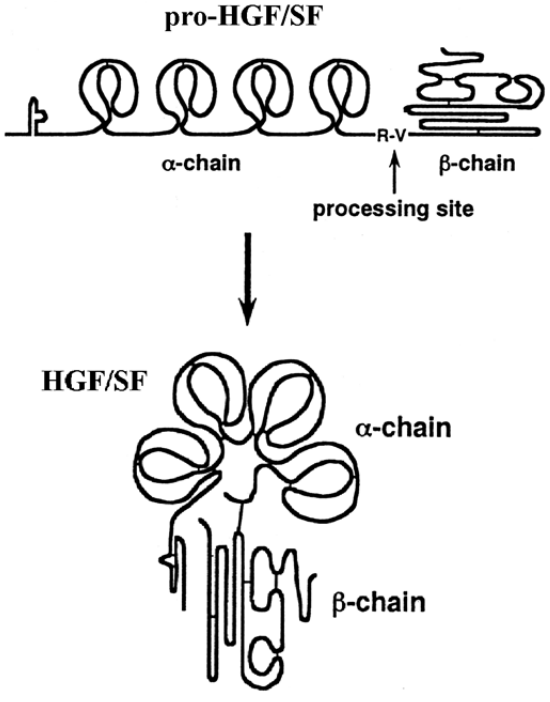

Fig. 1. Schematic representation of pro- HGF/SF and biologically active HGF/SF.

Structure of HGF/SF

HGF/SF is synthesized as an inactive single chain peptide of 728 amino acid residues containing a 29 amino acid signal sequence and a 25 amino acid pro-sequence (Nakamura et al., 1989). Single chain pro-HGF/SF requires enzymatic hydrolysis of the Arg^{494} - Val^{495} bond to be converted to the mature active heterodimeric structure consisting of an α and ß chain (Fig. 1). The 69 kD α-chain consists of four triple-disulphide kringle domains which are thought to be involved in protein and receptor-ligand binding and a N-terminal hairpin loop domain. The 34 kD ß-chain is similar in structure to a serine protease although it does not function as a protease. Deletion of kringle domains or the N-terminal hairpin structure in HGF/SF results in marked decreases in biological activity (Matsumoto et al., 1991).

Activators and inhibitors of HGF/SF

HGF/SF is expressed predominantly by mesenchymal or stromal cells. Hepatocyte Growth Factor Activator (HGFA) is the dominant activator of HGF/SF in human serum (Miyazawa et al., 1996). Matriptase, a matrix-degrading serine protease with trypsin-like activity also promotes conversion of pro-HGF/SF to its biologically active form (Lin et al., 1999). Other factors including humoral type factor, heparin, blood coagulation factor XIIa, tissue-plasminogen activator (t-PA) and urokinase plasminogen activator (uPA) also stimulate conversion of pro-HGF/SF to HGF/SF but to a lesser extent than HGFA (Naldini et al., 1992; Matsumoto et al., 1992; Shimomura et al., 1995; Mars et al., 1996). HGFA is activated by thrombin and this pathway links HGF/SF with the coagulation cascade, a prominent mechanism in the tissue damage and repair process. In addition, the production of HGF/SF in injured tissues is partly self-regulated suggesting local control (Miyazawa et al., 1994). HGFA mRNA levels have been demonstrated to increase during the acute inflammatory response to injury suggesting that HGFA may also act as an acute phase protein (Okajima et al., 1997).

In 1997 a protein purified from MKN45 human stomach carcinoma cells was cloned to reveal a novel kunitz-type serine protease inhibitor which inhibited HGFA. This serine protease inhibitor was originally named HGF activator inhibitor (HAI) but was later renamed HAI-type 1 (HAI-1) when a second, similar but not identical, novel kunitz-type serine protease inhibitor of HGFA was identified (Kaweaguchi et al., 1997; Shimomura et al., 1997), and named HAI-type 2 (HAI-2). Both HAI-1 and HAI-2 bind to HGFA and prevent it from binding to the single chain inactive pro HGF/SF thereby inhibiting the activation of HGF/SF (Fig. 2).

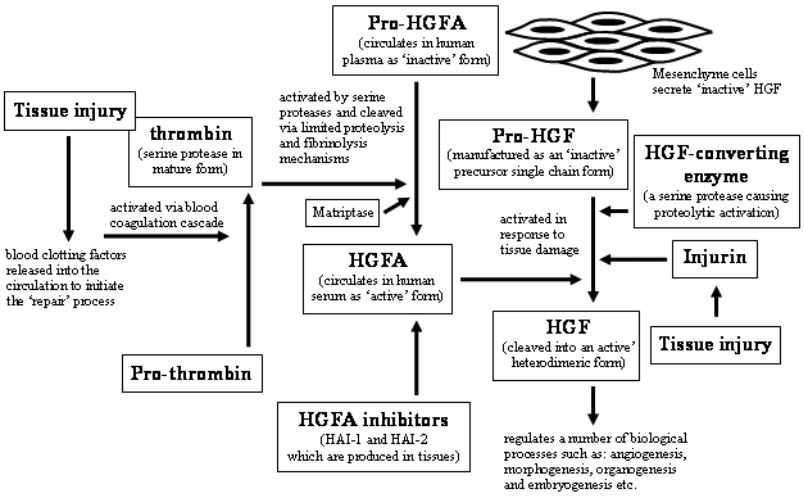

Fig. 2. Schematic flow diagram showing secretion, activation and regulation of HGF/SF. (Broken arrows indicate unknown mechanisms of HGF/SF activation involving injurin). With kind permission from Davies et al., 2004b.

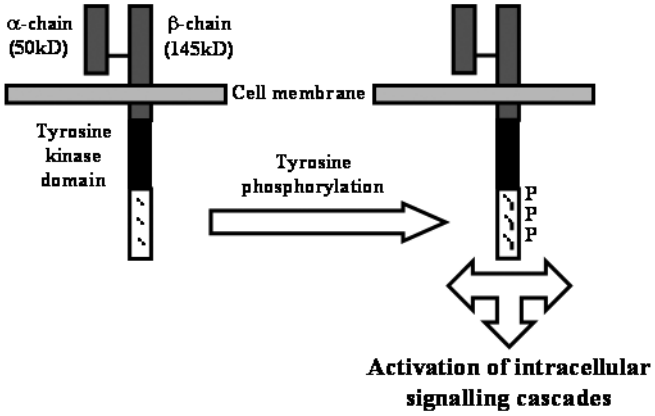

Fig. 3. Schematic representation of the HGF/SF receptor c-Met.

HGF/SF receptor site

HGF/SF mediates its multitude of biological effects by binding to a specific receptor site, c-Met (Fig. 3) which has been identified in many human tumours including prostate cancer (Humphrey et al., 1995). The c-Met receptor, first identified as an activated oncogene (Cooper et al., 1984) is a two-chain protein consisting of an extra cellular ß-chain (50kD) linked by a disulphide bond to a trans membrane ß-chain (145 kD) possessing a terminal intracellular tyrosine kinase domain (Ferracini et al., 1991).

Binding of HGF/SF to the extra cellular α-chain component of the c-Met receptor results in tyrosine phosphorylation (Fig. 3) of the terminal kinase domain and initiates a cascade of intracellular events (Faletto, 1993). The c-Met protein arises from a single polypeptide precursor which undergoes co- and post-translational glycosylation and endoproteolytic cleavage (Giordano et al., 1989). The c-Met receptor also belongs to a family of receptors whose members include Ron and c-sea (Huff et al., 1993; Ronsin et al., 1993; Gaudino et al., 1994; Ponzetto et al., 1994). Expression of c-Met has been shown to be induced by numerous factors including HGF/SF, Epithelial Growth Factor (EGF), Interleukin-1 (IL-1), TNF, oestrogen, progesterone and dexamethasone (Boccacio et al., 1994; Chen et al., 1994; Moghul et al., 1994). The Epstein-Barr virus has also been reported to promote c-Met expression (Weimar et al., 1997). Reports of degradation of c-Met by HGF/SF have led to the suggestion that this may be a mechanism for autocrine regulation. Mutations of c-Met have been identified in papillary renal carcinomas (Fischer et al., 1998) and it possible that a number of different c-Met receptors exist in different tumours.

Functions of HGF/SF

HGF/SF originally identified as a powerful mitogen for hepatocytes has since been shown to exert a number of effects in a wide variety of tissues (Zarnegar and Michalpoulos, 1995; Jiang and Hiscox, 1997). In addition to its mitogenic activity, HGF/SF inhibits apoptotis in several cell types (Bardelli et al., 1996), induces morphogenesis in ductal epithelial cells (Montesano et al., 1991) and is a potent angiogenic factor (Bussolino et al., 1992). The effects of HGF/SF have been studied in chronic disease states including chronic renal failure and indicate that it augments the regeneration of various organs (Matsumoto and Nakamura, 1997). These effects of HGF/SF on cell growth, migration, morphogenesis and angiogenesis are essential for normal tissue growth and development. For example, HGF/SF is essential for the long-distant migration of myogenic precursor cells during the development of the diaphragm. However, these effects

of HGF/SF on normal cell growth and regeneration suggest that the cytokine may also play a major role in the growth, progression and metastasis of tumours.

HGF/SF regulates the cellular function of a wide variety of tumours (Jiang et al., 1999) and has been demonstrated to exert a variety of effects in urological cancers including those of the kidney, bladder and prostate. The influence of HGF/SF on neoplastic cells is variable and ranges from stimulation to inhibition of growth, inhibition of apoptosis and as a mediator in the dynamic processes involved in the formation of metastases.

HGF/SF and cell adhesion

In order for tumour cells to spread from the site of origin they must initially cross the barriers of the basement membrane and extracellular matrix to enter the circulatory system. HGF/SF has been shown to regulate cell-matrix receptor expression (intergrins) and cytoskeleton proteins (Giancotti and Mainiero, 1994). HGF/SF also plays a role in matrix degradation and invasion through the stimulation of uPA and tPA (Morimoto et al., 1994) and has been shown to stimulate collagenase-1 and stromelysin-1 production in a dose and matrix dependant fashion (Dunsmore et al., 1996). HGF/SF also promotes angiogenesis and it is via these de novo vessels that that tumour cells may enter the circulation. HGF/SF stimulates cell-cell dissociation by inhibiting cell-cell adhesion by such mechanisms as disruption of cadherin function (Pasdar et al., 1997) and promoting the breakdown of cell-cell adhesion complexes (Hiscox and Jiang, 1998).

Many cancer cell types and their metastases express high levels of CD44, the expression of which has been linked with metastasis and tumour progression. The expression and distribution of CD44, a multifunctional cell surface adhesion molecule, its co-localisation and translocation with ezrin has been studied in DU-145 and PC-3 prostate cancer cells. The results of this work indicate that these prostate cancer cells express multiple isoforms of CD44 that co-localise with ezrin. HGF/SF up-regulates CD44 and its co-translocation with ezrin during tumour-endothelial cell interactions and in addition, tumour cell adhesion to endothelial cells and their invasiveness is increased after HGF/SF exposure (Harrison et al., 2002). This complex may play an important role in the capture and invasion of endothelial cells by prostate cancer cells.

Tight junctions control the permeability of endothelial and epithelial cells and create an intercellular and intra-membrane diffusion barrier. An inverse correlation between the reduced expression of tight junctions and tumour differentiation and experimental evidence has emerged suggesting that may be an important barrier that cancer cells must overcome in order to metastasise (Martin and Jiang, 2001). Studies on tight junctions, HGF/SF and prostate cancer are in their infancy.

Providing the tumour cell survives the passage through the surrounding tissue and into the circulation and evades the attention of the host immune defence system it must pass back through the endothelium of a circulatory vessel to form a metastatic site. HGF/SF has been shown to increase the adherence of tumour cells to endothelial cells (KawakamiKimura et al., 1997) and to reduce the communication between the endothelial cells (Jiang et al., 1997b). These observations suggest that HGF/SF may play an important role of in the metastatic process.

Elevated c-Met levels and disease progression

Prostate stromal cells grown in primary cell culture secrete HGF/SF whereas prostate epithelial cells express the HGF/SF receptor, c-Met (Krill et al., 1997). In the prostate HGF/SF synthesised by stromal cells acts on the epithelial cells and therefore functions as a paracrine growth factor. Expression of HGF/SF in prostate cancer cells is induced by androgen deprivation and c-Met is preferentially up-regulated in androgen-insensitive metastatic cells (Humphrey et al., 1995). These observations suggest a possible relationship between c-Met expression and prostate carcinoma progression.

The c-Met receptor is expressed by normal epithelial cells of most tissues and is located primarily at the intercellular junctions in close association with cell adhesion molecules such as E-cadherin (Crepaldi et al., 1994). Immunohistochemical studies of primary cultures of prostate cancer cells demonstrated that c-Met was present in all lymph node and bone marrow metastases, 84% of primary prostate cancers but only 18% of benign prostate hyperplasic samples. Furthermore, the same study demonstrated that 91% of high grade prostatic intraepithelial neoplasia (PIN) samples were positive for c-Met protein on immunostaining (Pisters et al., 1995). These findings suggest a relationship between c-Met expression and prostate cancer progression. Other studies reported c-Met in 36% of prostatic intraepithelial neoplasia samples, 33% of latent prostate cancer samples, 81% of clinical prostate cancer samples and all metastases samples (Watanabe et al., 1999) further supporting the relationship between the expression of the HGF/SF receptor and the progression of prostate cancer. Differential expression of the HGF/SF receptor has been demonstrated by Davies et al. (2000) in a panel of prostate cancer cell lines. This study revealed that high levels of c-Met were present in cell lines of high invasive potential (DU-145 and PC-3 cells), compared to moderate levels detected in cell lines of low invasive potential (LNCap, CAHPV10 and PZHPV7) as shown in Fig. 4.

A recent study conducted on ninety radical prostatectomy specimens with a Gleason sum of 6 or 7, together with 86 specimens of bone, lymph node, and soft-tissues demonstrated that all had metastases (with the exception of two lymph node metastases), and 51% of the primary prostate cancers expressed c-Met.

Moreover, the bone metastases expressed significantly more c-Met than lymph node metastases suggesting that the HGF/SF receptor may be a promising target for both nuclear imaging and for targeted treatment of metastases in patients with prostate cancer (Knudsen et al., 2002).

HGF/SF and hormone status

HGF/SF elicits a wide range of biological effects on cancer cells and plays a key role in cancer progression. c-Met is expressed by prostate cancer cells but not by interstitial cells. In contrast, HGF/SF is expressed by prostatic interstitial cells and the degree of expression is greater in hormone-treated cancers compared to non-treated cancers. These observations suggest that the expression of HGF/SF may be related to the hormonal status of the prostate tumour. Furthermore, whereas, low-grade prostate tumours express c-Met on the plasma membrane higher grade tumours tend to express c-Met in the cytoplasm suggesting that the receptor is internalised or down regulated in higher grade tumours (Kurimoto et al., 1998). Thus it would appear that the relationship between the HGF/SF and its receptor is thus influenced by both the hormonal status and the degree of differentiation of the prostate cancer.

Significantly higher levels of c-Met protein expression have been reported in malignant human prostate tissue (both hormone treated and not treated samples) than in the benign prostate tissue (Tsuka et al., 1998a). Interestingly, the same authors reported that c-Met mRNA expression was higher in the benign tissue and concluded that there was no relationship between mRNA and protein expressions of c-Met in prostate cancer and that endocrine therapy did not alter either c-

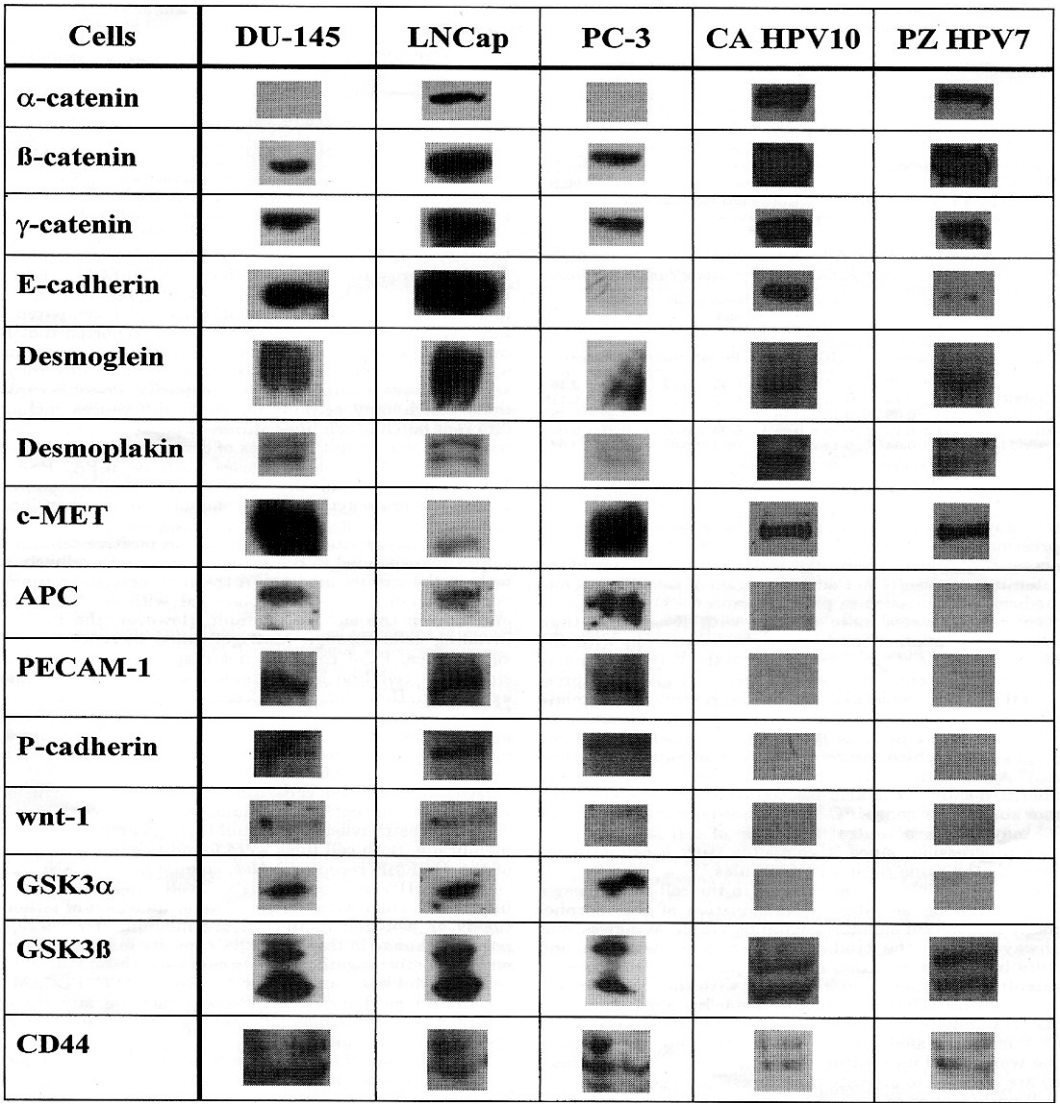

Fig. 4. Expression of HGF/SF receptor in prostate cancer cells. With kind permission from Davies et al., 2000.

Met mRNA or protein expression (Tsuka et al., 1998b). The same authors had suggested that the tissue level of biologically active HGF/SF in hormone treated and untreated prostate cancer depends on activation of pro-HGF/SF supplied from distal organs rather than de novo HGF/SF mRNA synthesis (Tsuka et al., 1998a).

HGF/SF and the cell cycle

Vitamin D and HGF/SF have been shown to exert a synergistic inhibitory effect on the growth of androgen unresponsive prostate tumour cells by slowing cell cycle progression via control at sites beyond the G1/S checkpoint, the major regulatory locus of growth control in androgen-sensitive prostate cells (Qadan et al., 2000). Others have reported that HGF/SF protects epithelial and carcinoma cells against the deleterious effects of cytotoxic and DNA-damaging agents and markedly enhanced the repair of DNA strand breaks caused by adriamycin or gamma radiation (Fan et al., 2000). These observations suggest that HGF/SF activates a DNA repair pathway and plays a role in cell survival.

HGF/SF effects on migration and invasion in prostate cancer cell

c-Met has been detected in androgen dependent DU145 and PC-3 human prostate cells, but not in the androgen-independent LNCaP cells and reported that HGF/SF increased cell motility (scatter assay) and invasive potential (matrigel invasion chamber assay) of DU145 but not PC-3 or LNCaP cells (Nishimura et al., 1998). The same authors suggested that HGF/SF acting as a parahormone via c-Met, increases the invasive potential and metastasis of DU145 but did not offer an explanation for the failure of the cytokine to elicit similar responses in PC-3 and LNCaP cells and went on to report that DU145 prostate cancer cells cultured in conditioned medium derived from prostate stromal cells, acquired invasive potential which was inhibited by a HGF/SF antibody (Nishimura et al., 1999). This observation suggest that the invasive activity of the prostate cancer DU145 cells occurs via some form of tumour-stromal interaction and is supported by further reports that HGF/SF produced by prostate-derived stromal cells acts as a paracrine growth factor that stimulates the growth of androgen independent prostate cancer cell lines (Nakashiro et al., 2000).

The expression of HGF/SF by DU145 prostate cancer cells has been reported to be approximately four fold greater than in benign epithelial cells in vitro. HGF/SF from prostatic stromal myofibroblasts significantly increased the expression of Interleukin-1beta (8.1-fold), platelet-derived growth factor (6.2-fold), basic fibroblast growth factor (4.0-fold), vascular endothelial growth factor (3.7-fold), and endothelial growth factor (2.9-fold) (Idini and Humphrey, 2000). DU 145-conditioned media, but not human prostatic stromal myofibroblastic conditioned media, displayed HGF/SF-inducing activity and was also shown to contain interleukin-1beta, basic fibroblast growth factor, and platelet-derived growth factor (Zhu and Humphrey, 2000). The results of this study further suggest that cytokines and growth factors produced by stromal cells can mediate the expression of HGF/SF in prostate cancer cells and hence their growth and progression.

HGF/SF acting via F-actin filaments, microtubles, intermediate filaments, focal contacts and cellular junctions results in a number of tissue specific epithelial morphogenic events (Brinkmann et al., 1995). HGF/SF stimulates ruffling of the free edges of apical cells and the development of distal branching long ducts in cultured prostate epithelial cells (Jiang et al., 1995). HGF/SF significantly increases the migration of both normal prostate epithelial cells and prostate cancer cells however; whereas HGF/SF stimulates the proliferation of prostate cancer cells it inhibits the proliferation of prostate epithelial cells (Gmyrek et al., 2001). This suggests that normal and malignant prostate epithelial cells have both common and differing response pathways to HGF/SF. Modulation of the interaction between the c-Met receptor and the E-cadherin/catenin complex by HGF/SF has been reported suggesting that HGF/SF may possibly alter the intercellular adhesion properties of prostate cancer cells and contribute to metastasis (Davies et al., 2001a).

Furthermore, *in vitro* invasion assays have demonstrated that HGF/SF modulates the invasiveness of prostate cancer cells. Matrilysin promotes the extracellular cleavage of E-cadherin from prostate cancer cells and has been suggested as a putative mechanism whereby HGF/SF induces cell-cell dissociation and *in vitro* invasion (Davis et al., 2001b). This suggestion is supported by observations which indicate that HGF/SF induces scattering of DU145 prostate cancer cells *in vitro* by decreasing the expression of E-cadherin and promoting translocation of the cytokine to the cytoplasm (Miura et al., 2001).

The migration of primary prostate epithelial cells is also regulated by the P13-kinase and Src-family kinase signalling pathways. Activation of the P13-kinase pathway requires stimulation by adhesion and motility factors secreted by prostate stromal cells. In the conditioned medium of primary prostate stromal cells HGF/SF is the principal stimulator of this P13-kinase pathway and has been demonstrated to mediate prostate epithelial cell migration (You et al., 2003).

HGF/SF and prostate bone metastasis

HGF/SF produced by human bone marrow stromal cells promotes the proliferation, adhesion and survival of human haematopoietic (CD34+) progenitor cells (Weimar et al., 1998). HGF/SF also influences the *in vitro* formation of prostate epithelial cell colonies on bone marrow stroma co-culture (Lang et al., 1999).

It has been proposed that osseous metastatic prostate cancer cells must be osteomimetic in order to

metastasise, grow, and survive in the skeleton. Bone stromal growth factors such as basic fibroblast growth factor, HGF/SF and insulin growth factors initiate bone tropism, an effect enhanced by prostate secreted endothelin-1 and urokinase-type plasminogen activator secreted by prostate cells (Koeneman et al., 1999).

Growth factors and peptides that possess differentiating activity can alter the production of the characteristic blastic phenotypes. Elucidation of common pathways, presumably driven by the same promoters, expressed by both prostate cancer and bone stromal cells, could result in the development of novel preventive and therapeutic strategies for the treatment of prostate cancer skeletal metastasis.

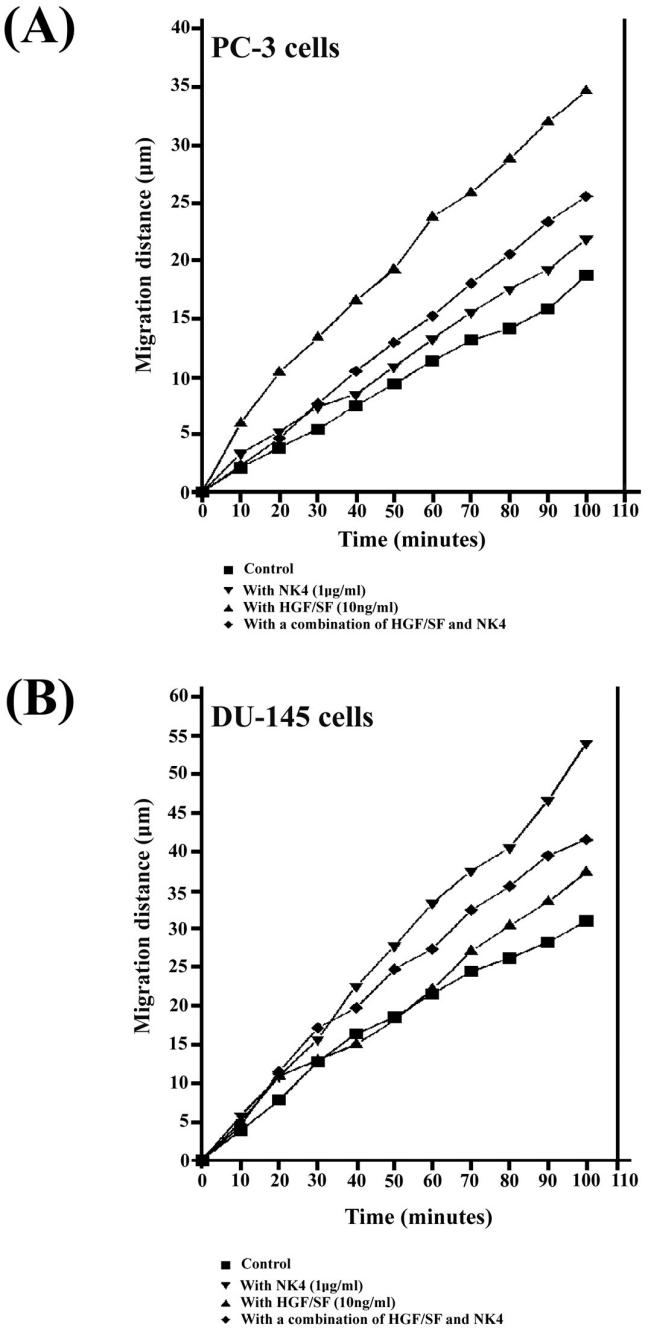

Fig. 5. Effect of NK4 on HGF/SF-induced cell motility of PC-3 cells **(A)** and DU-145 **(B)**, using motion analysis software package. These results indicate that HGF/SF (10 ng/ml) has the ability to induce tumour cell migration. However, importantly, NK4 (1 μg/ml) was able to antagonise the influence of HGF/SF. With kind permission from Parr et al., 2001.

Plasma and urinary levels of HGF/SF in patients with prostate cancer

HGF/SF content of urine samples and bladder tissue extracts have been measured by enzyme-linked immunosorbent assays. The urinary levels of HGF/SF were similar in patients with active prostate cancer and patients with bladder cancer in remission with both groups having higher urinary HGF/SF levels than normal controls (Rosen et al., 1997).

Differing levels of HGF/SF receptor expression have been observed between men of different races. Thus, African Americans, who have a 2 to 3 time higher incidence of prostate cancer than Caucasian Americans, also have a 4-fold increase in the level of HGF/SF receptor expression (Presnell et al., 2001).

Men with metastatic prostate cancer have significantly higher serum level of HGF/SF than men with localized prostate cancer and those without prostate cancer and serum levels of HGF/SF in men with metastatic prostate cancer patients are independent of the prostate specific antigen level and patient age (Naughton et al., 2001). Although further work is needed to identify whether there is a relationship between HGF/SF serum levels and Gleason grade, serum HGF/SF could potentially be a useful marker of prostate cancer progression.

HGF/SF and potential therapeutic implications

The therapeutic implications of HGF/SF in cancer treatments have been recently reviewed (Jiang et al., 2005). Of notable interest is NK4 a protein that contains the hair pin loop domain and all four kringle domains of HGF/SF but no ß-chain nor the amino acids responsible for dimerisation on the C-terminus of the α-chain. NK4 has been shown to bind to the c-Met receptor but importantly is unable to activate it and is therefore a competitive HGF/SF antagonist (Parr et al., 2001) and NK4 significantly reduces prostate tumour growth *in vivo* by inhibiting angiogenesis (Davies et al., 2003). Another effect of the HGF/SF antagonist NK4, is the reduced migration of prostate cancer cells as shown in Fig. 5. Other methods of inhibiting the c-Met receptor have been observed using ribozyme transgenes (Davies et al., 2004a,b). The same author reported that hammerhead ribozymes encoding antisense to c-Met reduced in vitro invasion and migration in prostate

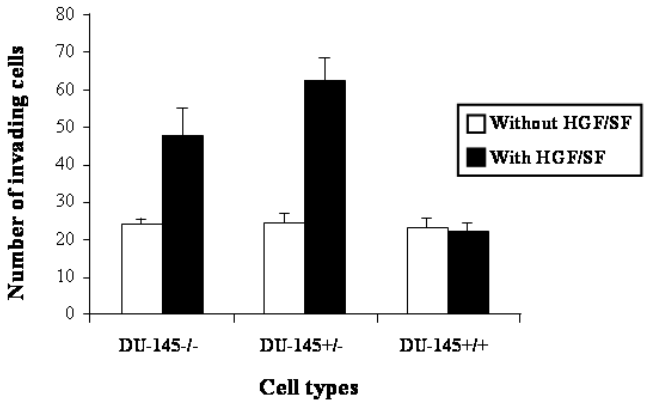

Fig. 6. Invasion in DU 145 cells with/without HGF/SF exposure after c-met knock out using a hammerhead ribozyme transgene. With kind permission from Davies et al., 2004a.

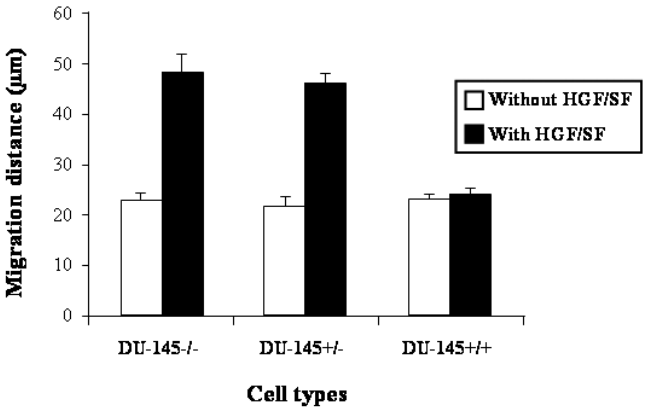

Fig. 7. Migration in DU 145 cells with/without HGF/SF exposure after c-met knock out using a hammerhead ribozyme transgene. With kind permission from Davies et al., 2004a.

cancer cells after addition of HGF/SF as shown in Figures 6 and 7. Inhibition of the c-Met receptor is therefore a possible mechanism to inhibit the neoplastic effects stimulated by HGF/SF and further work in this area could lead to novel therapeutic approaches in the management of prostate cancer and the development of a clinically useful anti-metastatic agent.

Conclusions

There is a considerable body of experimental evidence to suggest that HGF/SF plays a role as a mediator in the spread of prostate cancer. HGF/SF through its specific receptor c-Met has been demonstrated to modulate cell proliferation, tumour cell-cell interaction, cell migration, cell-matrix adhesion, invasion and angiogenesis in prostate cancer cells. The recent identification of NK4 is an exciting development in the understanding of possible methods to inhibit mechanisms promoting the spread of prostate cancer and work targeting the c-Met receptor using transgenes may provide valuable new and novel therapeutic approaches in preventing metastases. Further studies are however required to elucidate the complex inter-relationship between HGF/SF and its specific receptor c-Met in order to fully understand their role in the progression of prostate cancer and also their mechanism of action and inter-relationship with other growth regulatory systems. We hope that this review will stimulate further work towards the ultimate goal of developing new therapeutic strategies to eradicate the need for a palliative approach in men dieing of metastatic prostate cancer.

References

Bardelli A., Longati P., Albero D., Goruppi S., Schneider C., Ponzetto C. and Comoglio P.M. (1996). HGF receptor associates with the anti-apoptotic protein BAG-1 and prevents cell death. EMBO J. 15, 6205-6212.

Boccaccio C., Gaudino G., Gambarotta G., Galimi F. and Comoglio P.M. (1994). Hepatocyte growth factor (HGF) receptor expression is inducible and is part of the delayed-early response to HGF. J. Biol. Chem. 269, 12846-12851.

Breslow N., Chan C.W., Dhom G., Drury R.A., Franks L.M., Gellei B., Lee Y.S.. Lundberg S., Sparke B., Sternby N.H. and Tulinius H. (1977). Latent carcinoma of prostate at autopsy in seven areas. Int. J. Cancer 20, 680-688.

Brinkmann V., Foroutan H., Sach M., Weidner K.M. and Birchmeier W. (1995). HGF induces a variety of tissue-specific morphogenic programs in epithelial-cells. J. Cell Biol. 131, 1573-1586.

Bussolino F., Di Renzo M.F., Ziche M., Bocchietto E.. Olivero M., Naldini L., Gaudino G., Tamagnone L. Coffer A. and Comoglio P.M. (1992). Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. J. Cell Biol. 119, 629-641.

Cancer Research UK; www.cancerresearchuk.org/aboutcancer/statistics/incidence

Chen P., Xie H., Sekar M.C., Gupta K. and Wells A. (1994). Epidermal growth factor receptor-mediated cell motility: phospholipase C activity is required, but mitogen-activated protein kinase activity is not sufficient for induced cell movement. J. Cell Biol. 127, 847-857.

Cooper C.S., Park M., Blair D.G., Tainsky M.A.. Huebner K., Croce C.M and Vande Woude G.F. (1984). Molecular cloning of a new transforming gene from a chemically transformed human cell line. Nature 311, 29-33.

Crepaldi T., Pollack A.L., Prat M., Zborek A., Mostov K. and Comoglio P.M. (1994). Targeting of the HGF/SF receptor to the basolateral domain of polarized epithelial cells. J. Cell Biol. 125, 313-320.

Davies G., Jiang W.G. and Mason M.D. (2000). Cell-cell adhesion molecules and signalling intermediates and their role in the invasive potential of prostate cancer cells. J. Urol. 163, 985-992.

Davies G., Jiang W.G. and Mason M.D. (2001a). HGF/SF modifies the interaction between its receptor c-Met, and the E-cadherin/catenin complex in prostate cancer cells. Int. J. Mol. Med. 7, 385-388.

Davies G., Jiang W.G. and Mason M.D. (2001b). Matrilysin mediates extracellular cleavage of E-cadherin from prostate cancer cells: a

key mechanism in hepatocyte growth factor/scatter factor-induced cell-cell dissociation and in vitro invasion. Clin.Cancer Res. 7, 3289-3297.

Davies G., Mason M.D. and Martin T.A. (2003). The HGF/SF antagonist NK4 reverses fibroblast- and HGF-induced prostate tumour growth and angiogenesis in vivo. Int. J. Cancer 106, 348-354

Davies G., Watkins G., Mason M. and Jiang W.G. (2004a). Targeting the HGF/SF receptor c-Met using the hammerhead ribozyme transgene reduces in vitro invasion and migration in prostate cancer cells. Prostate 60, 317-324

Davies G., Jiang W.G. and Mason M.D. (2004b). Hepatocyte Growth Factor /Scatter Factor and prostate cancer metastasis. Cancer Metatastasis – Biology and Treatment of Metastasis of Prostate Cancer. Kluwer Academic Publishers.

Dunsmore S.E., Rubin J.S., Kovacs So, Chedid M.. Parks W.C. and Welgus H.G. (1996). Mechanisms of Hepatocyte growth factor stimulation of keratinocyte metalloproteinase production. J. Biol. Chem. 271, 24567-24582.

Faletto D.L. (1993). In: HGF/SF and the c-Met receptor. Goldberg I.D. and Rosen E.M. (eds). Basel. Birkhauser. pp 107-130

Fan S., Ma Y.X., Wang J.A., Yuan R.Q., Meng Q., Cao Y., Laterra J.J., Goldberg I.D. and Rosen E.M. (2000). The cytokine hepatocyte growth factor/scatter factor inhibits apoptosis and enhances DNA repair by a common mechanism involving signalling through phosphatidyl inositol 3' kinase. Oncogene 19, 2212-2223.

Ferracini R., Longati P., Naldini L., Vigna E. and Comoglio P.M. (1991). Identification of the major autophosphorylation site of the Met/hepatocyte growth factor receptor tyrosine kinase. J. Biol. Chem. 266, 19558-19564.

Fischer J., Palmedo G., von Knobloch R., Bugert P., Prayer-Galetti T., Pagano F. and Kovacs G. (1988). Duplication and overexpression of the mutant allele of the MET proto-oncogene in multiple hereditary papillary renal cell tumours. Oncogene 17, 733-739.

Fukuyama R., Ichijoh Y., Minoshima S., Kitamura N. and Shimizu N. (1991). Regional localization of the hepatocyte growth factor (HGF) gene to human chromosome 7 band q21.1. Genomics 11, 410-415.

Furlong R.A., Takehara T., Taylor W.G., Nakamura T. and Rubin J.S. (1991). Comparison of biological and immunochemical properties indicate that scatter factor and hepatocyte growth factor are indistinguishable. J. Cell Sci. 100, 173-177.

Gaudino G., Follenzi A., Naldini L, Collesi C. Santoro M., Gallo K.A., Godowski P.J. and Comoglio P.M. (1994). RON is a heterodimeric tyrosine kinase receptor activated by the HGF homologue MSP. EMBO J. 13, 3524-3532.

Gherardi E and Stoker M. (1990). Hepatocytes and scatter factor. Nature 346, 228.

Giancotti F.G and Mainiero F. (1994). Integrin-mediated adhesion and signalling in tumourgenesis. Biochem. Biophys. Acta. 1198, 4-64.

Giordano S., Di Renzo M.F., Narsimhan R.P., Cooper C.S., Rosa C. and Comoglio P.M. (1989). Biosynthesis of the protein encoded by the c-met proto-oncogene. Oncogene 4, 1383-1388.

Gmyrek G.A., Walburg M., Webb C.P., Yu H.M. You X. Vaughan E.D. Vande Woude G.F. and Knudsen B.S. (2001). Normal and malignant prostate epithelial cells differ in their response to hepatocyte growth factor/scatter factor. Am. J.Pathol. 159, 579-590.

Harrison G.M., Davies G., Martin T.A. Jiang W.G. and Mason M.D. (2002). Distribution and expression of CD44 isoforms and Ezrin during prostate cancer-endothelium interaction. J. Oncol. 21, 935-940.

Higashio K., Shima N., Goto M., Itagaki Y., Nagao M., Yasuda H. and Morinaga T. (1990). Identity of a tumor cytotoxic factor from human fibroblasts and hepatocyte growth factor. Biochem. Biophys. Res. Commun. 170, 397-404

Hiscox S. and Jiang W.G. (1998). HGF/SF regulates the phosphorylation of ß-catenin and cell-cell adhesion in cancer cells. Proc. Am. Assoc. Cancer Res. 139, 500-501.

Huff J.L., Jelinek M.A., Borgman C.A., Lansing T.J. and Parsons J.T. (1993). The protooncogene c-sea encodes a transmembrane protein-tyrosine kinase related to the Met/hepatocyte growth factor/scatter factor receptor. Proc. Natl. Acad. Sci. USA 90, 6140-6144.

Humphrey P.A., Zhu X., Zarnegar R.. Swanson P.E. Ratliff T.L., Vollmer R.T. and Day M.L. (1995). Hepatocyte growth factor and its receptor (c-MET) in prostatic carcinoma. Am. J. Pathol. 147, 386-396.

Idini L X. and Humphrey P.A. (2000). Overexpression and regulation of expression of scatter factor/hepatocyte growth factor in prostatic carcinoma. Urology 56, 1071-1074 .

Jiang W.G., Hiscox S., Singhrao S.K., Nakamura T., Puntis M.C. and Hallett M.B. (1995). Inhibition of HGF/SF-induced membrane ruffling and cell motility by transient elevation of cytosolic free Ca^{2+}. Exp. Cell Res. 220, 424-433.

Jiang W.G. and Hiscox S. (1997). Hepatocyte growth factor/scatter factor, a cytokine playing multiple and converse roles. Histol. Histopathol. 12, 537-555.

Jiang W.G., Bryce R.P., Horrobin D.F. and Mansel R.E. (1997). Gamma linolenic acid regulates gap junction communication in endothelial cells and their interaction with tumour cells. Prosta. Leuko. Essent. Fatty Acid 56, 307-316.

Jiang W., Hiscox S., Matsumoto K. and Nakamura T. (1999). Hepatocyte growth factor/scatter factor, its molecular, cellular and clinical implications in cancer. Crit. Rev. Oncol.-Hematol. 29, 209-248.

Jiang W.G., Martin T.A., Parr C., Davies G., Matsumoto K. and Nakamura T. (2005). Hepatocyte growth factor, its receptor, and their potential value in cancer therapies. Crit. Rev. Oncology-Hematology. 253, 35-69.

Kawaguchi T., Qin L., Shimomura T., Kondo J., Matsumoto K., Denda K. and Kitamura N. (1997). Purification and cloning of hepatocyte growth factor activator inhibitor type 2, a Kunitz-type serine protease inhibitor. J. Biol. Chem. 272, 27558-27564.

KawakamiKimura N., Narita T., Ohmori K., Yoneda T., Matsumoto K., Nakamura T. and Kannagi R. (1997). Involvement of HGF in increase integrin expression on HepG2 cells triggered by adhesion to endothelial cells. Br. J. Cancer 75, 47-53.

Knudsen B.S. Gmyrek G.A., Inra J., Scherr D.S. Vaughan E.D. Nanus D.M. Kattan M.W. Gerald W.L. and Vande Woude G.F. (2002). High expression of the Met receptor in prostate cancer metastasis to bone. Urology 60, 1113-1117.

Koeneman K.S., Yeung F. and Chung L.W. (1999). Osteomimetic properties of prostate cancer cells: a hypothesis supporting the predilection of prostate cancer metastasis and growth in the bone environment. Prostate 39, 246-261.

Krill D., Shuman M., Thompson M.T., Becich M.J. and Strom S.C. (1997). A simple method for the isolation and culture of epithelial and stromal cells from benign and neoplastic prostates. Urology 49, 981-988.

Kurimoto S., Moriyama N., Horie S., Sakai M., Kameyama S., Akimoto Y., Hirano H. and Kawabe K. (1998). Co-expression of hepatocyte

growth factor and its receptor in human prostate cancer. Histochem. J. 27-32.

Laguda B., Selden C., Jones M., Hodgson H. and Spurr N.K. (1991). Assignment of the hepatocyte growth factor (HGF) to chromosome 7q22-qter. Ann. Human Genet. 55, 213-216.

Lang S.H., Clarke N.W., George N.J. and Testa N.G. (1999). Scatter factor influences the formation of prostate epithelial cell colonies on bone marrow stroma in vitro. Clin. Exp. Metast. 17, 333-340.

Lin C.Y., Anders J., Johnson M., Sang Q.A. and Dickson R.B. (1999). Molecular cloning of cDNA for matriptase, a matrix-degrading serine protease with trypsin-like activity. J. Biol. Chem 274, 18231-18236.

Mars W.M., Kim T.H., Stolz D.B. Liu M.L and Michalopoulos G.K. (1996). Presence of urokinase in serum-free primary rat hepatocyte cultures and its role in activating hepatocyte growth factor. Cancer Res. 56, 2837-2843.

Martin T.A. and Jiang W.G. (2001). Tight junctions and their role in cancer metastasis. Histol. Histopathol. 16, 1183-1195.

Matsumoto K., Takehara T., Inoue H., Hagiya M., Shimizu S. and Nakamura T. (1991). Deletion of kringle domains or the N-terminal hairpin structure in hepatocyte growth factor results in marked decreases in related biological activities. Biochem. Biophys. Res. Commun. 181, 691-699.

Matsumoto K., Tajima H., Okazaki H. and Nakamura T. (1993). Heparin as an inducer of hepatocyte growth factor. J. Biochem. 114, 820-826.

Matsumoto K., Tajima H., Okazaki H. and Nakamura T. (1992). Negative regulation of hepatocyte growth factor gene expression in human lung fibroblasts and leukemic cells by transforming growth factor-beta 1 and glucocorticoids. J. Biol. Chem. 267, 24917-24920.

Matsumoto K. and Nakamura T. (1997). HGF: its organotrophic role and therapeutic potential. In: Plasminogen-related growth factors. Gherardi E. (ed). John Wiley & Sons. pp 198-214.

Michalopoulos G., Houck K,A., Dolan M.L. and Leutteke N.C. (1984). Control of hepatocyte replication by two serum factors. Cancer Res. 44, 4414-4419.

Miura H., Nishimura K., Tsujimura A., Matsumiya K.. Matsumoto K.. Nakamura T. and Okuyama A. (2001). Effects of hepatocyte growth factor on E-cadherin-mediated cell-cell adhesion in DU145 prostate cancer cells. Urology 58, 1064-1069.

Miyazawa K., Shimomura T., Naka D. and Kitamura N. (1994). Proteolytic activation of hepatocyte growth factor in response to tissue injury. J. Biol. Chem. 269, 8966-8970.

Miyazawa K., Shimomura T. and Kitamura N. (1996). Activation of hepatocyte growth factor in the injured tissues is mediated by hepatocyte growth factor activator. J. Biol. Chem. 271, 3615-3618

Mizuno K., Tanoue Y., Okano I., Harano T., Takada K. and Nakamura T. (1994). Purification and characterization of hepatocyte growth factor (HGF)-converting enzyme: activation of pro-HGF. Biochem. Biophysic. Res. Commun. 198, 1161-1169.

Moghul A., Lin L., Beedle A., Kanbour-Shakir A., DeFrances M.C. Liu Y. and Zarnegar R. (1994). Modulation of c-MET proto-oncogene (HGF receptor) mRNA abundance by cytokines and hormones: evidence for rapid decay of the 8 kb c-MET transcript. Oncogene 9, 2045-2052.

Montesano R., Matsumoto K., Nakamura T. and Orci L. (1991). Identification of a fibroblast-derived epithelial morphogen as hepatocyte growth factor. Cell 1991; 67, 901-908

Morimoto A., Tada K., Nakayama Y., Kohno K., Naito S., Ono M. and Kuwano M. (1994). Cooperative roles of hepatocyte growth factor and plasminogen activator in tubular morphogenesis by human microvascular endothelial cells. Jpn. J. Cancer Res. 85, 53-62.

Nakamura T., Nawa K. and Ichihara A. (1984). Partial purification and characterization of hepatocyte growth factor from serum of hepatectomized rats. Biochem. Biophys. Res. Commun. 122, 1450-1459.

Nakamura T., Nishizawa T., Hagiya M.. Seki T., Shimonishi M., Sugimura A., Tashiro K. and Shimizu S. (1989). Molecular cloning and expression of human hepatocyte growth factor. Nature 342, 440-443.

Nakashiro K., Okamoto M., Hayashi Y. and Oyasu R. (2000). Hepatocyte growth factor secreted by prostate-derived stromal cells stimulates growth of androgen-independent human prostatic carcinoma cells. Am. J. Pathol.157, 795-803.

Naldini L, Tamagnone L and Vigna E. (1992). Extracellular proteolytic cleavage by urokinase is required for activation of hepatocyte growth factor/scatter factor. EMBO J.11, 4825-4833.

Naughton M., Picus J., Zhu X., Catalona W.J., Vollmer R.T. and Humphrey P.A. (2001). Scatter factor-hepatocyte growth factor elevation in the serum of patients with prostate cancer. Journal of Urology 165, 1325-8

Nishimura K., Kitamura M., Takada S., Nonomura N., Tsujimura A., Matsumiya K., Miki T., Matsumoto K. and Okuyama A. (1998). Regulation of invasive potential of human prostate cancer cell lines by hepatocyte growth factor. Int. J. Urol. 5, 276-281.

Nishimura K., Kitamura M., Miura H., Nonomura N., Takada S., Takahara S., Matsumoto K., Nakamura T. and Matsumiya K. (1999). Prostate stromal cell-derived hepatocyte growth factor induces invasion of prostate cancer cell line DU145 through tumour-stromal interaction. Prostate 41, 145-153

Office for National Statistics. (1999). Mortality statistics – cause, England and Wales. London: Stationery Office, 2000

Okajima A., Miyazawa K., Naitoh Y., Inoue K. and Kitamura N. (1997). Induction of hepatocyte growth factor activator messenger RNA in the liver following tissue injury and acute inflammation. Hepatology 25, 97-102.

Parr C. and Jiang W.G. (2001). Hepatocyte growth factor activators, inhibitors and antagonists and their implication in cancer intervention. Histol. Histopathol. 16, 251-268.

Parr C., Davies G., Nakamura T., Matsumoto K., Mason M.D. and Jiang W.G. (2001). The HGF/SF-induced phosphorylation of paxillin, matrix adhesion, and invasion of prostate cancer cells were suppressed by NK4, an HGF/SF variant. Bioche. Biophys. Res. Commun. 285, 1330-1337.

Pasdar M., Li Z., Marreli M., Nguyen B.T., Park M. and Wong K. (1997). Inhibition of junction assembly in cultured epithelial cells by hepatocyte growth factor/scatter factor is concomitant with increased stability and altered phosphorylation of the soluble junctional molecules. Cell Growth Differ. 8, 451-462.

Pisters L.L., Troncoso P., Zhau H.E., Li W., von Eschenbach A.C. and Chung L.W. (1995). c-Met proto-oncogene expression in benign and malignant human prostate tissues. J. Urol. 154, 293-298.

Ponzetto C., Bardelli A., Zhen Z., Maina F., dalla Zonca P., Giordano S., Graziani A., Panayotou G. and Comoglio P.M. (1994). A multifunctional docking site mediates signalling and transformation by the hepatocyte growth factor/scatter factor receptor family. Cell 77, 261-271.

Presnell S.C., Borchert K., Gregory C., Maygarden S., Smith G. and Mohler J. (2001). Differential expression of hepatocyte growth factor

and c-met in prostate cancer amongst Caucasian American vs. African American. FASEB J.15, A239-239.

Qadan L.R., Perez-Stable C.M., Schwall R.H., Burnstein K.L., Ostenson R.C. Howard G.A. and Roos B.A. (2000). Hepatocyte growth factor and vitamin D cooperatively inhibit androgen-unresponsive prostate cancer cell lines. Endocrinology 141, 2567-2573.

Ronsin C., Muscatelli F., Mattei M.G. and Breathnach R. (1993). A novel putative receptor protein tyrosine kinase of the met family. Oncogene 8, 1195-1202.

Rosen E.M., Grant D., Kleinman H., Jaken S., Donovan M.A., Setter E., Luckett P.M., Carley W., Bhargava M. and Goldberg I.D. (1991). Scatter factor stimulates migration of vascular endothelium and capillary-like tube formation. EXS 59, 76-88.

Russell W.E., McGowan J.A. and Bucher N.L. (1984). Partial characterization of a hepatocyte growth factor from rat platelets. J. Cell. Physiol. 119, 183-192.

Shiraishi T., Watanabe M., Matsuura H., Kusano I., Yatani R. and Stemmermann G.N. (1994). The frequency of latent prostatic carcinoma in young males: the Japanese experience. In Vivo 8, 445-447.

Shimizu H., Ross R.K., Bernstein L., Yatani R., Henderson B.E. and Mack T.M. (1991). Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br. J. Cancer 63, 963-966.

Shimomura T., Miyazawa K., Komiyama Y., Hiraoka H. Naka D., Morimoto Y. and Kitamura N. (1995). Activation of hepatocyte growth factor by two homologous proteases, blood-coagulation factor XIIa and hepatocyte growth factor activator. Eur. J. Biochem. 229, 257-261.

Shimomura T., Denda K., Kitamura A., Kawaguchi T., Kito M., Kondo J., Kagaya S., Qin L., Takata H., Miyazawa K. and Kitamura N. (1997). Hepatocyte growth factor activator inhibitor, a novel Kunitz-type serine protease inhibitor. J. Biol. Chem. 272, 6370-6376.

Stoker M. and Perryman M. (1985). An epithelial scatter factor released by embryo fibroblasts. J. Cell Sci. 77, 209-223.

Tsuka H., Mori H., Li B., Kanamaru H., Matsukawa S. and Okada K. (1998). Enhanced hepatocyte growth factor level in human prostate cancer treated with endocrine therapy. Int. J. Oncol. 13, 169-176.

Tsuka H., Mori H., Li B., Kanamaru H., Matsukawa S. and Okada K. (1998). Expression of c-MET/HGF receptor mRNA and protein in human non-malignant and malignant prostate tissues. Int. J. Oncol. 13, 927-934.

You X., Yu H,M., Cohen-Gould L,, Cao B., Symons M., Vande Woude G.F. and Knudsen B.S. (2003). Regulation of migration of primary prostate epithelial cells by secreted factors from prostate stromal cells. Exp. Cell Res. 288, 246-256.

Watanabe M., Fukutome K., Kato H., Murata M. Kawamura J., Shiraishi T. and Yatani R. (1999). Progression-linked overexpression of c-Met in prostatic intraepithelial neoplasia and latent as well as clinical prostate cancers. Cancer Lett. 141, 173-178.

Weidner K.M., Behrens J., Vandekerckhove J. and Birchmeier W. (1990). Scatter factor: molecular characteristics and effect on the invasiveness of epithelial cells. J. Cell Biol. 11, 2097-2108.

Weimar I.S., de Jong D., Muller E.J., Nakamura T., van Gorp J,M., de Gast G.C. and Gerritsen W.R. (1997). Hepatocyte growth factor/scatter factor promotes adhesion of lymphoma cells to extracellular matrix molecules via alpha 4 beta 1 and alpha 5 beta 1 integrins. Blood 89, 990-1000.

Weimar I.S., Miranda N., Muller E.J., Hekman A., Kerst J.M., de Gast G.C. and Gerritsen W.R. (1998). Hepatocyte growth factor/scatter factor (HGF/SF) is produced by human bone marrow stromal cells and promotes proliferation, adhesion and survival of human hematopoietic progenitor cells (CD34+). Exp. Hematol. 26, 885 -894.

Zarnegar R., Muga S., Enghild J. and Michalopoulos G. (1989). NH2-terminal amino acid sequence of rabbit hepatopoietin A, a heparin-binding polypeptide growth factor for hepatocytes. Biochem. Biophys. Res. Commun. 163, 1370-1376.

Zarnegar R. and Michalopoulos G.K. (1995). The many faces of Hepatocyte growth factor: from hepatopoiesis to hematopoiesis. J. Cell Biol. 129,1170-1180.

Zhu X. and Humphrey P.A. (2000). Overexpression and regulation of expression of scatter factor/hepatocyte growth factor in prostatic carcinoma. Urology 56, 1071-1074.

Accepted July 6, 2005